

2024 ESC Guidelines for the management of chronic coronary syndromes

Developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC)

Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)

Authors/Task Force Members: Christiaan Vrints *[†], (Chairperson) (Belgium), Felicita Andreotti *[†], (Chairperson) (Italy), Konstantinos C. Koskinas[‡], (Task Force Co-ordinator) (Switzerland), Xavier Rossello [‡], (Task Force Co-ordinator) (Spain), Marianna Adamo  (Italy), James Ainslie (United Kingdom), Adrian Paul Banning  (United Kingdom), Andrzej Budaj  (Poland), Ronny R. Buechel  (Switzerland), Giovanni Alfonso Chiariello  (Italy), Alaide Chieffo  (Italy), Ruxandra Maria Christodorescu  (Romania), Christi Deaton  (United Kingdom), Torsten Doenst ¹ (Germany), Hywel W. Jones (United Kingdom), Vijay Kunadian  (United Kingdom), Julinda Mehilli  (Germany), Milan Milojevic ¹ (Serbia), Jan J. Piek  (Netherlands), Francesca Pugliese  (United Kingdom), Andrea Rubboli  (Italy), Anne Grete Semb  (Norway), Roxy Senior  (United Kingdom), Jurrien M. ten Berg  (Netherlands), Eric Van Belle  (France), Emeline M. Van Craenenbroeck  (Belgium), Rafael Vidal-Perez  (Spain), Simon Winther  (Denmark), and ESC Scientific Document Group

* Corresponding authors: Christiaan Vrints, Department of Cardiology, Antwerp University Hospital, Edegem, Belgium, and Research Group Cardiovascular Diseases, GENCOR, University of Antwerp, Antwerp, Belgium. Tel: +32 3 8213571, E-mail: christiaan.vrints@uantwerpen.be; and Felicita Andreotti, Cardiovascular Science Department, Fondazione Policlinico Universitario Gemelli IRCCS, Rome, Italy, and Cardio-Thoracic Department, Catholic University Medical School, Rome, Italy. Tel: +39-06-30154187, E-mail: felicita.andreotti@unicatt.it.

[†] The two Chairpersons contributed equally to the document and are joint first authors.

[‡] The two Task Force Co-ordinators contributed equally to the document.

Author/Task Force Member affiliations are listed in author information.

¹ Representing the Association European Association for Cardio-Thoracic Surgery (EACTS).

ESC Clinical Practice Guidelines (CPG) Committee: listed in the Appendix.

ESC subspecialty communities having participated in the development of this document:

Associations: Association of Cardiovascular Nursing & Allied Professions (ACNAP), Association for Acute CardioVascular Care (ACVC), European Association of Cardiovascular Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Association of Percutaneous Cardiovascular Interventions (EAPCI), Heart Failure Association (HFA).

Councils: Council for Cardiology Practice.

Working Groups: Cardiovascular Pharmacotherapy, Cardiovascular Surgery, Coronary Pathophysiology and Microcirculation, Thrombosis.

Patient Forum

Document Reviewers: Michael Borger, (CPG Review Co-ordinator) (Germany), Ingibjörg J. Gudmundsdóttir, (CPG Review Co-ordinator) (Iceland), Juhani Knuuti, (CPG Review Co-ordinator) (Finland), Ingo Ahrens (Germany), Michael Böhm (Germany), Sergio Buccheri (Italy), Davide Capodanno (Italy), Evald Høj Christiansen (Denmark), Jean-Philippe Collet[†] (France), Kenneth Dickstein (Norway), Christian Eek (Norway), Volkmar Falk (Germany), Peter A. Henriksen (United Kingdom), Borja Ibanez (Spain), Stefan James (Sweden), Sasko Kedev (Macedonia), Lars Køber (Denmark), Martha Kyriakou (Cyprus), Emma F. Magavern (United Kingdom), Angelia McInerney (Ireland), Caius Ovidiu Mersha (Romania), Borislava Mihaylova (United Kingdom), Richard Mindham (United Kingdom), Lis Neubeck (United Kingdom), Franz-Josef Neumann (Germany), Jens Cosedis Nielsen (Denmark), Pasquale Paolisso (Italy), Valeria Paradies (Netherlands), Agnes A. Pasquet (Belgium), Massimo Piepoli (Italy), Eva Prescott (Denmark), Amina Rakisheva (Kazakhstan), Bianca Rocca (Italy), Marc Ruel (Canada), Sigrid Sandner (Austria), Antti Saraste (Finland), Karolina Szummer (Sweden), Ilonca Vaartjes (Netherlands), William Wijns (Ireland), Stephan Windecker (Switzerland), Adam Witkowsky (Poland), Marija Zdrakovic (Serbia), and Katja Zeppenfeld (Netherlands)

† Professor Jean-Philippe Collet sadly passed away during the development of these guidelines. Professor Collet's contribution to these guidelines was, as always, highly valued.

SD All experts involved in the development of these guidelines have submitted declarations of interest, which are reported in a supplementary document to the guidelines. See the *European Heart Journal* online or <https://www.escardio.org/Guidelines> for supplementary documents as well as evidence tables.

Disclaimer. The ESC Guidelines represent the views of the ESC and were produced after careful consideration of the scientific and medical knowledge and the evidence available at the time of their publication. The ESC is not responsible in the event of any contradiction, discrepancy and/or ambiguity between the ESC Guidelines and any other official recommendations or guidelines issued by the relevant public health authorities, in particular in relation to good use of healthcare or therapeutic strategies. Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies; however, the ESC Guidelines do not override, in any way whatsoever, the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and, where appropriate and/or necessary, the patient's caregiver. Nor do the ESC Guidelines exempt health professionals from taking into full and careful consideration the relevant official updated recommendations or guidelines issued by the competent public health authorities, in order to manage each patient's case in light of the scientifically accepted data pursuant to their respective ethical and professional obligations. It is also the health professional's responsibility to verify the applicable rules and regulations relating to drugs and medical devices at the time of prescription. The ESC warns readers that the technical language may be misinterpreted and declines any responsibility in this respect.

Permissions. The content of these European Society of Cardiology (ESC) Guidelines has been published for personal and educational use only. No commercial use is authorized. No part of the ESC Guidelines may be translated or reproduced in any form without written permission from the ESC. Permissions can be obtained upon submission of a written request to Oxford University Press, the publisher of the *European Heart Journal* and the party authorized to handle such permissions on behalf of the ESC (journals.permissions@oup.com).

Keywords

Guidelines • Antianginal therapy • Antithrombotic therapy • Atherosclerosis • Clinical likelihood • Chronic coronary syndromes • Coronary artery disease • Diagnostic testing/algorithm • Heart team • Lipid-lowering therapy • Microvascular disease • Myocardial ischaemia • Myocardial revascularization • Outcomes • PROMS/PREMS • Shared decision-making • Stable angina • Vasospasm

Table of contents

1. Preamble	8	4.1.2.5. Physical activity and sedentary behaviour	42
2. Introduction	9	4.1.3. Exercise therapy	43
2.1. Evolving pathophysiological concepts of chronic coronary syndromes	9	4.2. Antianginal/anti- <i>ischaemic</i> medication	43
2.2. Chronic coronary syndromes: clinical presentations (Figure 1)	10	4.2.1. General strategy	43
2.3. Changing epidemiology and management strategies	10	4.2.2. Beta blockers	44
2.4. What is new	12	4.2.3. Combination therapy	45
3. Stepwise approach to the initial management of individuals with suspected chronic coronary syndrome	19	4.3. Medical therapy for event prevention	46
3.1. STEP 1: General clinical examination	19	4.3.1. Antithrombotic drugs	46
3.1.1. History, differential diagnosis, and physical examination	19	4.3.1.1. Antiplatelet drugs	46
3.1.2. Basic testing: 12-lead electrocardiogram and biochemistry	22	4.3.1.1.1. Aspirin monotherapy	46
3.1.2.1. Electrocardiogram	22	4.3.1.1.2. Oral P2Y ₁₂ inhibitor monotherapy	46
3.1.2.2. Biochemical tests	23	4.3.1.1.2.1. Clopidogrel monotherapy	46
3.2. STEP 2: Further evaluation	23	4.3.1.1.2.2. Ticagrelor monotherapy	46
3.2.1. Pre-test clinical likelihood of obstructive atherosclerotic coronary artery disease	23	4.3.1.1.3. Dual antiplatelet therapy post-percutaneous coronary intervention	48
3.2.2. Transthoracic echocardiography and cardiac magnetic resonance at rest	26	4.3.1.1.4. Extended intensified antithrombotic therapy	48
3.2.3. Exercise electrocardiogram testing	26	4.3.1.1.5. Genotype- and phenotype-guided dual antiplatelet therapy	49
3.2.4. Chest X-ray	27	4.3.1.2. Anticoagulant therapy	50
3.2.5. Ambulatory electrocardiogram monitoring	27	4.3.1.2.1. Monotherapy with oral anticoagulant	50
3.3. STEP 3: Confirming the diagnosis	27	4.3.1.2.2. Combination of anticoagulant and antiplatelet therapy after percutaneous coronary intervention in chronic coronary syndrome patients with AF or other indication for oral anticoagulant	50
3.3.1. Anatomical imaging: coronary computed tomography angiography	27	4.3.1.3. Coronary artery bypass grafting and antithrombotic therapy	51
3.3.1.1. Computed tomography perfusion imaging	27	4.3.1.4. Proton pump inhibitors	51
3.3.1.2. Prognosis, plaque features, and opportunity to improve outcomes	28	4.3.2. Lipid-lowering drugs	53
3.3.1.3. Recognized pre-requisites for coronary computed tomography angiography	28	4.3.3. Renin–angiotensin–aldosterone blockers/angiotensin receptor neprilysin inhibitor	53
3.3.2. Functional imaging	28	4.3.4. Sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists	54
3.3.2.1. Stress echocardiography	28	4.3.5. Anti-inflammatory agents for event prevention	54
3.3.2.2. Myocardial perfusion scintigraphy—single-photon emission computed tomography	29	4.4. Revascularization for chronic coronary syndromes	55
3.3.2.3. Positron emission tomography-computed tomography	30	4.4.1. Appropriate indication for myocardial revascularization ...	55
3.3.2.4. Cardiac magnetic resonance imaging	30	4.4.2. Additional considerations on reduced systolic left ventricular function: myocardial viability, revascularization, and its modality	56
3.3.2.5. Non-invasive testing for microvascular dysfunction	31	4.4.3. Additional considerations—complete vs. partial revascularization	57
3.3.3. Invasive tests	31	4.4.4. Assessment of clinical risk and anatomical complexity	57
3.3.3.1. Invasive coronary angiography	31	4.4.5. Choice of myocardial revascularization modality	58
3.3.3.2. Functional assessment of epicardial stenosis severity to guide coronary revascularization	32	4.4.5.1. Patients with single- or two-vessel coronary artery disease	58
3.3.3.3. Assessment of microvascular dysfunction	33	4.4.5.2. Patients with unprotected left main coronary artery disease	58
3.3.3.4. Testing for coronary vasospasm	33	4.4.5.3. Patients with multivessel coronary artery disease	60
3.3.4. Diagnostic algorithm and selection of appropriate tests	34	4.4.5.4. Impact of coronary pressure guidance on multivessel coronary artery disease patients undergoing percutaneous coronary intervention	60
3.3.5. Adverse-event risk assessment	39	4.4.5.5. Virtual percutaneous coronary intervention: combination of coronary pressure mapping with coronary anatomy for percutaneous coronary intervention planning	60
3.4. STEP 4: Initial therapy	40	4.4.5.6. Impact of intracoronary imaging guidance on multivessel coronary artery disease patients undergoing percutaneous coronary intervention	60
4. Guideline-directed therapy	41	4.4.5.7. Hybrid revascularization in multivessel coronary artery disease patients	61
4.1. Patient education, lifestyle optimization for risk-factor control, and exercise therapy	41		
4.1.1. Patient education	41		
4.1.2. Key lifestyle interventions for risk-factor control	41		
4.1.2.1. Smoking and substance abuse	42		
4.1.2.2. Weight management	42		
4.1.2.3. Diet and alcohol	42		
4.1.2.4. Mental health	42		

4.4.6. Patient–physician shared decision-making to perform and select revascularization modality	61
4.4.7. Institutional protocols, clinical pathways, and quality of care	61
5. Optimal assessment and treatment of specific groups	64
5.1. Coronary artery disease and heart failure	64
5.2. Angina/ischaemia with non-obstructive coronary arteries	65
5.2.1. Definition	65
5.2.2. Angina/ischaemia with non-obstructive coronary arteries endotypes	65
5.2.2.1. Microvascular angina	66
5.2.2.2. Epicardial vasospastic angina	67
5.2.3. Clinical presentations	67
5.2.4. Short- and long-term prognosis	67
5.2.5. Diagnosis	67
5.2.5.1. Non-invasive diagnosis	67
5.2.5.2. Invasive coronary functional testing	67
5.2.5.2.1. Basic coronary functional testing	67
5.2.5.2.2. Coronary vasomotor testing	67
5.2.6. Management of angina/ischaemia with non-obstructive coronary arteries	69
5.3. Other specific patient groups	71
5.3.1. Older adults	71
5.3.2. Sex differences in chronic coronary syndromes	71
5.3.3. High bleeding-risk patients	72
5.3.4. Inflammatory rheumatic diseases	72
5.3.5. Hypertension	72
5.3.6. Atrial fibrillation	72
5.3.7. Valvular heart disease	72
5.3.8. Chronic kidney disease	73
5.3.9. Cancer	73
5.3.10. Optimal treatment of patients with human immunodeficiency virus	73
5.3.11. Socially and geographically diverse groups	73
5.4. Screening for coronary artery disease in asymptomatic individuals	74
6. Long-term follow-up and care	75
6.1. Voice of the patient	75
6.1.1. Communication	75
6.1.2. Depression and anxiety	75
6.2. Adherence and persistence	75
6.2.1. Adherence to healthy lifestyle behaviours	75
6.2.1.1. Why behavioural changes are difficult	75
6.2.1.2. How to change behaviour and support healthy lifestyles	76
6.2.1.3. Digital and mHealth	77
6.2.1.4. How to assess adherence	78
6.2.2. Adherence to medical therapy	78
6.2.2.1. Strategies to improve medication adherence	78
6.2.2.2. mHealth strategies for medication adherence	78
6.3. Diagnosis of disease progression	78
6.3.1. Risk factors for recurrent coronary artery disease events	79
6.3.2. Organization of long-term follow-up	79
6.3.3. Non-invasive diagnostic testing	80
6.4. Treatment of myocardial revascularization failure	81
6.4.1. Percutaneous coronary intervention failure	81
6.4.2. Managing graft failure after coronary artery bypass grafting	81
6.5. Recurrent or refractory angina/ischaemia	82
6.6. Treatment of disease complications	83

7. Key messages	83
8. Gaps in evidence	84
9. 'What to do' and 'What not to do' messages from the guidelines	85
10. Evidence tables	91
11. Data availability statement	91
12. Author information	91
13. Appendix	92
14. References	93

Tables of Recommendations

Recommendation Table 1 — Recommendations for history taking, risk factor assessment, and resting electrocardiogram in individuals with suspected chronic coronary syndrome (see also Evidence Table 1)	22
Recommendation Table 2 — Recommendations for basic biochemistry in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 2)	23
Recommendation Table 3 — Recommendations for estimating, adjusting and reclassifying the likelihood of obstructive atherosclerotic coronary artery disease in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 3)	24
Recommendation Table 4 — Recommendations for resting transthoracic ultrasound and cardiac magnetic resonance imaging in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 4)	26
Recommendation Table 5 — Recommendations for exercise ECG in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 5)	27
Recommendation Table 6 — Recommendations for chest X-ray in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 6)	27
Recommendation Table 7 — Recommendations for ambulatory ECG monitoring in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 7)	27
Recommendation Table 8 — Recommendations for non-invasive anatomical imaging tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—coronary computed tomography angiography, if available, and supported by local expertise (see also Evidence Table 8)	28
Recommendation Table 9 — Recommendations for non-invasive tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—stress echocardiography, if available, and supported by local expertise (see also Evidence Table 9)	29
Recommendation Table 10 — Recommendations for non-invasive functional myocardial imaging tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—resting and stress single-photon emission computed tomography/positron emission tomography—cardiac magnetic resonance imaging, if available, and supported by local expertise (see also Evidence Table 10)	30
Recommendation Table 11 — Recommendations for invasive coronary angiography in the diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 11)	32
Recommendation Table 12 — Recommendations for functional assessment of epicardial artery stenosis severity during invasive	

coronary angiography to guide revascularization (see also Evidence Table 12)	33
Recommendation Table 13 — Recommendations for selection of initial diagnostic tests in individuals with suspected chronic coronary syndrome (see also Evidence Table 13)	39
Recommendation Table 14 — Recommendations for definition of high risk of adverse events (see also Evidence Table 14)	40
Recommendation Table 15 — Recommendations for cardiovascular risk reduction, lifestyle changes, and exercise interventions in patients with established chronic coronary syndrome (see also Evidence Table 15)	43
Recommendation Table 16 — Recommendations for antianginal drugs in patients with chronic coronary syndrome (see also Evidence Table 16)	45
Recommendation Table 17 — Recommendations for antithrombotic therapy in patients with chronic coronary syndrome (see also Evidence Table 17)	51
Recommendation Table 18 — Recommendations for lipid-lowering drugs in patients with chronic coronary syndrome (see also Evidence Table 18)	53
Recommendation Table 19 — Recommendations for sodium–glucose cotransporter 2 inhibitors and/or glucagon-like peptide-1 receptor agonists in patients with chronic coronary syndrome (see also Evidence Table 19)	54
Recommendation Table 20 — Recommendations for anti-inflammatory drugs in patients with chronic coronary syndrome (see also Evidence Table 20)	55
Recommendation Table 21 — Recommendations for angiotensin-converting enzyme inhibitors in patients with chronic coronary syndrome (see also Evidence Table 21)	55
Recommendation Table 22 — Recommendations for revascularization in patients with chronic coronary syndrome (see also Evidence Table 22)	62
Recommendation Table 23 — Recommendations for mode of revascularization in patients with chronic coronary syndrome (see also Evidence Table 23)	63
Recommendation Table 24 — Recommendations for management of chronic coronary syndrome patients with chronic heart failure (see also Evidence Table 24)	64
Recommendation Table 25 — Recommendations for diagnosis and management of patients with angina/ischaemia with non-obstructive coronary arteries (see also Evidence Table 25)	71
Recommendation Table 26 — Recommendations for older, female, high bleeding risk, comorbid, and socially/geographically diverse patients (see also Evidence Table 26)	74
Recommendation Table 27 — Recommendations for screening for coronary artery disease in asymptomatic individuals (see also Evidence Table 27)	74
Recommendation Table 28 — Recommendations for adherence to medical therapy and lifestyle changes (see also Evidence Table 28) ...	78
Recommendation Table 29 — Recommendations for diagnosis of disease progression in patients with established chronic coronary syndrome (see also Evidence Table 29)	81
Recommendation Table 30 — Recommendations for treatment of revascularization failure (see also Evidence Table 30)	82
Recommendation Table 31 — Recommendations for recurrent or refractory angina/ischaemia (see also Evidence Table 31)	82

List of tables

Table 1 Classes of recommendations	8
Table 2 Levels of evidence	9

Table 3 New major recommendations in 2024	12
Table 4 Revised recommendations	16
Table 5 Grading of effort angina severity according to the Canadian Cardiovascular Society	22
Table 6 Overview of non-invasive tests used for first-line testing in individuals with suspected chronic coronary syndrome	37
Table 7 Practical advice on lifestyle counselling and interventions	41
Table 8 Options for extended intensified antithrombotic therapy	50
Table 9 Summary of trial-based evidence for the comparison of percutaneous coronary intervention and coronary artery bypass grafting in patients with left main coronary artery disease	59
Table 10 'What to do' and 'What not to do'	85

List of figures

Figure 1 (Central Illustration) Clinical presentations of chronic coronary syndrome and mechanisms of myocardial ischaemia	11
Figure 2 Stepwise approach to the initial management of individuals with suspected chronic coronary syndrome	20
Figure 3 Main CCS symptoms: angina and exertional dyspnoea	21
Figure 4 Estimation of the clinical likelihood of obstructive coronary artery disease	25
Figure 5 Adjustment and reclassification of the estimated clinical likelihood of obstructive coronary artery disease	34
Figure 6 Appropriate first-line testing in symptomatic individuals with suspected chronic coronary syndrome	35
Figure 7 Initial management of symptomatic individuals with suspected chronic coronary syndrome	36
Figure 8 Ruling in and ruling out functionally significant obstructive coronary artery disease by sequential anatomical (coronary computed tomography angiography) and functional (dobutamine stress echocardiography) testing. ^a	38
Figure 9 Possible combinations of antianginal drugs	44
Figure 10 Antithrombotic drugs for chronic coronary syndromes: pharmacological targets	47
Figure 11 Antithrombotic treatment in chronic coronary syndrome patients undergoing percutaneous coronary intervention	49
Figure 12 Prevalence of disease characteristics in patients with ANOCA/INOCA referred for invasive coronary functional testing ...	66
Figure 13 Diagnostic algorithm for patients with angina/ischaemia with non-obstructive coronary arteries	68
Figure 14 Spasm provocation and functional testing protocol	69
Figure 15 Treatment of angina/ischaemia with non-obstructive coronary arteries	70
Figure 16 Actions on the five dimensions of adherence to therapy ...	76
Figure 17 Strategies for long-term adherence to a healthy lifestyle	77
Figure 18 Approach for the follow-up of patients with established chronic coronary syndrome	80

Abbreviations and acronyms

99mTc	Technetium-99m
ACE-I	Angiotensin-converting enzyme inhibitor
Ach	Acetylcholine
ACS	Acute coronary syndrome(s)
AF	Atrial fibrillation
AKI	Acute kidney injury
ALPHEUS	Assessment of Loading with the P2Y ₁₂ Inhibitor Ticagrelor or Clopidogrel to Halt Ischemic Events in Patients Undergoing Elective Coronary Stenting
ANOCA	Angina with non-obstructive coronary arteries
ARB	Angiotensin receptor blocker

ARC-HBR	Academic Research Consortium for High Bleeding Risk	dPR	Diastolic pressure ratio
ARNI	Angiotensin receptor neprilysin inhibitor	DSE	Dobutamine stress echocardiography
ART	Antiretroviral therapy	EACTS	European Association for Cardio-Thoracic Surgery
ASCVD	Atherosclerotic cardiovascular disease	EACVI	European Association of Cardiovascular Imaging
ASE	American Society of Echocardiography	ECG	Electrocardiogram
AUGUSTUS	Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban versus Vitamin K Antagonist and Aspirin versus Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention	EF	Ejection fraction
		eGFR	Estimated glomerular filtration rate
BARC	Bleeding Academic Research Consortium	EMA	European Medicines Agency
b.i.d.	bis in die (twice daily)	ESC	European Society of Cardiology
BMI	Body mass index	EXCEL	Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization
BP	Blood pressure	FAME	Fractional Flow Reserve versus Angiography for Multivessel Evaluation
b.p.m.	Beats per minute	FFR	Fractional flow reserve
CABG	Coronary artery bypass grafting	FFR-CT	Coronary computed tomography angiography-derived fractional flow reserve
CAC	Coronary artery calcification	FREEDOM	Strategies for Multivessel Revascularization in Patients with Diabetes
CACS	Coronary artery calcium score	GDMT	Guideline-directed medical therapy
CACS-CL	CACS + risk-factor-weighted clinical likelihood (RF-CL) model	GI	Gastrointestinal
CAD	Coronary artery disease	GIP	Glucose-dependent insulinotropic polypeptide
CANTOS	Canakinumab Antiinflammatory Thrombosis Outcome Study	GLOBAL	Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs. aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent (DES): a multicentre, open-label, randomized superiority trial
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events	LEADERS	Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs. aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent (DES): a multicentre, open-label, randomized superiority trial
CCB	Calcium channel blocker		
CCS	Chronic coronary syndrome(s)	GLP-1	Glucagon-like peptide-1
CCTA	Coronary computed tomography angiography	GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries
CFC	Coronary flow capacity	HbA1c	Glycated haemoglobin
CFR	Coronary flow reserve	HBR	High bleeding risk
CFVR	Coronary flow velocity reserve	HDL-C	High-density lipoprotein cholesterol
CHA ₂ DS ₂ -VASc	Congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, sex category (female)	HF	Heart failure
		HFmrEF	Heart failure with mildly reduced ejection fraction
CI	Confidence interval	HFpEF	Heart failure with preserved ejection fraction
CKD	Chronic kidney disease	HFrEF	Heart failure with reduced ejection fraction
CMD	Coronary microvascular dysfunction	HIV	Human immunodeficiency virus
CMR	Cardiac magnetic resonance	HMR	Hyperaemic myocardial velocity resistance
COLCOT	Colchicine Cardiovascular Outcomes Trial	HOST-EXAM	Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-EXtended Antiplatelet Monotherapy
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies		
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation	HR	Hazard ratio
CRT	Cardiac resynchronization therapy	hs-CRP	High-sensitivity C-reactive protein
CT	Computed tomography	HSR	Hyperaemic stenosis resistance
CVD	Cardiovascular disease	i.c.	Intracoronary
CYP2C19	Cytochrome P450 2C19	i.v.	Intravenous
CYP3A4	Cytochrome P450 3A4	ICA	Invasive coronary angiography
CZT	Cadmium–zinc–telluride	ICD	Implantable cardioverter defibrillator
DAPT	Dual antiplatelet therapy	ICFT	Invasive coronary functional testing
DEFINE GPS	Distal Evaluation of Functional Performance with Intravascular Sensors to Assess the Narrowing Effect: Guided Physiologic Stenting	iFR	Instantaneous wave-free ratio
		iFR-SWEDEHEART	Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome
DES	Drug-eluting stent	ILIAS	Inclusive Invasive Physiological Assessment in Angina Syndromes
DEFINE-FLAIR	Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation	IMR	Index of microcirculatory resistance
DHP	Dihydropyridine	INOCA	Ischaemia with non-obstructive coronary arteries
DM	Diabetes mellitus	INR	International normalized ratio
DOAC	Direct oral anticoagulant	IQR	Interquartile range

ISCHEMIA	Initial Invasive or Conservative Strategy for Stable Coronary Disease (trial)	PDE-5	Phosphodiesterase-5
ISR	In-stent restenosis	PEGASUS-TIMI 54	Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin Thrombolysis In Myocardial Infarction
ISTH	International Society on Thrombolysis and Haemostasis	PESA	Progression of Early Subclinical Atherosclerosis
IVUS	Intravascular ultrasound	PET	Positron emission tomography
LAD	Left anterior descending	PRECISE-DAPT	PREdicting bleeding Complications In patients undergoing Stent implantation and subSequent Dual AntiPlatelet Therapy
LBBB	Left bundle branch block	PRECOMBAT	Randomized Trial of Stents versus Bypass Surgery for Left Main Coronary Artery Disease (trial)
LDL-C	Low-density lipoprotein cholesterol	PRIZE	Precision Medicine with Zibotentan in Microvascular Angina
LGE	Late gadolinium enhancement	PROM	Patient-reported outcome measure
LIMA	Left internal mammary artery	PROMISE	Prospective Multicenter Imaging Study for Evaluation of Chest Pain
LITA	Left internal thoracic artery	PTP	Pre-test probability
LMCA	Left main coronary artery	QFR	Quantitative flow ratio
LMCAD	Left main coronary artery disease	QoL	Quality of life
LODOCO2	LOW-DOse COLchicine 2	R3F	French FFR Registry
LOE	Level of evidence	RAAS	Renin–angiotensin–aldosterone system
LV	Left ventricular	RCT	Randomized controlled trial
LVEF	Left ventricular ejection fraction	REVIVED-BCIS2	Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction
MACCE	Major adverse cardiac or cerebrovascular events	RF-CL	Risk-factor-weighted clinical likelihood
MACE	Major adverse cardiovascular events	RFR	Relative flow reserve
MASTER-DAPT	Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen	RIPCORDER	Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain trial
MBF	Myocardial blood flow	RR	Relative risk
MCE	Myocardial contrast echocardiography	RWTA	Regional systolic wall-thickening abnormalities
MCS	Mechanical circulatory support	SAPT	Single antiplatelet therapy
MFR	Myocardial flow reserve	SCORE2	Systematic Coronary Risk Estimation 2
mHealth	Mobile device-based healthcare	SCORE2-OP	Systematic Coronary Risk Estimation 2–Older Persons
MI	Myocardial infarction	SCOT-HEART	Scottish Computed Tomography of the Heart
MIDCAB	Minimally invasive direct coronary artery bypass	SELECT	Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity
MRA	Mineralocorticoid receptor antagonist	SGLT2	Sodium–glucose cotransporter 2
MRI	Magnetic resonance imaging	SLE	Systemic lupus erythematosus
MRR	Microvascular resistance reserve	SPECT	Single-photon emission computed tomography
MVA	Microvascular angina	STEMI	ST-segment elevation myocardial infarction
MVD	Multivessel disease	STICH	Surgical Treatment for Ischemic Heart Failure
NNH	Number needed to harm	STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality
NNT	Number needed to treat to prevent an adverse event	SURMOUNT	Efficacy and Safety of Tirzepatide Once Weekly in Participants Without Type 2 Diabetes Who Have Obesity or Are Overweight With Weight-Related Comorbidities: A Randomized, Double-Blind, Placebo-Controlled Trial
NOBLE	Nordic–Baltic–British Left Main Revascularisation Study	SYNTAX	SYNergy between PCI with TAXUS and Cardiac Surgery
NSTEMI	Non-ST-segment elevation myocardial infarction	THEMIS	The Effect of Ticagrelor on Health Outcomes in diabEtes Mellitus patients Intervention Study
NTG	Nitroglycerine	TID	Transient ischaemic dilatation
NYHA	New York Heart Association	TIMI	Thrombolysis In Myocardial Infarction
OAC	Oral anticoagulant	Tx	Thromboxane
OCT	Optical coherence tomography		
OR	Odds ratio		
ORBITA	Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina		
ORBITA-COSMIC	Coronary Sinus Reducer Objective Impact on Symptoms, MRI Ischaemia and Microvascular Resistance		
PAD	Peripheral artery disease		
PAR	Protease-activated receptor		
PARR-2	F-18-Fluorodeoxyglucose Positron Emission Tomography Imaging-Assisted Management of Patients with Severe Left Ventricular Dysfunction and Suspected Coronary Disease: a Randomized, Controlled Trial		
PCI	Percutaneous coronary intervention		
PCSK9	Proprotein convertase subtilisin/kexin type 9		
Pd/Pa	Distal coronary pressure to aortic pressure ratio		

TWILIGHT	Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention
vFFR	Vessel fractional flow reserve
VKA	Vitamin K antagonist
VSA	Vasospastic angina
VTE	Venous thrombo-embolism
WARRIOR	Women's Ischemia Trial to Reduce Events in Non-Obstructive Coronary Artery Disease
WOMEN	What is the Optimal Method for Ischemia Evaluation of Women
X-ECG	Exercise ECG testing

1. Preamble

Guidelines evaluate and summarize available evidence with the aim of assisting health professionals in proposing the best diagnostic or therapeutic approach for an individual patient with a given condition. Guidelines are intended for use by health professionals, and the European Society of Cardiology (ESC) makes its guidelines freely available.

ESC Guidelines do not override the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable in each country to drugs and devices at the time of prescription and to respect the ethical rules of their profession.

ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated when warranted by new evidence. ESC Policies and Procedures for formulating and issuing ESC Guidelines can be found on the ESC website (<https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines>). These guidelines update and replace the previous version from

2019 and partly replace the myocardial revascularization guidelines from 2018.

The Members of this task force were selected by the ESC to include professionals involved in the medical care of patients with this pathology, as well as patient representatives and methodologists. The selection procedure included an open call for authors and aimed to include members from across the whole of the ESC region and from relevant ESC Subspecialty Communities. Consideration was given to diversity and inclusion, notably with respect to gender and country of origin. The task force performed a critical review and evaluation of the published literature on diagnostic and therapeutic approaches including assessment of the risk–benefit ratio. The strength of every recommendation and the level of evidence supporting them were weighed and scored according to predefined scales as outlined in [Tables 1](#) and [2](#) below. Patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) were also evaluated as the basis for recommendations and/or discussion in these guidelines. The task force followed ESC voting procedures and all approved recommendations were subject to a vote and achieved at least 75% agreement among voting members. Members of the task force with declared interests on specific topics were asked to abstain from voting on related recommendations.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest were reviewed according to the ESC declaration of interest rules, which can be found on the ESC website (<http://www.escardio.org/guidelines>) and have been compiled in a report published in a supplementary document with the guidelines. Funding for the development of ESC Guidelines is derived entirely from the ESC with no involvement of the healthcare industry.

The ESC Clinical Practice Guidelines (CPG) Committee supervises and co-ordinates the preparation of new guidelines and is responsible

Table 1 Classes of recommendations

	Definition	Wording to use
Classes of recommendations	Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
	Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
	Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
	Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
	Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

©ESC 2024

for the approval process. In addition to review by the CPG Committee, ESC Guidelines undergo multiple rounds of double-blind peer review by external experts, including members from across the whole of the ESC region, all National Cardiac Societies of the ESC and from relevant ESC Subspecialty Communities. After appropriate revisions, the guidelines are signed off by all the experts in the task force. The finalized document is signed off by the CPG Committee for publication in the *European Heart Journal*.

ESC Guidelines are based on analyses of published evidence, chiefly on clinical trials and meta-analyses of trials, but potentially including other types of studies. Evidence tables summarizing key information from relevant studies are generated early in the guideline development process to facilitate the formulation of recommendations, to enhance comprehension of recommendations after publication, and reinforce transparency in the guideline development process. The tables are published in their own section of the ESC Guidelines and are specifically related to the recommendation tables.

Off-label use of medication may be presented in these guidelines if a sufficient level of evidence shows that it can be considered medically appropriate for a given condition. However, the final decisions concerning an individual patient must be made by the responsible health professional giving special consideration to:

- The specific situation of the patient. Unless otherwise provided for by national regulations, off-label use of medication should be limited to situations where it is in the patient's interest with regard to the quality, safety, and efficacy of care, and only after the patient has been informed and has provided consent.
- Country-specific health regulations, indications by governmental drug regulatory agencies and the ethical rules to which health professionals are subject, where applicable.

2. Introduction

The 2019 ESC (European Society of Cardiology) Guidelines for the diagnosis and management of chronic coronary syndromes introduced the term chronic coronary syndromes (CCS)¹ to describe the clinical presentations of coronary artery disease (CAD) during stable periods, particularly those preceding or following an acute coronary syndrome (ACS). CAD was defined as the pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries, whether obstructive or non-obstructive. Based on expanded pathophysiological concepts, a new, more comprehensive definition of CCS is introduced:

'CCS are a range of clinical presentations or syndromes that arise due to structural and/or functional alterations related to chronic diseases of the coronary arteries and/or microcirculation. These alterations can lead to transient, reversible, myocardial demand vs. blood supply mismatch resulting in hypoperfusion (ischaemia), usually (but not always) provoked by exertion, emotion or other stress, and may manifest as angina, other chest discomfort, or dyspnoea, or be asymptomatic. Although stable for long periods, chronic coronary diseases are frequently progressive and may destabilize at any moment with the development of an ACS.'

Of note, 'disease' refers to the underlying coronary pathology, and 'syndrome' refers to the clinical presentation.

2.1. Evolving pathophysiological concepts of chronic coronary syndromes

Our understanding of the pathophysiology of CCS is transitioning from a simple to a more complex and dynamic model. Older concepts

considered a fixed, focal, flow-limiting atherosclerotic stenosis of a large or medium coronary artery as a *sine qua non* for inducible myocardial ischaemia and ischaemic chest pain (angina pectoris). Current concepts have broadened to embrace structural and functional abnormalities in both the macro- and microvascular compartments of the coronary tree that may lead to transient myocardial ischaemia. At the macrovascular level, not only fixed, flow-limiting stenoses but also diffuse atherosclerotic lesions without identifiable luminal narrowing may cause ischaemia under stress;^{2,3} structural abnormalities such as myocardial bridging⁴ and congenital arterial anomalies⁵ or dynamic epicardial vasospasm may be responsible for transient ischaemia. At the microvascular level, coronary microvascular dysfunction (CMD) is increasingly acknowledged as a prevalent factor characterizing the entire spectrum of CCS;⁶ functional and structural microcirculatory abnormalities may cause angina and ischaemia even in patients with non-obstructive disease of the large or medium coronary arteries [angina with non-obstructive coronary arteries (ANOCA); ischaemia with non-obstructive coronary arteries (INOCA)].⁶ Finally, systemic or extracoronary conditions, such as anaemia, tachycardia, blood pressure (BP) changes, myocardial hypertrophy, and fibrosis, may contribute to the complex pathophysiology of non-acute myocardial ischaemia.⁷

The risk factors that predispose to the development of epicardial coronary atherosclerosis also promote endothelial dysfunction and abnormal vasomotion in the entire coronary tree, including the arterioles that regulate coronary flow and resistance,^{8–10} and adversely affect myocardial capillaries,^{6,11–14} leading to their rarefaction. Potential consequences include a lack of flow-mediated vasodilation in the epicardial conductive arteries⁹ and macro- and microcirculatory vasoconstriction.¹⁵ Of note, different mechanisms of ischaemia may act concomitantly.

2.2. Chronic coronary syndromes: clinical presentations (Figure 1)

In clinical practice, the following, not entirely exclusive, CCS patients seek outpatient medical attention: (i) the symptomatic patient with reproducible stress-induced angina or ischaemia with epicardial obstructive CAD; (ii) the patient with angina or ischaemia caused by epicardial vasomotor abnormalities or functional/structural microvascular alterations in the absence of epicardial obstructive CAD (ANOCA/INOCA); (iii) the non-acute patient post-ACS or after a revascularization; (iv) the non-acute patient with heart failure (HF) of ischaemic or cardiometabolic origin. A further growing category (v) are the asymptomatic individuals in whom epicardial CAD is detected during an imaging test for refining cardiovascular risk assessment,¹⁶ screening for personal or professional purposes, or as an incidental finding for another indication.¹⁷ Patients may experience a variable and unpredictable course, transitioning between different types of CCS and ACS presentations throughout their lifetime.

The clinical presentations of CCS are not always specific for the mechanism causing myocardial ischaemia; thus, symptoms of

dysfunctional microvascular angina (MVA) may overlap with those of vasospastic or even obstructive large–medium artery angina. Furthermore, it is important to note that CCS doesn't always present as classical angina pectoris and symptoms may vary depending on age and sex. Sex-stratified analyses indicate that women with suspected angina are usually older and have a heavier cardiovascular risk factor burden, more frequent comorbidities, non-anginal symptoms such as dyspnoea and fatigue, and greater prevalence of MVA than men.^{18–21}

2.3. Changing epidemiology and management strategies

Contemporary primary prevention,¹⁶ including lifestyle changes and guideline-directed medical therapy (GDMT), has led to a decline of the age-standardized prevalence^{22,23} of obstructive epicardial coronary atherosclerosis in patients with suspected CCS.^{24–28} As a consequence, the diagnostic and prognostic risk prediction models applied in the past to identify obstructive epicardial CAD in patients with suspected angina pectoris have required updating and refinement.^{27,29,30} Initial use of coronary computed tomography angiography (CCTA)^{31,32} for detecting and assessing epicardial coronary atherosclerosis is increasingly being adopted since it has shown similar performance to non-invasive stress testing for detecting segmental myocardial ischaemia.^{33–35} Invasive coronary angiography (ICA), classically used to detect anatomically significant stenoses, has expanded to become a functional test³⁶ that includes refined haemodynamic assessment of epicardial stenoses, provocative testing for the detection of epicardial or microvascular spasm,^{37–40} and a functional assessment of CMD.^{41–43} Moreover, there is a growing interest in non-invasive imaging methods such as stress positron emission tomography (PET)^{44,45} or stress magnetic resonance imaging (MRI),⁴⁶ which allow accurate assessment of the coronary microcirculation in a quantitative manner.

Medical therapy for CCS patients, including antithrombotic strategies, anti-inflammatory drugs, statins and new lipid-lowering, metabolic, and anti-obesity agents, has significantly improved survival after conservative treatment, making it harder to demonstrate the benefits of early invasive therapy.⁴⁷ However, revascularization can still benefit patients with obstructive CAD at high risk of adverse events, not only for symptom relief^{48–52} but also to prevent spontaneous myocardial infarction (MI) and cardiac death and, in some groups, to improve overall survival^{53–56} during long-term follow-up. Recently, revascularization through percutaneous coronary intervention (PCI) was shown to provide more angina relief than a placebo procedure in patients with stable angina and evidence of ischaemia, on minimal or no antianginal therapy, confirming the beneficial effects of revascularization.⁵²

The present guidelines deal with the assessment and diagnostic algorithm in patients with symptoms suspected of CCS (Section 3) and their treatment (Section 4), special subgroups of CCS patients (Section 5) and finally, long-term follow-up and care (Section 6).

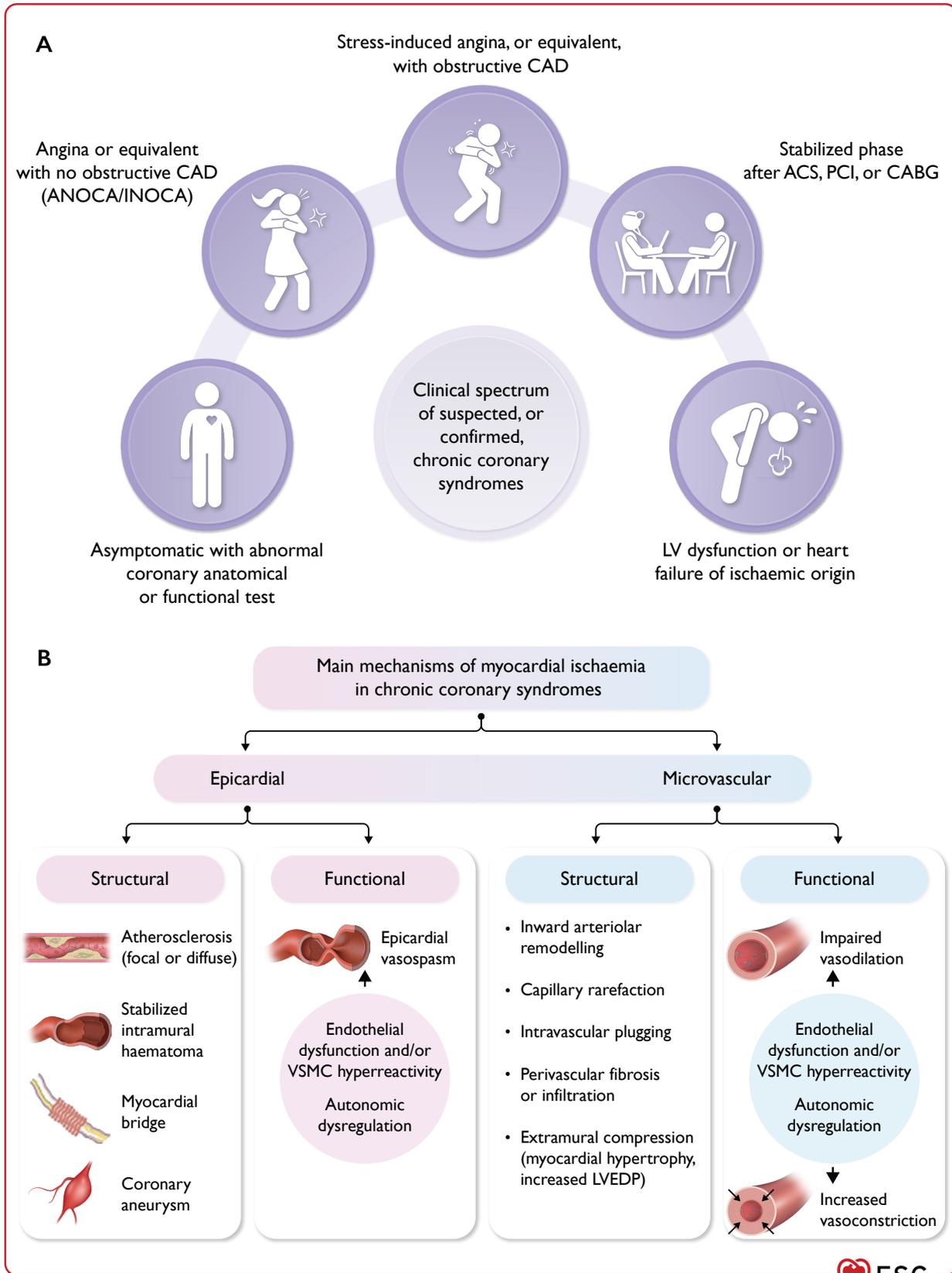


Figure 1 (Central Illustration) Clinical presentations of chronic coronary syndrome and mechanisms of myocardial ischaemia. ACS, acute coronary syndrome; ANOCA, angina with non-obstructive coronary arteries; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, chronic coronary syndrome; INOCA, ischaemia with non-obstructive coronary arteries; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; PCI, percutaneous coronary intervention; VSMC, vascular smooth muscle cell.

2.4. What is new

The 2024 Guidelines contain a number of new and revised recommendations, which are summarized in [Tables 3](#) and [4](#), respectively.

Table 3 New major recommendations in 2024

Recommendations	Class ^a	Level ^b
History taking and risk factor assessment and resting electrocardiogram in individuals with suspected chronic coronary syndrome—Section 3		
In individuals reporting symptoms of suspected myocardial ischaemic origin, a detailed assessment of cardiovascular risk factors, medical history, and symptom characteristics (including onset, duration, type, location, triggers, relieving factors, time of day) is recommended.	I	C
Symptoms like chest pain triggered by emotional stress; dyspnoea or dizziness on exertion; pain in the arms, jaw, neck, or upper back; or fatigue should be considered as potential angina equivalents.	IIa	B
Basic biochemistry in the initial diagnostic management of individuals with suspected chronic coronary syndrome—Section 3		
• Additionally, high-sensitivity C-reactive protein and/or fibrinogen plasma levels should be considered.	IIa	B
Likelihood of obstructive atherosclerotic coronary artery disease in the initial diagnostic management of individuals with suspected chronic coronary syndrome—Section 3		
It is recommended to estimate the pre-test likelihood of obstructive epicardial CAD using the Risk Factor-weighted Clinical Likelihood model.	I	B
It is recommended to use additional clinical data (e.g. examination of peripheral arteries, resting ECG, resting echocardiography, presence of vascular calcifications on previously performed imaging tests) to adjust the estimate yielded by the Risk Factor-weighted Clinical Likelihood model.	I	C
In individuals with a very low ($\leq 5\%$) pre-test likelihood of obstructive CAD, deferral of further diagnostic tests should be considered.	IIa	B
In individuals with a low ($> 5\%$ – 15%) pre-test likelihood of obstructive CAD, CACS should be considered to reclassify subjects and to identify more individuals with very low ($\leq 5\%$) CACS-weighted clinical likelihood.	IIa	B
In individuals with an initially low ($> 5\%$ – 15%) likelihood of obstructive CAD, exercise ECG and detection of atherosclerotic disease in non-coronary arteries may be considered to adjust the pre-test likelihood estimate.	IIb	C
Ambulatory electrocardiogram in the initial diagnostic management of individuals with suspected chronic coronary syndrome—Section 3		
Ambulatory ECG monitoring should be considered in subjects with suspected vasospastic angina.	IIa	B
Non-invasive anatomical imaging tests in the initial diagnostic management of individuals with suspected obstructive coronary artery disease—coronary computed tomography angiography, if available and supported by local expertise—Section 3		
In individuals with suspected CCS and low or moderate ($> 5\%$ – 50%) pre-test likelihood of obstructive CAD, CCTA is recommended to diagnose obstructive CAD and to estimate the risk of MACE.	I	A
Non-invasive tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—stress echocardiography, if available and supported by local expertise—Section 3		
In individuals with suspected CCS and moderate or high ($> 15\%$ – 85%) pre-test likelihood of obstructive CAD, stress echocardiography is recommended to diagnose myocardial ischaemia and to estimate the risk of MACE.	I	B
During stress echocardiography, when two or more contiguous myocardial segments are not visualized, it is recommended to use commercially available intravenous ultrasound contrast agents (microbubbles) to improve diagnostic accuracy.	I	B
During stress echocardiography, myocardial perfusion using commercially available intravenous ultrasound contrast agents (microbubbles) is recommended to improve diagnostic accuracy and to refine risk stratification beyond wall motion.	I	B
During stress echocardiography, Doppler left anterior descending coronary artery flow reserve may be considered to improve risk stratification beyond wall motion and to assess microvascular function.	IIb	B
Non-invasive functional myocardial imaging tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—resting and stress single-photon emission computed tomography/positron emission tomography—cardiac magnetic resonance imaging, if available and supported by local expertise—Section 3		
In individuals with suspected CCS and moderate or high ($> 15\%$ – 85%) pre-test likelihood of obstructive CAD, SPECT or, preferably, PET myocardial perfusion imaging is recommended to: <ul style="list-style-type: none"> • diagnose and quantify myocardial ischaemia and/or scar; • estimate the risk of MACE; • quantify myocardial blood flow (PET). 	I	B
In patients selected for PET or SPECT myocardial perfusion imaging, it is recommended to measure CACS from unenhanced chest CT imaging (used for attenuation correction) to improve detection of both non-obstructive and obstructive CAD.	I	B
In individuals with suspected CCS and moderate or high ($> 15\%$ – 85%) pre-test likelihood of obstructive CAD, CMR perfusion imaging is recommended to diagnose and quantify myocardial ischaemia and/or scar and estimate the risk of MACE.	I	B

Continued

Indications for invasive coronary angiography in individuals with suspected obstructive coronary artery disease—Section 3		
When ICA is indicated, radial artery access is recommended as the preferred access site.	I	A
When ICA is indicated, it is recommended to have coronary pressure assessment available and to use it to evaluate the functional severity of intermediate non-left main stem stenoses prior to revascularization.	I	A
In individuals with de novo symptoms highly suggestive of obstructive CAD that occur at a low level of exercise, ICA with a view towards revascularization is recommended as first diagnostic test after clinical assessment by a cardiologist.	I	C
Functional assessment of epicardial artery stenosis severity during invasive coronary angiography—Section 3		
During ICA, selective assessment of functional severity of intermediate diameter stenoses is recommended to guide the decision to revascularize, using the following techniques:		
• FFR/iFR (significant ≤ 0.8 or ≤ 0.89 , respectively);	I	A
• QFR (significant ≤ 0.8).	I	B
In addition:		
• CFR/HSR/CFC should be considered as a complementary investigation;	IIa	B
• resting invasive measurement of Pd/Pa, dPR, RFR, or angiography-derived vessel FFR may be considered as alternative parameters.	IIb	C
Systematic and routine wire-based coronary pressure assessment of all coronary vessels is not recommended.	III	A
Selection of individual diagnostic tests in individuals with suspected chronic coronary syndrome—Section 3		
To rule out obstructive CAD in individuals with low or moderate (>5%–50%) pre-test likelihood, CCTA is recommended as the preferred diagnostic modality.	I	B
CCTA is recommended in individuals with low or moderate (>5%–50%) pre-test likelihood of obstructive CAD if functional imaging for myocardial ischaemia is not diagnostic.	I	B
Invasive coronary angiography with the availability of invasive functional assessments is recommended to confirm or exclude the diagnosis of obstructive CAD or ANOCA/INOCA in individuals with an uncertain diagnosis on non-invasive testing.	I	B
In patients with a known intermediate coronary artery stenosis in a proximal or mid coronary segment on CCTA, CT-based FFR may be considered.	IIb	B
Definition of high risk of adverse events		
An initial stratification of risk of adverse events is recommended based on basic clinical assessment (e.g. age, ECG, anginal threshold, diabetes, CKD, LVEF).	I	B
The use of one or more of the following test results is recommended to identify individuals at high risk of adverse events:		
• exercise ECG: <ul style="list-style-type: none"> ◦ Duke Treadmill Score < -10; 	I	B
• stress SPECT or PET perfusion imaging: <ul style="list-style-type: none"> ◦ area of ischaemia $\geq 10\%$ of the LV myocardium; 		
• stress echocardiography: <ul style="list-style-type: none"> ◦ ≥ 3 of 16 segments with stress-induced hypokinesia or akinesia; 		
• stress CMR: <ul style="list-style-type: none"> ◦ ≥ 2 of 16 segments with stress perfusion defects or ◦ ≥ 3 dobutamine-induced dysfunctional segments; 		
• CCTA: <ul style="list-style-type: none"> ◦ left main disease with $\geq 50\%$ stenosis, ◦ three-vessel disease with $\geq 70\%$ stenosis, or ◦ two-vessel disease with $\geq 70\%$ stenosis, including the proximal LAD or ◦ one-vessel disease of the proximal LAD with $\geq 70\%$ stenosis and FFR-CT ≤ 0.8 		
Cardiovascular risk, lifestyle changes, and exercise interventions in patients with established chronic coronary syndrome—Section 4		
An informed discussion on CVD risk and treatment benefits tailored to individual patient needs is recommended.	I	C
Multidisciplinary behavioural approaches to help patients achieve healthy lifestyles, in addition to appropriate pharmacological management, are recommended.	I	A
Aerobic physical activity of at least 150–300 min per week of moderate intensity or 75–150 min per week of vigorous intensity and reduction in sedentary time are recommended.	I	B
Home-based cardiac rehabilitation and mobile health interventions should be considered to increase patients' long-term adherence to healthy behaviours, and to reduce hospitalizations or cardiac events.	IIa	B
Antianginal drugs in patients with chronic coronary syndrome—Section 4		
It is recommended to tailor the selection of antianginal drugs to the patient's characteristics, comorbidities, concomitant medications, treatment tolerability, and underlying pathophysiology of angina, also considering local drug availability and cost.	I	C
Ivabradine should be considered as add-on antianginal therapy in patients with left ventricular systolic dysfunction (LVEF <40%) and inadequate control of symptoms, or as part of initial treatment in properly selected patients.	IIa	B

Continued

Ivabradine is not recommended as add-on therapy in patients with CCS, LVEF >40%, and no clinical heart failure.	III	B
Combination of ivabradine with non-DHP-CCB or other strong CYP3A4 inhibitors is not recommended.	III	B
Antithrombotic therapy in patients with chronic coronary syndrome—Section 4		
Long-term antithrombotic therapy in patients with chronic coronary syndrome and no clear indication for oral anticoagulation		
In CCS patients with a prior MI or PCI, clopidogrel 75 mg daily is recommended as a safe and effective alternative to aspirin monotherapy.	I	A
After CABG, aspirin 75–100 mg daily is recommended lifelong.	I	A
In CCS patients <i>without</i> prior MI or revascularization but with evidence of significant obstructive CAD, aspirin 75–100 mg daily is recommended lifelong.	I	B
Lipid-lowering drugs in patients with chronic coronary syndrome—Section 4		
Lipid-lowering treatment with an LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction in LDL-C vs. baseline is recommended.	I	A
For patients who are statin intolerant and do not achieve their goal on ezetimibe, combination with bempedoic acid is recommended.	I	B
For patients who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with bempedoic acid should be considered.	IIa	C
Sodium–glucose cotransporter 2 inhibitors and/or glucagon-like peptide-1 receptor agonists in patients with chronic coronary syndrome—Section 4		
SGLT2 inhibitors with proven CV benefit are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A
The GLP-1 receptor agonist semaglutide should be considered in CCS patients without diabetes, but with overweight or obesity (BMI >27 kg/m ²), to reduce CV mortality, MI, or stroke.	IIa	B
Anti-inflammatory drugs in patients with chronic coronary syndrome—Section 4		
In CCS patients with atherosclerotic CAD, low-dose colchicine (0.5 mg daily) should be considered to reduce myocardial infarction, stroke, and need for revascularization.	IIa	A
Revascularization in patients with chronic coronary syndrome—Section 4		
Informed and shared decisions		
For complex clinical cases, to define the optimal treatment strategy, in particular when CABG and PCI hold the same level of recommendation, a Heart Team discussion is recommended, including representatives from interventional cardiology, cardiac surgery, non-interventional cardiology, and other specialties if indicated, aimed at selecting the most appropriate treatment to improve patient outcomes and quality of life.	I	C
It is recommended that the decision for revascularization and its modality be patient-centred, considering when possible patient preferences, health literacy, cultural circumstances, and social support.	I	C
Revascularization to improve outcomes		
In CCS patients with LVEF ≤35%, it is recommended to choose between revascularization or medical therapy alone, after careful evaluation, preferably by the Heart Team, of coronary anatomy, correlation between coronary artery disease and LV dysfunction, comorbidities, life expectancy, individual risk-to-benefit ratio, and patient perspectives.	I	C
Assessment of procedural risks and post-procedural outcomes		
Intracoronary imaging guidance by IVUS or OCT is recommended for performing PCI on anatomically complex lesions, in particular left main stem, true bifurcations and long lesions.	I	A
Intracoronary pressure measurement (FFR or iFR) or computation (QFR):		
• is recommended to guide lesion selection for intervention in patients with multivessel disease;	I	A
• should be considered at the end of the procedure to identify patients at high risk of persistent angina and subsequent clinical events;	IIa	B
• may be considered at the end of the procedure to identify lesions potentially amenable to treatment with additional PCI.	IIb	B
Choice of revascularization modality		
It is recommended that physicians select the most appropriate revascularization modality based on patient profile, coronary anatomy, procedural factors, LVEF, patient preferences and outcome expectations.	I	C
Mode of revascularization in patients with chronic coronary syndrome		
Left main disease		
In CCS patients at low surgical risk with significant left main coronary stenosis, CABG:		
• is recommended over medical therapy alone to improve survival;	I	A
• is recommended as the overall preferred revascularization mode over PCI, given the lower risk of spontaneous myocardial infarction and repeat revascularization.	I	A
In CCS patients with significant left main coronary stenosis of low complexity (SYNTAX score ≤22), in whom PCI can provide equivalent completeness of revascularization to that of CABG, PCI is recommended as an alternative to CABG, given its lower invasiveness and non-inferior survival.	I	A

Continued

Management of chronic coronary syndrome patients with chronic heart failure—Section 5		
In HF patients with LVEF \leq 35% in whom obstructive CAD is suspected, ICA is recommended with a view towards improving prognosis by CABG, taking into account the risk-to-benefit ratio of the procedures.	I	B
In HF patients with LVEF >35% and suspected CCS with low or moderate (>5%–50%) pre-test likelihood of obstructive CAD, CCTA or functional imaging is recommended.	I	C
In patients with HFpEF with angina or equivalent symptoms and normal or non-obstructive epicardial coronary arteries, PET or CMR perfusion or invasive functional coronary testing should be considered to detect or rule out coronary microvascular dysfunction.	IIa	B
In selected patients with HFrEF undergoing high-risk PCI for complex CAD, the use of a microaxial flow pump may be considered in experienced centres.	IIb	C
It is recommended that CCS patients with heart failure be enrolled in a multidisciplinary heart failure management programme to reduce the risk of heart failure hospitalization and to improve survival.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I or ARB in CCS patients with HFrEF to reduce the risk of heart failure hospitalization and death.	I	B
Diagnosis and management of patients with angina/ischæmia with non-obstructive coronary arteries—Section 5		
Management of ANOCA/INOCA		
In symptomatic patients with ANOCA/INOCA, medical therapy based on coronary functional test results should be considered to improve symptoms and quality of life.	IIa	A
For the management of endothelial dysfunction, ACE-I should be considered for symptom control.	IIa	B
For the management of microvascular angina associated with reduced coronary/myocardial blood flow reserve, beta-blockers should be considered for symptom control.	IIa	B
For the treatment of isolated vasospastic angina:	I	A
• calcium channel blockers are recommended to control symptoms and to prevent ischæmia and potentially fatal complications;	IIa	B
• nitrates should be considered to prevent recurrent episodes.	IIb	B
In patients with evidence of overlapping endotypes, combination therapy with nitrates, calcium channel blockers, and other vasodilators may be considered.	IIb	B
Older, female, high bleeding risk, comorbid, and socially/geographically diverse patients—Section 5		
Similar guideline-directed cardiovascular preventive therapy is recommended in women and men.	I	C
Bleeding risk assessment is recommended using the PRECISE-DAPT score, the qualitative ARC-HBR tool or other, validated methods.	I	B
Attention to interaction between antiretroviral treatment and statins is recommended in patients with HIV.	I	B
Socioeconomic, geographical, and under-investigated groups		
Continued targeted efforts are recommended:	I	C
• to increase delivery of safe and effective cardiac care to all CCS patients, especially those of lower socioeconomic classes, and		
• to enhance inclusion in future clinical trials of geographical, social, or other groups that are currently underrepresented.		
Screening for coronary artery disease in asymptomatic individuals—Section 5		
When coronary artery calcification findings are available from previous chest CT scans, using these findings to enhance risk stratification and guide treatment of modifiable risk factors should be considered.	IIa	C
Coronary artery calcium scoring (CACS) may be considered to improve risk classification around treatment decision thresholds.	IIb	C
Adherence to medical therapy and lifestyle changes—Section 6		
Mobile health interventions (e.g. using text messages, apps, wearable devices) are recommended to improve patient adherence to healthy lifestyles and medical therapy.	I	A
Behavioural interventions are recommended to improve adherence.	I	B
Simplifying medication regimens (e.g. using fixed-dose drug combinations) is recommended to increase patient adherence to medications.	I	B
Multiprofessional and family involvement is recommended to promote adherence, in addition to patient education and involvement.	I	C
Recurrent or refractory angina/ischæmia		
In patients with refractory angina leading to poor quality of life and with documented or suspected ANOCA/INOCA, invasive coronary functional testing is recommended to define ANOCA/INOCA endotypes and appropriate treatment, considering patient choices and preferences.	I	B

ACE-I, angiotensin-converting enzyme inhibitor; ANOCA, angina with non-obstructive coronary arteries; ARB, angiotensin receptor blocker; ARC-HBR, Academic Research Consortium for High Bleeding Risk; BMI, body mass index; CABG, coronary artery bypass grafting; CACS, coronary artery calcium score; CAD, coronary artery disease; CCB, calcium channel blocker; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CFC, coronary flow capacity; CFR, coronary flow reserve; CKD, chronic kidney disease; CMR, cardiac magnetic resonance; CT, computed tomography; CV, cardiovascular; CVD, cardiovascular disease; CYP3A4, cytochrome P450 3A4; DHP, dihydropyridine; dPR, diastolic pressure ratio; ECG, electrocardiogram; FFR, fractional flow reserve; FFR-CT, coronary computed tomography angiography-derived fractional flow reserve; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HIV, human immunodeficiency virus; HSR, hyperaemic stenosis resistance; ICA, invasive coronary angiography; iFR, instantaneous wave-free ratio; INOCA, ischæmia with non-obstructive coronary arteries; IVUS, intravascular ultrasound; LAD, left anterior descending; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MCS, mechanical circulatory support; MI, myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; Pd/Pa, distal coronary pressure to aortic pressure ratio; PET, positron emission tomography; PRECISE-DAPT, PREdicting bleeding Complications In patients undergoing Stent implantation and subseQuent Dual AntiPlatelet Therapy; QFR, quantitative flow ratio; RFR, relative flow reserve; SGLT2, sodium–glucose cotransporter 2; SPECT, single-photon emission computed tomography; T2DM, type 2 diabetes mellitus.

^aClass of recommendation.

^bLevel of evidence.

Table 4 Revised recommendations

Recommendations in 2019 version	Class ^a	Level ^b	Recommendations in 2024 version	Class ^a	Level ^b
Recommendations for antianginal drugs in patients with chronic coronary syndrome—Section 4					
Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates.	IIa	B	Long-acting nitrates or ranolazine should be considered as add-on therapy in patients with inadequate control of symptoms while on treatment with beta-blockers and/or CCBs, or as part of initial treatment in properly selected patients.	IIa	B
In selected patients, the combination of a beta-blocker or a CCB with second-line drugs (ranolazine, nicorandil, ivabradine, and trimetazidine) may be considered for first-line treatment according to heart rate, blood pressure, and tolerance.	IIb	B	Nicorandil or trimetazidine may be considered as add-on therapy in patients with inadequate control of symptoms while on treatment with beta-blockers and/or CCBs, or as part of initial treatment in properly selected patients.	IIb	B
Antithrombotic therapy in patients with chronic coronary syndrome—Section 4					
Aspirin 75–100 mg daily is recommended in patients with a previous MI or revascularization.	I	A	In CCS patients with a prior MI or remote PCI, aspirin 75–100 mg daily is recommended lifelong after an initial period of DAPT.	I	A
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in patients with aspirin intolerance.	I	B	In CCS patients with a prior MI or remote PCI, clopidogrel 75 mg daily is recommended as a safe and effective alternative to aspirin monotherapy.	I	A
Clopidogrel 75 mg daily may be considered in preference to aspirin in symptomatic and asymptomatic patients with either PAD or a history of ischaemic stroke or transient ischaemic attack.	IIb	B			
Aspirin 75–100 mg daily may be considered in patients without a history of MI or revascularization, but with definitive evidence of CAD on imaging.	IIb	C	In patients <i>without</i> prior MI or revascularization but with evidence of significant obstructive CAD, aspirin 75–100 mg daily is recommended lifelong.	I	B
Antithrombotic therapy post-percutaneous coronary intervention in patients with chronic coronary syndrome and no indication for oral anticoagulation—Section 4					
Aspirin 75–100 mg daily is recommended following stenting.	I	A	In CCS patients with no indication for oral anticoagulation, DAPT consisting of aspirin 75–100 mg and clopidogrel 75 mg daily for up to 6 months is recommended as the default antithrombotic strategy after PCI-stenting.	I	A
Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) is recommended, in addition to aspirin, for 6 months following coronary stenting, irrespective of stent type, unless a shorter durations (1–3 months) is indicated due to risk of occurrence of life-threatening bleeding.	I	A			
Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) may be considered for 1 month in patients with very high risk of life-threatening bleeding.	IIb	C	In patients at high bleeding risk but not at high ischaemic risk, it is recommended to discontinue DAPT 1–3 months after PCI and continue single antiplatelet therapy.	I	A
Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) should be considered for 3 months in patients with a higher risk of life-threatening bleeding.	IIa	A	Stopping DAPT after 1–3 months from PCI-stenting may be considered in patients who are not at high bleeding risk nor at high risk of ischaemic events.	IIb	B

Continued

Long-term antithrombotic therapy in patients with chronic coronary syndrome and an indication for oral anticoagulation—Section 4					
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC, a NOAC is recommended in preference to a VKA.	I	A	In CCS patients with a long-term indication for OAC, an AF-therapeutic-dose of VKA alone or, preferably, of DOAC alone (unless contraindicated) is recommended lifelong.	I	B
Long-term OAC therapy (NOAC or VKA with time in therapeutic range >70%) is recommended in patients with AF and a CHA ₂ DS ₂ -VASc score ≥2 in males and ≥3 in females.	I	A			
Long-term OAC therapy (NOAC or VKA with time in therapeutic range >70%) should be considered in patients with AF and a CHA ₂ DS ₂ -VASc score of 1 in males and 2 in females.	IIa	B			
Aspirin 75–100 mg daily (or clopidogrel 75 mg daily) may be considered in addition to long-term OAC therapy in patients with AF, history of MI, and at high risk of recurrent ischaemic events who do not have a high bleeding risk.	IIb	B			
Antithrombotic therapy post-percutaneous coronary intervention in chronic coronary syndrome patients and an indication for oral anticoagulation—Section 4					
After uncomplicated PCI, early cessation (≤1 week) of aspirin and continuation of dual therapy with an OAC and clopidogrel should be considered if the risk of stent thrombosis is low, or if concerns about bleeding risk prevail over concerns about the risk of stent thrombosis, irrespective of the type of stent used.	IIa	B	After uncomplicated PCI in CCS patients with concomitant indication for OAC: <ul style="list-style-type: none"> • early cessation of aspirin (≤1 week); • followed by continuation of OAC and clopidogrel: <ul style="list-style-type: none"> ○ up to 6 months in patients not at high ischaemic risk or ○ up to 12 months in patients at high ischaemic risk; • followed by OAC alone; is recommended. 	I	A
Triple therapy with aspirin, clopidogrel, and an OAC for ≥1 month should be considered when the risk of stent thrombosis outweighs the bleeding risk, with the total duration (≤6 months) decided according to assessment of these risks and clearly specified at hospital discharge.	IIa	C	Continuation of aspirin up to 1 month after PCI, in addition to OAC and clopidogrel, should be considered in patients at high thrombotic risk or with anatomical/procedural characteristics judged to outweigh the bleeding risk.	IIa	B
Recommendations for lipid-lowering drugs in patients with chronic coronary syndrome—Section 4					
Statins are recommended in all patients with CCS.	I	A	A high-intensity statin up to the highest tolerated dose to reach the LDL-C goals is recommended for all patients with CCS.	I	A
Diagnosis and management of patients with angina/ischaemia with non-obstructive coronary arteries—Section 5					
Guidewire-based CFR and/or microcirculatory resistance measurements should be considered in patients with persistent symptoms, but coronary arteries that are either angiographically normal or have moderate stenoses with preserved iwFR/FFR.	IIa	B	In persistently symptomatic patients despite medical treatment with suspected ANOCA/INOCA (i.e. anginal symptoms with normal coronary arteries or non-obstructive lesions at non-invasive imaging, or intermediate stenoses with normal FFR/iFR at coronary arteriography) and poor quality of life, invasive coronary functional testing is recommended to identify potentially treatable endotypes and to improve symptoms and quality of life, considering patient choices and preferences.	I	B
Intracoronary acetylcholine with ECG monitoring may be considered during angiography, if coronary arteries are either angiographically normal or have moderate stenoses with preserved iwFR/FFR, to assess microvascular vasospasm.	IIb	B			
Diagnostic tests for vasospastic angina—Section 5					
Ambulatory ST-segment monitoring should be considered to identify ST-segment deviation in the absence of increased heart rate.	IIa	C	In individuals with suspected vasospastic angina and frequent symptoms, ambulatory ST-segment monitoring should be considered to identify ST-segment deviation during angina.	IIa	B

Continued

Screening for coronary artery disease in asymptomatic individuals—Section 5					
Total risk estimation using a risk-estimation system such as SCORE is recommended for asymptomatic adults >40 years of age without evidence of CVD, diabetes, CKD, or familial hypercholesterolaemia.	I	C	Opportunistic screening of healthy individuals for cardiovascular risk factors and to estimate risk of future cardiovascular events using scoring systems, e.g. SCORE2 and SCORE2-OP, is recommended to detect individuals at high risk and guide treatment decisions.	I	C
Diagnosis of disease progression in patients with established chronic coronary syndrome—Section 6					
Risk stratification is recommended in patients with new or worsening symptom levels, preferably using stress imaging or, alternatively, exercise stress ECG.	I	B	Risk stratification is recommended in patients with new or worsening symptoms, preferably using stress imaging.	I	C
2018 ESC/EACTS Guidelines on myocardial revascularization	Class ^a	Level ^b	Recommendations in 2024 version	Class ^a	Level ^b
Recommendations for revascularization in patients with chronic coronary syndrome—Section 4					
Revascularization to improve outcomes					
<i>In CCS patients with LV ejection fraction ≤35%</i>					
In patients with one- or two-vessel disease, PCI should be considered as an alternative to CABG when complete revascularization can be achieved.	Ila	C	In selected CCS patients with functionally significant MVD and LVEF ≤35% who are at high surgical risk or not operable, PCI may be considered as an alternative to CABG.	IIb	B
In patients with three-vessel disease, PCI should be considered based on the evaluation by the Heart Team of the patient's coronary anatomy, the expected completeness of revascularization, diabetes status, and comorbidities.	Ila	C			
Anatomically and clinically based recommendations for revascularization in chronic coronary syndrome—Section 4					
Left main disease					
Left main disease with low SYNTAX score (0–22), PCI.	I	A	In CCS patients with significant left main coronary stenosis of low complexity (SYNTAX score ≤22), in whom PCI can provide equivalent completeness of revascularization to that of CABG, PCI is recommended as an alternative to CABG, given its lower invasiveness and non-inferior survival.	I	A
Left main disease with intermediate SYNTAX score (23–32), PCI.	Ila	A	In CCS patients with significant left main coronary stenosis of intermediate complexity (SYNTAX score 23–32), in whom PCI can provide equivalent completeness of revascularization to that of CABG, PCI should be considered, given its lower invasiveness and non-inferior survival.	Ila	A
Left main with multivessel disease					
For left main disease with high SYNTAX score (≥33), PCI.	III	B	In CCS patients at high surgical risk, PCI may be considered over medical therapy alone.	IIb	B
Multivessel disease and diabetes					
For CCS patients with diabetes and three-vessel disease with low SYNTAX score 0–22, PCI.	IIb	A	In CCS patients at very high surgical risk, PCI should be considered over medical therapy alone to reduce symptoms and adverse outcomes.	IIa	B
For CCS patients with diabetes and three-vessel disease with intermediate or high SYNTAX score (>22), PCI.	III	A			
Single- or double-vessel disease involving the proximal LAD					
For one or two-vessel disease with proximal LAD stenosis, CABG, or PCI are recommended.	I	A	In CCS patients with significant single- or double-vessel disease involving the proximal LAD and insufficient response to guideline-directed medical therapy, CABG or PCI is recommended over medical therapy alone to improve symptoms and outcomes.	I	A
			In CCS patients with complex significant single- or double-vessel disease involving the proximal LAD, less amenable to PCI, and insufficient response to guideline-directed medical therapy, CABG is recommended over PCI to improve symptoms and reduce revascularization rates.	I	B

Continued

Single- or double-vessel disease not involving the proximal LAD					
For one or two-vessel disease without proximal LAD stenosis PCI is recommended.	I	C	In symptomatic CCS patients with single- or double-vessel disease not involving the proximal LAD and with insufficient response to guideline-directed medical therapy, PCI is recommended to improve symptoms.	I	B
For one or two-vessel disease without proximal LAD stenosis, CABG may be considered.	IIb	C	In symptomatic CCS patients with single- or double-vessel disease not involving the proximal LAD and with insufficient response to guideline-directed medical therapy, not amenable to revascularization by PCI, CABG may be considered to improve symptoms.	IIb	C

AF, atrial fibrillation; ANOCA, angina with non-obstructive coronary arteries; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blocker; CCS, chronic coronary syndrome; CFR, coronary flow reserve; CHA₂DS₂-VASc, congestive heart failure or left ventricular dysfunction, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, sex category (female); CKD, chronic kidney disease; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; EACTS, European Association for Cardio-Thoracic Surgery; ECG, electrocardiogram; ESC, European Society of Cardiology; FFR, fractional flow reserve; iFR(iwFR), instantaneous wave-free ratio; INOCA, ischaemia with non-obstructive coronary arteries; LAD, left anterior descending; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MVD, multivessel disease; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SCORE2, Systematic Coronary Risk Estimation 2; SCORE-OP, Systematic Coronary Risk Estimation 2–Older Persons; SYNTAX, SYNergy Between PCI with TAXUS and Cardiac Surgery; VKA, vitamin K antagonist.

^aClass of recommendation.

^bLevel of evidence.

3. Stepwise approach to the initial management of individuals with suspected chronic coronary syndrome

Managing individuals with suspected CCS involves four steps (Figure 2):

STEP 1. The first step is a general clinical evaluation that focuses on assessing symptoms and signs of CCS, differentiating non-cardiac causes of chest pain and ruling out ACS. This initial clinical evaluation requires recording a 12-lead resting electrocardiogram (ECG), basic blood tests, and in selected individuals, chest X-ray imaging and pulmonary function testing. This evaluation can be done by the general practitioner.

STEP 2. The second step is a further cardiac examination, including echocardiography at rest to rule out left ventricular (LV) dysfunction and valvular heart disease. After that, it is recommended to estimate the clinical likelihood of obstructive CAD to guide deferral or referral to further non-invasive and invasive testing.

STEP 3. The third step involves diagnostic testing to establish the diagnosis of CCS and determine the patient's risk of future events.

STEP 4. The final step includes lifestyle and risk-factor modification combined with disease-modifying medications. A combination of antianginal medications is frequently needed, and coronary revascularization is considered if symptoms are refractory to medical treatment or if high-risk CAD is present. If symptoms persist after obstructive CAD is ruled out, coronary microvascular disease and vasospasm should be considered.

3.1. STEP 1: General clinical examination

3.1.1. History, differential diagnosis, and physical examination

Careful and detailed history taking is the initial step in diagnostic management for all clinical scenarios within the spectrum of CCS. Although

chest pain or discomfort (Figure 3) is the most cardinal symptom of CCS, it must be emphasized that many patients do not present with characteristic anginal symptoms and that the symptomatology may vary with age, sex, race, socioeconomic class, and geographical location. In contemporary studies, only 10% to 25% of patients with suspected CCS present with angina with classic aggravating and relieving factors, while 57% to 78% have symptoms less characteristic of angina and 10% to 15% have dyspnoea on exertion.^{33,57}

While older studies suggested that women were more likely to experience less characteristic chest pain symptoms,⁵⁸ recent data show that anginal chest pain is equally prevalent in both men and women, albeit with slightly different characteristics.⁵⁹ Symptoms were classified as non-characteristic angina in over two-thirds of the patients of both sexes.^{21,60} Of note, the absence of anginal symptoms does not preclude CCS, as it may be absent in patients with diabetes with autonomic neuropathy or in elderly patients with a very sedentary lifestyle despite very severe obstructive CAD. Of course, chest pain is not always angina (i.e. of ischaemic origin), since it can be related to non-coronary (e.g. pericarditis) or non-cardiovascular conditions.^{61,62}

Anginal pain symptoms have been traditionally classified as “typical, atypical, or non-anginal/non-cardiac” based on the location of the pain, as well as precipitating and relieving factors. Although angina that meets all three characteristics, with retrosternal chest discomfort provoked by exertion or emotional stress and relieved by rest or nitroglycerine, is highly suggestive of ischaemia caused by obstructive CAD, these characteristics are rarely all present when ischaemia is caused by microvascular dysfunction and vasospasm. Furthermore, patients with “typical” vs. “atypical” angina included in the PRECISE study had similar 1-year outcomes,⁵⁷ highlighting the limited prognostic value of symptom classification on typicality of angina used in obstructive CAD prediction models. Because this terminology to describe anginal symptoms no longer aligns with current concepts of CCS, it should be replaced by a detailed description of symptoms (Figure 3). It is important to thoroughly evaluate chest pain, including an objective exclusion of myocardial ischaemia caused by obstructive CAD, microvascular disease, and/or coronary vasospasm, before classifying it as non-cardiac.

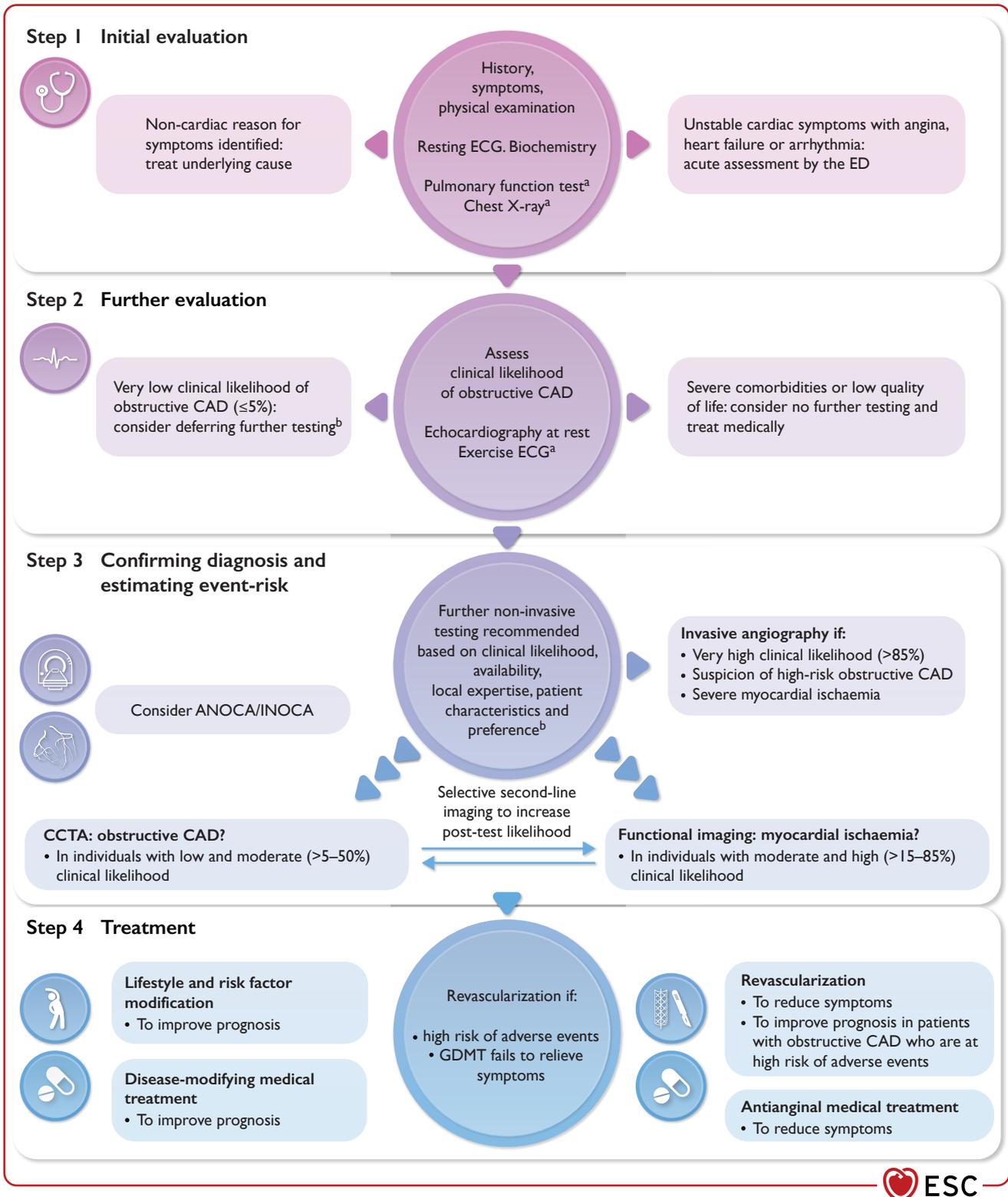


Figure 2 Stepwise approach to the initial management of individuals with suspected chronic coronary syndrome. ANOCA, angina with non-obstructive coronary arteries; CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; ECG, electrocardiogram; ED, emergency department; GDMT, guideline-directed medical therapy; INOCA, ischaemia with non-obstructive coronary arteries. ^aIn selected patients. ^bConsider also coronary spasm or microvascular dysfunction.

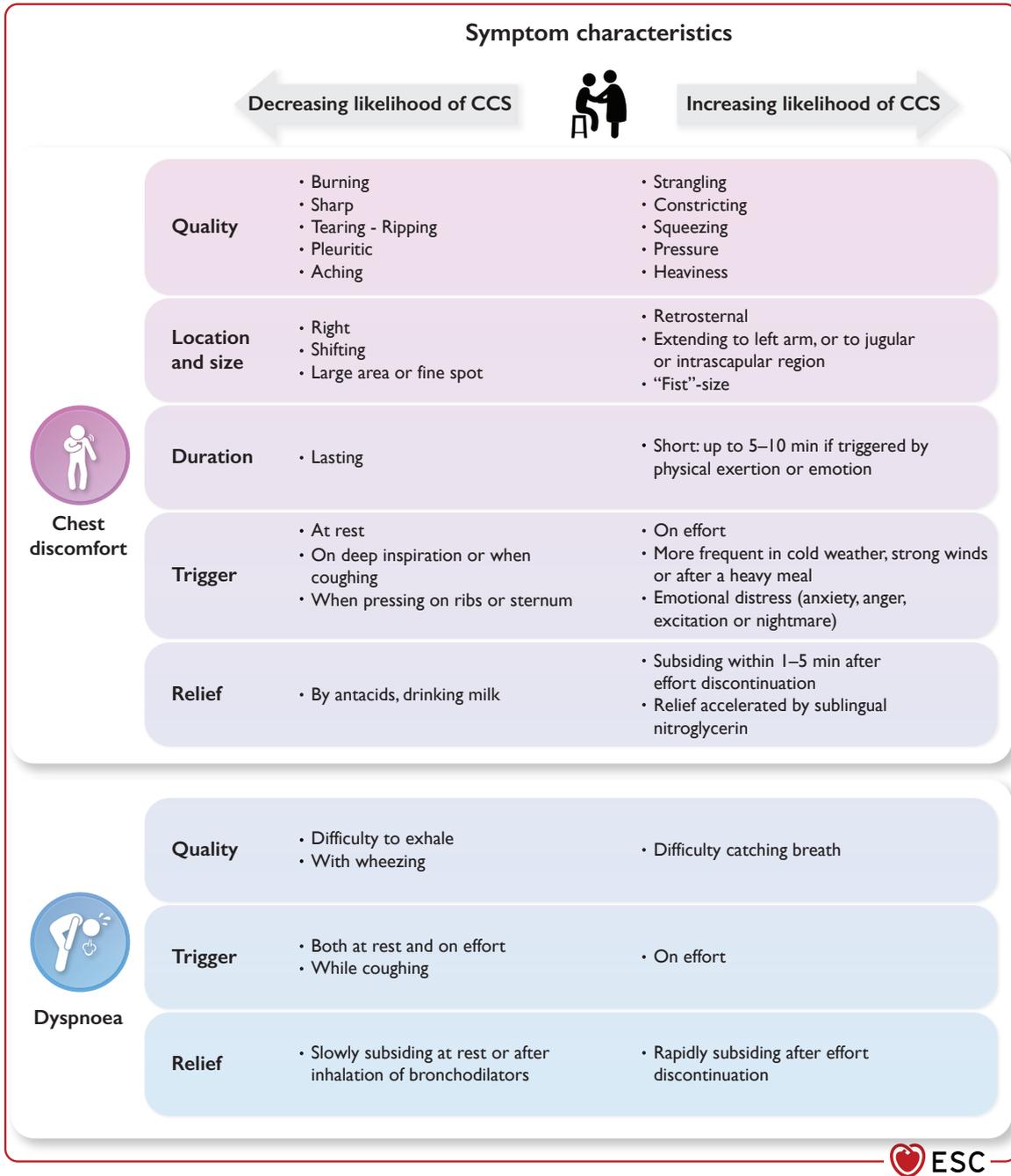


Figure 3 Main CCS symptoms: angina and exertional dyspnoea. CCS, chronic coronary syndrome.

The Canadian Cardiovascular Society classification is still widely used as a grading system for effort-induced angina to quantify the threshold at which symptoms occur with physical activities (Table 5). Importantly, the severity of symptoms is not well associated with the severity of obstructive CAD and appears to differ by sex. Women have more frequent angina, independent of less extensive epicardial CAD, and less severe myocardial ischaemia than men.⁶³ Angina at rest is not always indicative of severe, fixed obstructive CAD, as it may also occur in patients with transient epicardial or microvascular coronary vasospasm.

It is essential to document coronary risk factors during history taking, as they may be modifiable and will be used for the pre-test likelihood

estimation of obstructive CAD. Smoking cessation counselling starts with a quantitative assessment of prior and current tobacco use to make the risk factor more evident to the patient. In addition, detailed family history looking for premature cardiovascular disease (CVD) or sudden cardiac death should always be obtained. If available, cholesterol levels help define familial hypercholesterolaemia.⁶⁴ It is also essential to assess the presence of comorbidities that affect the likelihood of CAD and overall survival. Because of their high prevalence in CCS patients, diabetes, chronic obstructive pulmonary disease, kidney disease, and peripheral and cerebral vascular disease are particularly relevant.

Table 5 Grading of effort angina severity according to the Canadian Cardiovascular Society

Grade	Description of angina severity ⁶⁶	
I	Angina only with strenuous exertion	Presence of angina during strenuous, rapid, or prolonged ordinary activity (walking or climbing the stairs)
II	Angina with moderate exertion	Slight limitation of ordinary activities when they are performed rapidly, after meals, in the cold, in the wind, under emotional stress, or during the first few hours after waking up, but also walking uphill, climbing more than one flight of ordinary stairs at a normal pace, and in normal conditions
III	Angina with mild exertion	Having difficulties walking one or two blocks or climbing one flight of stairs at a normal pace and conditions
IV	Angina at rest	No exertion is needed to trigger angina

© ESC 2024

Recent-onset anginal symptoms with changing frequency or intensity should raise the suspicion that a coronary atherosclerotic plaque may be destabilizing. In these patients, the diagnostic algorithm recommended by the 2023 ESC Guidelines for the management of patients with acute coronary syndromes should be used to rule out an acute event.⁶⁵

When investigating suspected CCS, it is important to perform a thorough physical examination that includes BP measurement and body mass index (BMI) calculation, to assess the presence of anaemia, hypertension, valvular heart disease, LV hypertrophy, or arrhythmias. It is also recommended to search for evidence of non-coronary vascular disease, which may be asymptomatic (palpation of peripheral pulses; auscultation of carotid and femoral arteries), and signs of other comorbid conditions, such as thyroid disease, renal disease, or diabetes. This should be used in the context of other clinical information, such as the presence of cough or stinging pain, making CCS less likely. One should also try to reproduce the symptoms by palpation and test the effect of sublingual nitroglycerine to classify the symptoms.

3.1.2. Basic testing: 12-lead electrocardiogram and biochemistry

Basic testing in individuals with suspected CCS includes a 12-lead ECG, standard laboratory tests, resting echocardiography, and, in selected patients, a chest X-ray, and a pulmonary function test if dyspnoea is the main symptom. Such tests can be done on an outpatient basis.

3.1.2.1. Electrocardiogram

The paradigm of diagnosing myocardial ischaemia has, for almost a century, been based on detecting repolarization abnormalities, mainly in the form of ST-segment depressions or T wave abnormalities. Thus, the resting 12-lead ECG remains an indispensable component of the initial evaluation of a patient with chest pain.⁶⁷

A normal resting ECG is frequently recorded after an anginal attack. However, even in the absence of repolarization abnormalities, the ECG at rest may suggest CCS indirectly, through signs of previous MI (pathological Q or R waves) or conduction abnormalities [mainly left bundle

branch block (LBBB) and impaired atrioventricular conduction]. Atrial fibrillation (AF) is not rarely associated with CCS.⁶⁸ ST-segment depression during supraventricular tachyarrhythmias, however, is not a strong predictor of obstructive CAD.^{69–72}

The ECG can be crucial for diagnosing transient myocardial ischaemia by recording dynamic ST-segment changes during ongoing angina. Vasospastic angina (VSA) should be suspected when observing typical transient ST-segment elevations or depressions with U-wave changes during an angina attack at rest.⁷³

Long-term ambulatory ECG monitoring can be considered in selected patients to detect ischaemia during anginal episodes unrelated to physical activities. ECG changes suggesting ischaemia on ambulatory ECG monitoring are frequent in women but do not correlate with findings during stress testing.⁷⁴ Ambulatory ECG monitoring may also reveal 'silent' ischaemia in patients with CCS, but therapeutic strategies targeting it have not demonstrated clear survival benefits.^{75,76}

Recommendation Table 1 — Recommendations for history taking, risk factor assessment, and resting electrocardiogram in individuals with suspected chronic coronary syndrome (see also Evidence Table 1)

Recommendations	Class ^a	Level ^b
History taking and risk factor assessment		
In individuals reporting symptoms of suspected myocardial ischaemic origin, a detailed assessment of cardiovascular risk factors, medical history, and symptom characteristics (including onset, duration, type, location, triggers, relieving factors, time of day) is recommended.	I	C
Symptoms like chest pain triggered by emotional stress; dyspnoea or dizziness on exertion; pain in the arms, jaw, neck, or upper back; or fatigue should be considered as potential angina equivalents. ^{18,33,57,59,77}	IIa	B
Resting ECG		
If clinical or ECG assessment suggests ACS rather than CCS, immediate referral to the emergency department and/or repeated measurement of blood troponin, preferably using high-sensitivity or ultrasensitive assays, to rule out acute myocardial injury, is recommended. ^{78,79}	I	B
A resting 12-lead ECG is recommended in all individuals reporting chest pain (unless an obvious non-cardiac cause is identified), particularly during, or immediately after, an episode suggestive of myocardial ischaemia.	I	C
Using ST-segment deviations during supraventricular tachyarrhythmias, particularly during re-entrant atrioventricular tachycardias, per se, as reliable evidence of obstructive CAD, is not recommended. ^{80–84}	III	B

ACS, acute coronary syndrome; CAD, coronary artery disease; CCS, chronic coronary syndrome; ECG, electrocardiogram.

^aClass of recommendation.

^bLevel of evidence.

3.1.2.2. Biochemical tests

Laboratory blood tests identify potential causes of ischaemia (e.g. severe anaemia, hyperthyroidism), cardiovascular risk factors (e.g. lipids, fasting glucose), and yield prognostic information (e.g. renal disease, inflammation). When fasting plasma glucose and glycated haemoglobin (HbA1c) are both inconclusive, an additional oral glucose tolerance test is useful.^{85,86}

A lipid profile, including total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides, allowing calculation of low-density lipoprotein cholesterol (LDL-C), is necessary in every person with suspected CCS to refine his/her risk profile and guide treatment.^{16,64} Fasting values are needed to characterize severe dyslipidaemia or follow-up hypertriglyceridaemia,⁶⁴ but not in other situations.⁸⁷ Elevated lipoprotein(a) is a marker of cardiovascular risk, particularly early-onset atherosclerotic disease;⁸⁸ lipoprotein(a)-lowering strategies are currently being investigated in phase 3 cardiovascular outcomes trials.^{89–91} Given that circulating lipoprotein(a) levels are genetically determined and do not fluctuate substantially over a lifetime,^{89,91} a single measure is sufficient in persons with suspected CCS.⁹²

Renal dysfunction increases the likelihood of CAD and has a negative impact on prognosis.^{93–95} Glomerular filtration rate (GFR) also impacts renally cleared drugs. It is reasonable to also measure uric acid levels, as hyperuricaemia is frequent, and may affect renal function.

If there is a clinical suspicion of CAD instability, biochemical markers of myocardial injury—such as troponin T or troponin I—should be measured, preferably using high-sensitivity assays, and management should follow the 2023 ESC Guidelines for the management of patients with acute coronary syndromes.⁶⁵ If high-sensitivity assays are employed, low troponin levels can be detected in many patients with stable angina. Increased troponin levels are associated with adverse outcomes,^{96–100} and small studies have indicated a possible incremental value in diagnosing obstructive CAD,^{101–104} but larger trials are needed to verify the utility of systematic assessment in individuals suspected of CCS. While multiple biomarkers may be useful for prognostication, they do not yet have a role in diagnosing obstructive CAD, but some promising results have been published.^{105–108} Measuring NT-proBNP helps confirm or exclude suspected HF.

Markers of inflammation such as C-reactive protein^{109–113} and fibrinogen^{114–118} are predictors of an individual's risk of CAD and can predict cardiovascular event risk in CCS patients,^{99,111} but their value is limited beyond traditional risk factors.¹¹¹ However, in patients taking contemporary statins, high-sensitivity C-reactive protein (hs-CRP) was a stronger predictor for future cardiovascular events and death than LDL-C.^{119,120} These patients may benefit from additional LDL-C reduction through adjunctive lipid-lowering therapies, such as ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition,¹²¹ inclisiran, and bempedoic acid.^{122–124} Elevated hs-CRP levels in patients taking statins and PCSK9 inhibitors may indicate residual inflammatory risk that could be further reduced through inflammation modulation.^{119,125,126} Experimental inhibition of interleukin-6, a pivotal factor in atherothrombosis, resulted in a marked parallel reduction of C-reactive protein and fibrinogen in patients with chronic kidney disease (CKD) and high cardiovascular risk.¹²⁷

Recommendation Table 2 — Recommendations for basic biochemistry in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 2)

Recommendations	Class ^a	Level ^b
The following blood tests are recommended in all individuals to refine risk stratification, diagnose comorbidities, and guide treatment:		
• lipid profile including LDL-C; ^{64,128}	I	A
• full blood count (including haemoglobin); ^{129–133}	I	B
• creatinine with estimation of renal function; ¹³⁴	I	B
• glycaemic status with HbA1c and/or fasting plasma glucose. ^{16,86,135,136}	I	B
In patients with suspected CCS, it is recommended to assess thyroid function at least once. ^{137,138}	I	B
Additionally, hs-CRP and/or fibrinogen plasma levels should be considered. ^{109–118,121,125}	IIa	B

CCS, chronic coronary syndrome; HbA1c, glycated haemoglobin; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

^aClass of recommendation.

^bLevel of evidence.

3.2. STEP 2: Further evaluation

3.2.1. Pre-test clinical likelihood of obstructive atherosclerotic coronary artery disease

The diagnosis of CCS is based on interpreting the individual's symptoms, balancing the impact of age, sex, risk factors, and comorbidities on the likelihood that CCS is present, and choosing the most appropriate diagnostic test to confirm the clinically suspected diagnosis. To aid diagnosis, prediction tables for obstructive CAD can be used that integrate these clinical factors and provide guidance on selecting diagnostic tests based on their capacities to rule in and rule out obstructive atherosclerotic CAD. Importantly, these models do not include the probability of ANOCA/INOCA, which always needs to be considered if symptoms persist after deferral of further testing or diagnostic testing that excludes obstructive CAD.

The tables used to estimate the likelihood of obstructive CAD as confirmed by ICA were initially based on the Diamond–Forrester approach, which considered sex, age, and angina symptoms.²⁵ However, these tables have had to be updated several times owing to the declining prevalence of obstructive CAD at invasive angiography in contemporary Western cohorts.^{26,29} The overestimation of obstructive CAD prevalence has limited the utility of these tables in clinical routine and in accurately estimating the post-test likelihood of obstructive CAD by diagnostic imaging methods.^{1,29,30}

The 2019 ESC Guidelines for the diagnosis and management of CCS introduced the concept of clinical likelihood as a more comprehensive and individualized assessment of the probability of obstructive CAD.¹

Compared with a basic pre-test probability model, incorporation of risk factors in the basic pre-test likelihood model (based on age, sex, and

symptoms) leads to improved prediction of obstructive CAD, down-classes more individuals to very low and low likelihood of disease, and maintains high calibration.^{30,139,140} The Risk-Factor-weighted Clinical Likelihood (RF-CL) model includes sex, age, angina symptoms, and number of risk factors without losing diagnostic accuracy compared with more advanced models requiring computed calculation (Figure 4).^{139,141,142} The RF-CL model increases three-fold the number of subjects categorized as at very low ($\leq 5\%$) likelihood of obstructive CAD compared with the ESC pretest probability (ESC-PTP) model (38% vs. 12%),¹³⁹ while predicting annualized event rates of MI and death of 0.5%, 1.1%, and 2.1% for individuals having very low, low, and moderate likelihood of obstructive CAD, respectively.¹⁴³

Individual adjustment of the likelihood may be necessary for individuals with severe single risk factors or comorbidities associated with an increased prevalence of obstructive CAD, which are not reflected in the RF-CL model, e.g. familial hypercholesterolaemia, severe kidney dysfunction, rheumatic/inflammatory diseases, and peripheral artery disease (PAD).

Exercise ECG testing may modify the likelihood of obstructive CAD and can be used in patients with low ($>5\%$ – 15%) clinical likelihood, in whom a negative test allows reclassification to the very low ($\leq 5\%$) clinical likelihood group with a favourable prognosis.¹⁴⁴ However, CCTA as a first-line diagnostic test can give more accurate information and has been associated with fewer angina symptoms during follow-up than a strategy with exercise ECG as the first investigation.^{145–148} In addition, more adverse events were observed in randomized trials with an exercise ECG than with a CCTA-based diagnostic strategy.^{34,146} However, exercise ECG remains clinically useful for reproducing anginal symptoms, which have a prognostic value.^{149,150}

In contrast to exercise ECG, visualization of calcified atherosclerotic plaque in the coronary artery significantly impacts the clinical likelihood of atherosclerotic obstructive CAD. Coronary artery calcification (CAC) can be measured using the coronary artery calcium score (CACS), which is derived from an ECG-gated non-contrast-enhanced computed tomography (CT) scan. Alternatively, the presence of CAC can be evaluated qualitatively by visually inspecting the coronary arteries on a previous non-cardiac chest CT scan, if available. The absence of CAC (CACS = 0) has a very high negative predictive value ($>95\%$) for obstructive CAD.¹⁵¹ Of note, in younger patients, obstructive CAD is rare, but when present, a higher percentage (58% of those younger than 40 years) have a CACS of 0 compared with older patients with obstructive CAD (9% among those aged 60 to 69 years).¹⁵²

Small, randomized studies have shown that further testing can safely be deferred in patients without CAC, without increased event rates during follow-up.^{146,153} Finally, in a larger prospective observational study, absence of CAC alone was sufficient to define a low-risk group with no need for further testing with improved accuracy compared with basic clinical prediction models.¹⁵⁴ The combination of CACS with the RF-CL model [CACS + RF-CL (the Coronary Artery Calcium Score-Weighted Clinical Likelihood—CACS-CL)] showed the strongest potential to effectively defer cardiac testing compared with other clinical prediction models or CACS alone (adjustment of the estimation of the clinical likelihood of obstructive CAD).^{139,154} With the CACS-CL model, substantially more individuals (54%) compared with the RF-CL model (38%) were categorized as having a very low clinical likelihood of obstructive CAD in the external validation cohorts.¹³⁹ Finally, the CACS-CL model was superior to other clinical prediction models in predicting MI and death during follow-up.¹⁴³

Detection of atherosclerotic disease in non-coronary arteries with ultrasound or CT scans of, e.g. the aorta, and the carotid or femoral arteries, may increase the clinical likelihood of obstructive CAD,^{155–158} and the risk for future CVD events.^{159,160} However, how accurately the detection of non-coronary atherosclerotic disease impacts the likelihood estimation of obstructive CAD needs further investigation.

In general, individuals with a very low ($\leq 5\%$) likelihood of obstructive CAD do not require further diagnostic testing unless symptoms persist and non-cardiac causes have been excluded. In patients with a low ($>5\%$ – 15%) likelihood of obstructive CAD, the benefit of diagnostic testing is uncertain but may be performed if symptoms are limiting and require clarification. Patients with moderate ($>15\%$ – 50%), high ($>50\%$ – 85%), and very high ($>85\%$) likelihood of obstructive CAD are encouraged to undergo further diagnostic testing.

By using pre-test likelihood estimates and diagnostic imaging-test positive and negative likelihood ratios, it is possible to calculate the post-test probability of obstructive CAD. Hence, pre-test likelihood estimation is useful to guide non-invasive diagnostic test strategies for detecting obstructive CAD (Section 3.3.4).

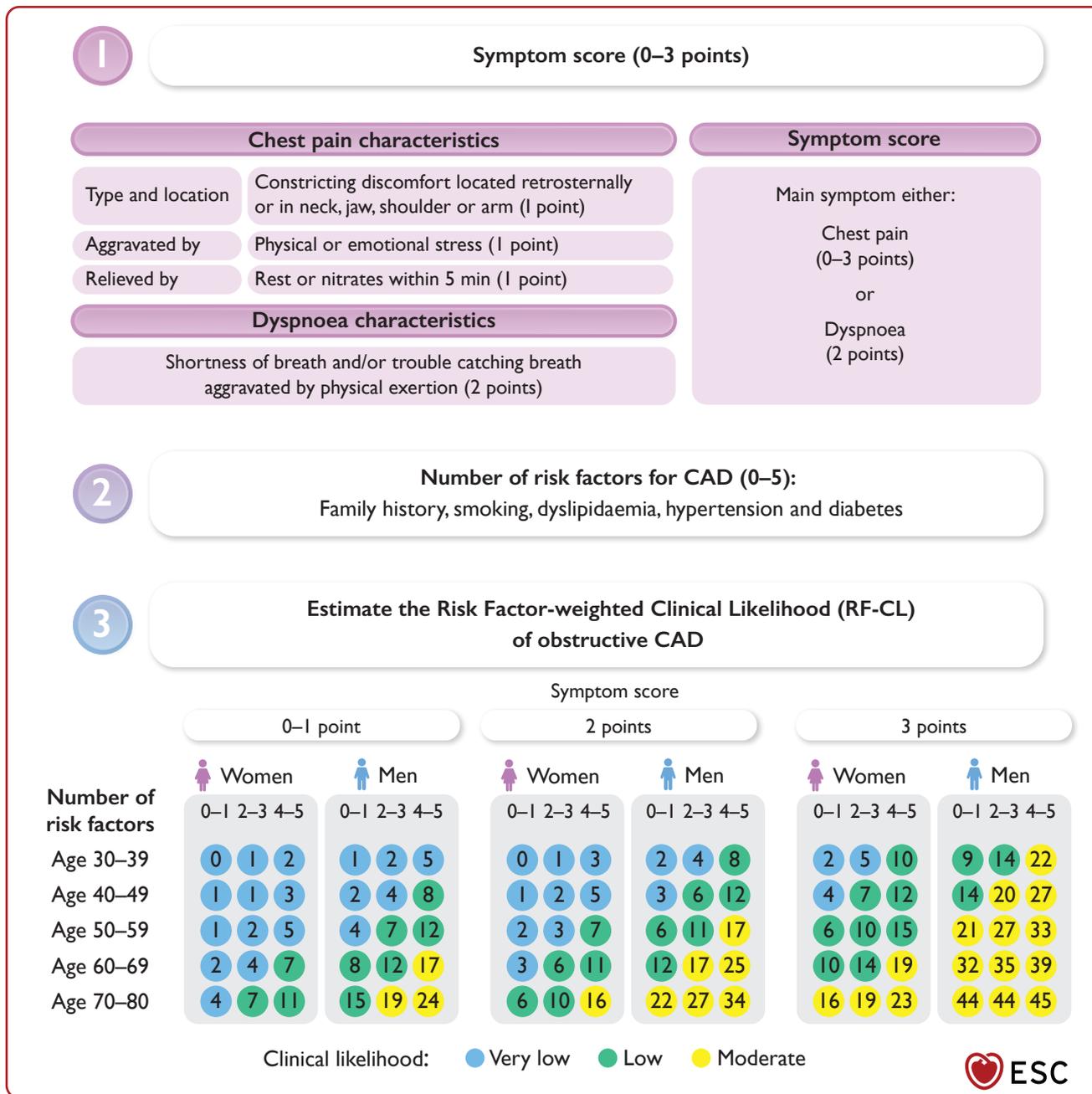
Recommendation Table 3 — Recommendations for estimating, adjusting and reclassifying the likelihood of obstructive atherosclerotic coronary artery disease in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 3)

Recommendations	Class ^a	Level ^b
It is recommended to estimate the pre-test likelihood of obstructive epicardial CAD using the Risk Factor-weighted Clinical Likelihood model. ^{139,140,142,143,161,162}	I	B
It is recommended to use additional clinical data (e.g. examination of peripheral arteries, resting ECG, resting echocardiography, presence of vascular calcifications on previously performed imaging tests) to adjust the estimate yielded by the Risk Factor-weighted Clinical Likelihood model. ¹⁶³	I	C
In individuals with a very low ($\leq 5\%$) pre-test likelihood of obstructive CAD, deferral of further diagnostic tests should be considered. ^{139,164}	IIa	B
In individuals with a low ($>5\%$ – 15%) pre-test likelihood of obstructive CAD, CACS should be considered to reclassify subjects and to identify more individuals with very low ($\leq 5\%$) CACS-weighted clinical likelihood. ^{139,143,165}	IIa	B
In individuals with an initially low ($>5\%$ – 15%) likelihood of obstructive CAD, exercise ECG and detection of atherosclerotic disease in non-coronary arteries may be considered to adjust the pre-test likelihood estimate. ^{144,166}	IIb	C

CACS, coronary artery calcium score; CAD, coronary artery disease; ECG, electrocardiogram.

^aClass of recommendation.

^bLevel of evidence.



3.2.2. Transthoracic echocardiography and cardiac magnetic resonance at rest

An echocardiographic study will provide important information about cardiac function and anatomy. Patients with CCS have often preserved left ventricular ejection fraction (LVEF).¹⁶⁷ A decreased LV function and/or regional wall motion abnormalities may increase the suspicion of ischaemic myocardial damage,¹⁶⁷ and a pattern of LV dysfunction following the anatomical perfusion territory of the coronary arteries is typical in patients who have already had an MI.^{168,169} The detection of regional wall motion abnormalities can be challenging by visual assessment, and detection of early systolic lengthening, decreased systolic shortening, or post-systolic shortening by strain imaging techniques,^{170–172} or new parameters such as global myocardial work,¹⁷³ may be helpful in individuals with apparently normal LV function but with clinical suspicion of CCS. Diastolic LV dysfunction has been reported to be an early sign of ischaemic myocardial dysfunction and may also be indicative of microvascular dysfunction.^{174,175}

Echocardiography can help in detecting alternative causes of chest pain (e.g. pericarditis) and in diagnosing valvular heart diseases, ischaemic HF, and most cardiomyopathies,¹⁷⁶ though these diseases may co-exist with obstructive CAD. The use of an echocardiographic contrast agent can be helpful in patients with poor acoustic windows.¹⁷⁷

Cardiac magnetic resonance (CMR) is an alternative in patients with suspected CAD when the echocardiogram (having used ultrasound contrast agent) is inconclusive.¹⁷⁸ Cardiac magnetic resonance can assess global and regional function,¹⁷⁹ and the use of late gadolinium enhancement (LGE) CMR can reveal a typical pattern of scarred myocardium in patients who have already experienced an MI.¹⁸⁰ Moreover, CMR provides information on myocardial ischaemia through the evaluation of stress-induced perfusion defects.¹⁸¹

The strongest predictor of long-term survival is systolic LV function. Hence, risk stratification through the assessment of systolic LV function is useful in all symptomatic individuals with suspected CCS. Mortality increases as LVEF declines.¹⁸² Management of patients with either angina or HF symptoms, with reduced LVEF $\leq 40\%$ or mildly reduced LVEF 41%–49%, is described in Section 4.

Recommendation Table 4 — Recommendations for resting transthoracic ultrasound and cardiac magnetic resonance imaging in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 4)

Recommendations	Class ^a	Level ^b
A resting transthoracic echocardiogram is recommended: to measure LVEF, volumes and diastolic function; • identify regional wall motion abnormalities; • identify non-coronary cardiac disease (e.g. hypertrophy, cardiomyopathy, valve disease, pericardial effusion); • assess right ventricular function and estimate systolic pulmonary artery pressure; to refine risk stratification and guide treatment. ^{167,183,184}	I	B
CMR, if available, may be considered as an alternative imaging test in individuals with inconclusive echocardiographic evaluation. ^{185,186}	IIb	C

© ESC 2024

CMR, cardiac magnetic resonance; LVEF, left ventricular ejection fraction.

^aClass of recommendation.

^bLevel of evidence.

3.2.3. Exercise electrocardiogram testing

Exercise ECG testing is low cost, does not use ionizing radiation, is widely accessible, and remains an alternative for diagnostic testing depending on local resources and individual characteristics.

The classical exercise ECG, involving graded exercise until the occurrence of fatigue, limiting chest pain or discomfort, significant ischaemic ECG changes, arrhythmias, excessive hypertension, a BP drop or after reaching 85% of the maximal predicted heart rate, has been the mainstay of the examination techniques used in clinical cardiology for assessing individuals with suspected CCS. Exercise ECG testing has a lower diagnostic performance of obstructive CAD compared with modern functional imaging and CCTA,¹⁴⁸ which, therefore, should be preferred as a first-line test in subjects with suspected CCS. Several clinical trials have confirmed that a strategy based on anatomical^{34,146,187,188} or functional imaging¹⁸⁹ simplifies the diagnosis, enables the targeting of preventive therapies and interventions, and potentially reduces the risk of MI compared with usual care based on exercise ECG. In addition, two randomized trials showed that patients reported fewer anginal complaints during follow-up when randomized to CCTA as an index investigation for stable chest pain compared with exercise ECG.^{145,146}

Although the Scottish Computed Tomography of the Heart (SCOT-HEART) trial favoured CCTA as first-line test in CCS, a *post hoc* analysis suggested that abnormal results of exercise ECG remain a specific indicator of obstructive CAD, and are associated with future coronary revascularization and risk of MI.¹⁸⁸ Exercise ECG testing with clearly abnormal results was most predictive for these outcomes; however, in a large proportion of individuals who underwent exercise ECG, particularly those with normal or inconclusive results, there was still a significant amount of unrecognized non-obstructive and obstructive CAD, which can be detected by additional CCTA imaging.¹⁸⁸ In the WOMEN trial (What is the Optimal Method for Ischemia Evaluation of Women), including low-risk symptomatic women, exercise ECG was equally effective compared with exercise myocardial perfusion scintigraphy, with a similar 2-year incidence of major adverse cardiovascular events (MACE), defined as CAD death, or hospitalization for an ACS or HF, while providing significant diagnostic cost savings.¹⁹⁰ Individuals exercising >10 metabolic equivalents with a negative exercise ECG and a low-risk Duke Treadmill Score have a good prognosis with limited need for downstream testing and revascularization.^{166,191} Patients with marked ischaemia at a low workload and a high-risk Duke Treadmill Score may benefit from further anatomical or functional testing. In regions with limited access to functional imaging or CCTA, or in individuals with a low (>5%–15%) pre-test likelihood of obstructive CAD,¹⁴⁴ exercise ECG remains, therefore, useful for risk stratification and prognostication.¹⁴⁴ Particularly, in subjects with a low (>5%–15%) likelihood of obstructive CAD, a negative exercise ECG may help to down-classify patients into the very low likelihood (<5%) class, in whom further testing can be deferred.¹⁴⁴

An exercise ECG is of no diagnostic value in patients with ECG abnormalities at rest that prevent interpretation of the ST-segment changes during stress (i.e. LBBB, paced rhythm, Wolff–Parkinson–White syndrome, ≥ 0.1 mV ST-segment depression on resting ECG, or treatment with digitalis). In patients with known CAD, exercise ECG may be considered in selected patients to complement their clinical evaluation for assessing symptoms, ST-segment changes, exercise tolerance, arrhythmias, BP response, and event risk.

In summary, due to its low sensitivity (58%) and specificity (62%), exercise ECG testing has low diagnostic performance for the diagnosis of obstructive CAD¹⁴⁸ and should mainly be used for risk stratification.

Recommendation Table 5 — Recommendations for exercise ECG in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 5)

Recommendations	Class ^a	Level ^b
Exercise ECG is recommended in selected patients ^c for the assessment of exercise tolerance, symptoms, arrhythmias, BP response, and event risk.	I	C
Exercise ECG may be considered as an alternative test to rule in and rule out CAD when non-invasive imaging tests are unavailable. ^{148,166,188,190,191}	IIb	B
An exercise ECG may be considered to refine risk stratification and treatment. ¹⁸⁸	IIb	B
In individuals with a low (>5%–15%) pre-test likelihood of obstructive CAD, an exercise ECG may be considered to identify patients in whom further testing can be deferred. ¹⁴⁴	IIb	C
Exercise ECG is not recommended for diagnostic purposes in patients with ≥0.1 mV ST-segment depression on resting ECG, left bundle branch block or who are being treated with digitalis.	III	C
In individuals with a low or moderate (>5%–50%) pre-test likelihood of obstructive CAD, an exercise ECG is not recommended to rule out CAD if CCTA or functional imaging tests are available. ¹⁴⁸	III	C

BP, blood pressure; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; ECG, electrocardiogram.

^aClass of recommendation.

^bLevel of evidence.

^cWhen this information will have an impact on diagnostic strategy or management.

3.2.4. Chest X-ray

Chest X-ray is commonly utilized in the evaluation of patients experiencing chest pain. However, in the context of CCS, it does not yield specific information for accurate diagnosis or risk stratification. The test may provide assistance in assessing patients with suspected HF. Additionally, chest X-ray may prove beneficial in diagnosing pulmonary conditions that often co-exist with CAD, or in ruling out other potential causes of chest pain.

3.2.5. Ambulatory electrocardiogram monitoring

Ambulatory ECG monitoring can assist in evaluating patients with chest pain and palpitations. It can also help in detecting and evaluating silent myocardial ischaemia, as well as suspected VSA.^{192–194}

Recommendation Table 6 — Recommendations for chest X-ray in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 6)

Recommendations	Class ^a	Level ^b
A chest X-ray should be considered for individuals with: <ul style="list-style-type: none"> • signs and symptoms suggestive of heart failure; • suspected acute pulmonary disease; • suspected aortic, non-coronary cardiac, or other thoracic causes of chest pain. 	IIa	C

^aClass of recommendation.

^bLevel of evidence.

Recommendation Table 7 — Recommendations for ambulatory ECG monitoring in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 7)

Recommendations	Class ^a	Level ^b
Ambulatory ECG monitoring is recommended in subjects with chest pain and suspected arrhythmias.	I	C
Ambulatory ECG monitoring should be considered in subjects with suspected vasospastic angina. ^{192–194}	IIa	B

ECG, electrocardiogram.

^aClass of recommendation.

^bLevel of evidence.

3.3. STEP 3: Confirming the diagnosis

3.3.1. Anatomical imaging: coronary computed tomography angiography

Through the intravenous (i.v.) injection of contrast agent, CCTA allows direct anatomical visualization of the coronary artery lumen and wall. CCTA offers a practical, non-invasive test, with proven diagnostic performance in detecting obstructive coronary artery stenoses when compared with ICA.^{32,148}

Obstructive coronary stenoses have typically been defined using visual thresholds of either 50% or 70% diameter reduction. It is accepted that not all anatomical stenoses above such thresholds, especially those of moderate (50%–69%) stenosis severity, are haemodynamically or functionally significant¹⁹⁵ or induce myocardial ischaemia.¹⁹⁶ Depending on the clinical context, it may be necessary to complement CCTA with functional data either from non-invasive imaging techniques or from invasive angiography with fractional flow reserve (FFR) (see Section 3.3.3.2), when the haemodynamic consequence of a stenosis is deemed questionable for management options.

While several earlier trials (publication date during or before 2016) reported a higher rate of *downstream* ICA in patients receiving CCTA compared with functional imaging,¹⁹⁷ this was no longer observed in more recent trials (publication date after 2016). Moreover, increased downstream use of invasive procedures was linked to non-adherence to guideline recommendations as these procedures were used significantly less when the guidelines were adopted.¹⁹⁸

Coronary computed tomography angiography-derived fractional flow reserve (FFR-CT) can complement CCTA by providing values of model-based computational FFR along the coronary tree. FFR-CT has shown good agreement with invasive FFR,¹⁹⁹ and has clinical utility by reducing the number of unnecessary ICA procedures.²⁰⁰ However, in patients with severe disease at CCTA, FFR-CT has less impact on patient management.²⁰¹ FFR-CT does not require pharmacological stress, additional contrast agent injection, or radiation exposure. FFR-CT, however, is not ubiquitous and depends on image quality. Nevertheless, the rejection rate is reported to be quite low in real-world data with newest-generation scanners.^{202–204}

3.3.1.1. Computed tomography perfusion imaging

Computed tomography perfusion imaging, performed under pharmacological stress, has been validated against several reference standards, including single-photon computed tomography (SPECT) and

invasive FFR. It has shown adequate diagnostic performance in selected cohorts,^{205,206} and a potential to reduce the number of unnecessary downstream invasive angiography procedures, when compared with functional tests (mostly symptom-limited exercise ECG).¹⁵³ While CT perfusion imaging could complement CCTA during the same visit, this technique requires the administration of a pharmacological stressor, contrast agent, and further patient irradiation. Imaging techniques and analysis methods are not yet widely standardized (e.g. static and dynamic imaging techniques, visual and quantitative assessment).^{207–209}

3.3.1.2. Prognosis, plaque features, and opportunity to improve outcomes

The SCOT-HEART trial demonstrated a small but significant decrease of the combined endpoint of cardiovascular death or non-fatal MI (from 3.9% to 2.3% during 5-year follow-up) in patients in whom CCTA was performed in addition to routine testing (exercise ECG).³⁴ In a *post hoc* analysis of this trial, CCTA features (low-attenuation plaque, positive remodelling, spotty calcifications, and napkin-ring sign) conferred an increased risk of death or non-fatal MI, although these plaque features were not independent of CACS.²¹⁰ Systematically evaluating adverse plaque features by CCTA can be challenging due to technical limitations (spatial resolution) and patient characteristics (calcifications).

A network meta-analysis of randomized trials suggested that diagnostic testing with CCTA was associated with clinical outcomes similar to those with functional imaging in patients with suspected stable CAD.¹⁹⁷ In another pairwise meta-analysis, CCTA showed a lower rate of MI compared with functional testing, but the absolute per cent risk difference was small (0.4%).²¹¹

In the available randomized trials comparing CCTA and functional testing (all testing a diagnostic strategy),^{33,210,212} test reporting and patient management variability could in part help explain the improved outcomes observed in the CCTA arm of SCOT-HEART. In this trial, CCTA findings, including non-obstructive atherosclerosis, emphasized the need to trigger the start or intensification of medical treatment. Increased standardization in reporting CCTA to encompass key plaque features (accepting inherent limitations) will be warranted to systematically harvest prognostic information and help fine-tune risk management strategies.²¹³

3.3.1.3. Recognized pre-requisites for coronary computed tomography angiography

Generally, a slow and regular heart rate, and compliance with breath-holding instructions are necessary to achieve good image quality. This includes suitability to receive pre-medication (typically oral or i.v. beta-blockers) when needed. Kidney function and allergy to contrast agents should be assessed prior to referral. Temporal and spatial resolution remain technical limitations and can hinder precision in adjudicating coronary stenosis severity. This is most problematic in older patients with heavily calcified coronary arteries, in whom functional testing may be more appropriate than CCTA. Contemporary CT technology (64-slice technology or above) and a well-trained imaging team can help mitigate these limitations and must be considered a pre-requisite for CCTA.

Recommendation Table 8 — Recommendations for non-invasive anatomical imaging tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—coronary computed tomography angiography, if available, and supported by local expertise (see also Evidence Table 8)

Recommendations	Class ^a	Level ^b
In individuals with suspected CCS and low or moderate (>5%–50%) pre-test likelihood of obstructive CAD, CCTA is recommended to diagnose obstructive CAD and to estimate the risk of MACE. ^{33,34,145,212,214–221}	I	A
CCTA is recommended in individuals with low or moderate (>5%–50%) pre-test likelihood of obstructive CAD to refine diagnosis if another non-invasive test is non-diagnostic. ²²²	I	B
CCTA is not recommended in patients with severe renal failure (eGFR <30 mL/min/1.73 m ²), decompensated heart failure, extensive coronary calcification, fast irregular heart rate, severe obesity, inability to cooperate with breath-hold commands, or any other conditions that can make obtaining good imaging quality unlikely.	III	C

CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular events.

^aClass of recommendation.

^bLevel of evidence.

3.3.2. Functional imaging

3.3.2.1. Stress echocardiography

Stress echocardiography is used to detect myocardial ischaemia by assessing regional systolic wall-thickening abnormalities (RWTA) during stress. It relies on inducing myocardial ischaemia by increasing myocardial oxygen demand beyond the myocardial blood supply. Because ischaemia starts in the subendocardium, which contributes to more than 50% of systolic myocardial wall thickening, stress testing will precipitate wall-thickening abnormalities in the perfusion territory of narrowed coronary arteries. Stress modalities used to increase myocardial oxygen demand are exercise (treadmill or bicycle), or i.v. administration of dobutamine, or vasodilators (adenosine, dipyridamole, regadenoson) combined with atropine (to increase heart rate adequately—a major determinant of oxygen demand). Stress echocardiography using demand stress has provided diagnostic accuracy and risk-stratification capabilities similar to those obtained with other contemporary functional imaging testing modalities.^{148,223} The advantages of stress echocardiography are that it is widely available, low-cost, can be performed and interpreted at the bedside, rapid, free of ionizing radiation, and can be repeated without safety concerns.^{224–227} Although stress echocardiography is operator-dependent, which may compromise reproducibility, the technique is within reach of every cardiology department or office. Compromised image quality, especially in obese and chronic obstructive pulmonary disease subjects, is a significant

limitation. RWTA may not occur if the myocardial oxygen demand increase is inadequate or if the induced perfusion abnormalities are not large enough (<10% of the myocardium), such as in mild atherosclerotic CAD or single-vessel obstructive CAD.²²⁸ As stress echocardiography relies on RWTA as a marker of ischaemia, it may under-estimate ischaemia in patients with microvascular disease not affecting the subendocardium as in ANOCA/INOCA.³⁶

Ultrasound contrast agents considerably enhance the quality of diagnostic images obtained during stress echocardiography. These microbubbles, consisting of stable gas and shells about the size and rheology of red blood cells, can pass through the pulmonary microcirculation and induce a dense opacification of the left heart chambers. The enhanced image quality and endocardial border definition by using ultrasound contrast agents markedly improve the accuracy of stress echocardiography.^{229,230} Ultrasound contrast agents may be required in individuals with obesity and chronic obstructive pulmonary disease and must be used in all cases if it is evident at baseline that all segments may not be visible during stress. Passage of ultrasound contrast agents through the myocardium allows assessment of myocardial perfusion simultaneously with regional wall motion, improving the sensitivity of stress echocardiography (better detection of single-vessel and microvascular disease) and risk stratification beyond RWTA.^{231–235} The use of ultrasound contrast agents during stress echocardiography for assessing regional and global LV function is strongly recommended by the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) guidelines—both class I indications. Similarly, myocardial perfusion assessment has received a class I recommendation by the EACVI and a class IIa recommendation by the ASE.^{177,236} Ultrasound contrast agents are generally safe, but rare cases of anaphylactic reactions have been reported.²³⁷

Measurement of the coronary flow velocity reserve (CFVR) based on Doppler flow velocity recordings at rest and during stress in the left anterior descending (LAD) artery, and assessment of lung congestion through the visualization of B-lines on lung ultrasound, can easily be added to routine stress echocardiography procedures. In a prospective observational multicentre study, a reduced CFVR was often accompanied by RWTA, abnormal LV contractile reserve, and pulmonary congestion during stress, and showed independent value over RWTA in predicting an adverse outcome.²³⁸ The inclusion of these additional parameters in routine stress echocardiography procedures provides insights on coronary microcirculatory dysfunction.

Finally, carotid ultrasound may be performed in the same session with stress echocardiography to assess extracoronary atherosclerosis; while this does not add value for confirming a CCS diagnosis per se, it provides incremental prognostic value beyond myocardial ischaemia.^{239,240}

Recommendation Table 9 — Recommendations for non-invasive tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—stress echocardiography, if available, and supported by local expertise (see also Evidence Table 9)

Recommendations	Class ^a	Level ^b
In individuals with suspected CCS and moderate or high (>15%–85%) pre-test likelihood of obstructive CAD, stress echocardiography is recommended to diagnose myocardial ischaemia and to estimate the risk of MACE. ^{33,241–246}	I	B

Continued

During stress echocardiography, when two or more contiguous myocardial segments are not visualized, it is recommended to use commercially available intravenous ultrasound contrast agents (microbubbles) to improve diagnostic accuracy. ^{177,229,236,247,248}	I	B
During stress echocardiography, myocardial perfusion using commercially available intravenous ultrasound contrast agents (microbubbles) is recommended to improve diagnostic accuracy and to refine risk stratification beyond wall motion. ^{177,230,232,236,249–254}	I	B
During stress echocardiography, Doppler left anterior descending coronary artery flow reserve may be considered to improve risk stratification beyond wall motion and to assess microvascular function. ^{177,238,255}	IIb	B

CAD, coronary artery disease; CCS, chronic coronary syndrome; MACE, major adverse cardiovascular events.

^aClass of recommendation.

^bLevel of evidence.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehae177/7743115 by guest on 30 August 2024 © ESC 2024

3.3.2.2. Myocardial perfusion scintigraphy—single-photon emission computed tomography

Myocardial perfusion SPECT imaging relies on the myocardial uptake and retention of a radiopharmaceutical. Technetium-99m (99mTc)-based tracers are the most commonly used radiopharmaceuticals, whereas Thallium 201 (201Tl) should be avoided as it is associated with higher radiation exposure. Myocardial perfusion SPECT produces images of regional myocardial tracer retention, which reflects relative regional myocardial blood flow (MBF). Myocardial hypoperfusion is characterized by relative reduced radionuclide tracer uptake and retention during vasodilatation or stress, compared with the uptake and retention at rest. The inherent need for a normally perfused myocardial reference territory allowing for visualization of the myocardium with relative hypoperfusion constitutes the main limitation of SPECT (and stress CMR), particularly in multivessel CAD. Coronary calcium scoring from non-contrast-enhanced CT, acquired for attenuation correction, as well as transient ischaemic dilatation (TID) and reduced post-stress ejection fraction (EF) are important non-perfusion predictors of severe obstructive CAD.

Ischaemia can be demonstrated by physical exercise or through the administration of pharmacological stressors (e.g. dobutamine) or vasodilators (e.g. dipyridamole, adenosine, or regadenoson). Pharmacological agents are indicated in patients who cannot exercise adequately or may be used as an alternative or an adjunct to exercise stress. The possibility to use physical exercise and/or different pharmacological stressors in combination with the wide-spread availability of the technique and the lack of absolute contraindications contributes to the high versatility and applicability of myocardial perfusion SPECT in clinical routine.

SPECT myocardial perfusion imaging is associated with good accuracy for the detection of flow-limiting coronary lesions,^{148,256–258} and has been shown to provide prognostic information^{223,259} and to improve patient management in a randomized controlled trial (RCT).¹⁷⁸

Newer-generation SPECT cameras based on cadmium–zinc–telluride (CZT) semiconductor detector technology enable a substantial reduction in radiation dose exposure and acquisition time, as well as an increased diagnostic accuracy²⁶⁰ and absolute quantification of MBF. Hence, its diagnostic performance for multivessel CAD has improved substantially.²⁶¹

However, non-obstructive coronary atherosclerosis not linked with ischaemia remains undetected by functional testing in general.

If available, assessment of myocardial perfusion using SPECT is recommended in patients with suspected CCS with moderate or high pre-test likelihood of obstructive CAD (15%–85%) or known CCS. Importantly, if non-contrast-enhanced CT for attenuation correction is acquired, this allows for additional CAC scoring, providing important information for risk stratification even in the absence of flow-limiting coronary lesions.

3.3.2.3. Positron emission tomography-computed tomography

Similarly to myocardial perfusion SPECT imaging, PET also relies on radiopharmaceuticals. Contrary to SPECT, however, the radionuclides commonly used (i.e. ¹³N-ammonia, ¹⁵O-water, and ⁸²Rubidium) are short-lived, with half-lives in the range of minutes, requiring production of these radionuclides *ad hoc* for every investigation. As attenuation correction is mandatory, PET is routinely performed in combination with non-contrast-enhanced CT. Scans are performed during both rest and infusion of pharmacological stressors (e.g. dobutamine) or vasodilators (e.g. dipyridamole, adenosine, or regadenoson).

While myocardial perfusion PET-CT produces retention images depicting relative differences in regional MBF similar to those from SPECT—albeit with superior image quality and at much lower radiation dose exposure—the unique strength of PET-CT imaging is its ability to provide robust absolute quantitative measures of MBF. Measuring MBF with cardiac PET does not increase radiation or imaging time. Several measurements of MBF can be routinely obtained, including MBF during hyperaemia, MBF at rest, the MBF reserve, and the relative MBF reserve, and confer added diagnostic and prognostic value beyond relative perfusion assessment.^{262,263}

Quantitative measures of MBF offer the ability to assess individuals with known or suspected diffusely impaired MBF, e.g. with multivessel CAD, or microvascular dysfunction.^{45,264} In general, PET-CT myocardial perfusion imaging is associated with high accuracy for detecting flow-limiting coronary lesions,^{148,258,265} and has been shown to provide prognostic information.^{223,262,263} In several head-to-head comparisons, PET-CT myocardial perfusion imaging outperformed other functional imaging modalities.^{257,266–269} However, whether the superiority in diagnostic accuracy leads to improved clinical effectiveness and post-test management remains to be elucidated.²⁷⁰ In a large retrospective study, a low MBF reserve measured by PET independently predicted mortality and helped identify patients with a survival benefit from early revascularization with PCI or coronary artery bypass grafting (CABG) beyond the extent of myocardial ischaemia.²⁷¹

Limitations of PET-CT arise from its limited availability compared with other imaging modalities. Furthermore, methodological heterogeneity exists, particularly regarding thresholds for abnormality of quantitative measurements. Finally, physical exercise is challenging to perform.

If available, assessment of myocardial perfusion using PET-CT is particularly recommended in obese patients (due to the high photon energy), in young patients (due to the low radiation dose exposure), and in those with known or suspected diffusely impaired MBF, e.g. those with multivessel CAD or microvascular dysfunction.²⁶⁴ Notably, the mandatory non-contrast-enhanced CT for attenuation correction allows for additional CAC scoring, providing essential information for risk stratification even in the absence of flow-limiting coronary lesions.

3.3.2.4. Cardiac magnetic resonance imaging

Aside from providing highly accurate and reproducible assessments of overall cardiac anatomy, cardiac volumes, function, and tissue characterization, CMR also offers the ability to assess myocardial perfusion,

which relies on the first-pass myocardial perfusion of gadolinium-based contrast agents.

Recently, CMR methods using various parameters for quantitative MBF assessment have been introduced. However, the diagnostic performance of these parameters varies extensively among studies, and standardized protocols and software are lacking.²⁷² Therefore, visual assessment of perfusion defects is currently used in clinical practice. Myocardial perfusion imaging by stress CMR combines high spatial resolution with the absence of ionizing radiation. This has been shown to provide high diagnostic accuracy in detecting flow-limiting coronary lesions,^{148,257,258} prognostic value,^{223,273–275} and improving patient management.^{178,276} Pharmacological vasodilators (e.g. adenosine or regadenoson) or stressors (e.g. dobutamine) are commonly applied, as physical exercise is challenging to perform. In conjunction with a dobutamine infusion, wall motion abnormalities induced by ischaemia can also be detected.²⁷⁷ Of note, and as for all non-invasive imaging modalities used for assessing myocardial perfusion, incorporating all available imaging and non-imaging information as part of an integrative approach is mandatory. For CMR, a multiparametric protocol, including LV function and assessment of LGE along with myocardial perfusion, increases the ability to rule in or rule out obstructive CAD in suspected CCS.²⁷⁸

Coronary magnetic resonance angiography allows non-invasive visualization of the coronary arteries.²⁷⁹ However, CMR angiography remains primarily a research tool due to limitations arising from long imaging times, low spatial resolution, and operator dependency. General limitations of CMR for myocardial perfusion arise from its limited availability, the claustrophobia experienced by patients, duration of image acquisition,²⁸⁰ and possible contraindications to CMR [e.g. non-conditional pacemakers and implantable cardioverter defibrillators (ICDs)] or to gadolinium-based contrast agents (e.g. renal failure due to the potential risk of nephrogenic systemic fibrosis). Finally, and contrary to SPECT/CT or PET-CT, stress CMR does not currently provide information on presence or absence of coronary calcifications.

If available, and if no contraindications are met, stress CMR is recommended as an option in patients with suspected CCS with moderate or high (>15%–85%) pre-test likelihood of obstructive CAD or known CCS, particularly if additional information on cardiac function and tissue characterization is warranted.

Recommendation Table 10 — Recommendations for non-invasive functional myocardial imaging tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—resting and stress single-photon emission computed tomography/positron emission tomography—cardiac magnetic resonance imaging, if available, and supported by local expertise (see also Evidence Table 10)

Recommendations	Class ^a	Level ^b
In individuals with suspected CCS and moderate or high (>15%–85%) pre-test likelihood of obstructive CAD, stress SPECT or, preferably, PET myocardial perfusion imaging is recommended to: <ul style="list-style-type: none"> • diagnose and quantify myocardial ischaemia and/or scar; • estimate the risk of MACE; • quantify myocardial blood flow (PET).^{33,44,223,257,263,268,270,271,281–288} 	I	B

Continued

In patients selected for PET or SPECT myocardial perfusion imaging, it is recommended to measure CACS from unenhanced chest CT imaging (used for attenuation correction) to improve detection of both non-obstructive and obstructive CAD. ^{289–293}	I	B
In individuals with suspected CCS and moderate or high (>15%–85%) pre-test likelihood of obstructive CAD, stress CMR perfusion imaging is recommended to diagnose and quantify myocardial ischaemia and/or scar and estimate the risk of MACE. ^{148,273,276,278,294–297}	I	B

© ESC 2024

CACS, coronary artery calcium score; CAD, coronary artery disease; CCS, chronic coronary syndrome; CMR, cardiac magnetic resonance; CT, computed tomography; MACE, major adverse cardiovascular events; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

^aClass of recommendation.

^bLevel of evidence.

3.3.2.5. Non-invasive testing for microvascular dysfunction

Angina/ischaemia with non-obstructive coronary arteries (ANOCA/INOCA) may be caused by transient and/or sustained impairments in the supply–demand of myocardial perfusion. Functional disorders leading to ANOCA/INOCA (e.g. MVA and VSA) are more common in women than in men.^{298,299} A recent meta-analysis reported an overall prevalence of MVA of 41% and VSA of 40% in selected patients without obstructive CAD.²⁹⁹ However, the true prevalence in unselected patient populations with suspected CCS remains unclear. Patients with ANOCA/INOCA have increased morbidity/mortality,^{300,301} impaired quality of life (QoL), and weigh on health resource utilization. Early, accurate, and preferably non-invasive diagnosis is, therefore, of importance.

The possibility of a microcirculatory origin of angina should be considered in individuals with symptoms suggestive of myocardial ischaemia and coronary arteries that are either normal or with non-obstructive lesions on CCTA or ICA. Several measurements that rely on quantifying blood flow through the coronary circulation are used to describe the function of the microvasculature to identify cases of MVA. Among the non-invasive imaging modalities, transthoracic Doppler echocardiography has been used as a non-invasive means to measure coronary blood flow but is limited to the assessment of the LAD artery and is affected by high inter- and intra-operator variability.^{302,303} Furthermore, this modality cannot distinguish between impairment of coronary flow caused by epicardial CAD or coronary microcirculatory dysfunction.

A more direct and accurate microvascular function assessment is based on MBF measurement. This is commonly achieved by PET-CT myocardial perfusion imaging.²⁹⁹ PET allows for the quantification of MBF (expressed as millilitres per minute per gram of myocardium) and myocardial flow reserve (MFR). The latter reflects the magnitude of the increase in MBF that can be achieved by maximal coronary vasodilation conferred by vasodilators, such as adenosine or regadenoson. Since the microvasculature primarily determines vascular resistance, MFR measures the ability of the microvasculature to respond to a stimulus and therefore represents small vessel function. An MFR of less than 2.0 (2.5 for non-obstructive CAD) is often considered abnormal for PET.³⁰⁴ Of note, however, no definitive references are available across imaging modalities due to the moderate correlation among different MBF estimates.²⁶⁴

Recently, quantitative CMR has been proposed as an emerging technique for the assessment of microvascular dysfunction through MBF quantification but is currently limited to experienced centres.²⁷⁵ Quantitative myocardial perfusion can also be achieved by myocardial contrast echocardiography (MCE) through destruction–reperfusion imaging and analysis of the time–intensity curves from different regions of interest in the myocardium.^{231,233–235} Of note, MCE assesses capillary blood flow, and capillaries comprise 90% of the microvasculature. Measuring MBF at rest and during hyperaemia allows calculation of MBF reserve, which is associated with severity of coronary stenoses in patients with stable angina. In a meta-analysis, MBF reserve had high accuracy for predicting flow-limiting CAD.²³¹ However, in the absence of obstructive CAD, reduced MBF reserve by MCE depicts microcirculatory abnormalities. Transthoracic Doppler evaluation of the LAD artery is also used to assess coronary flow reserve (CFR) during stress hyperaemia and has prognostic value.^{238,255,305,306}

In contrast, the diagnosis of VSA ideally relies on the results of provocation tests in the catheterization laboratory through selective intracoronary acetylcholine (ACh) infusion (see Section 5.2.5.2).

It is important to note that there is only a modest correlation between the values of MBF reserve measured by different techniques and modalities.^{269,305,307}

3.3.3. Invasive tests

Invasive coronary angiography has undergone significant advancements over time. It is no longer just an angiographic technique that provides *anatomical* information about the presence of coronary atherosclerosis and luminal obstructions of the epicardial coronary arteries. It can also determine the *functional* consequences of these obstructions on coronary blood flow [FFR and instantaneous wave-free ratio (iFR)] by direct measurement of the coronary BP^{49,308–311} or by calculating the coronary pressure drop across a stenosis based on two or more angiographic projections.³¹² Furthermore, new technologies allow measurement of CFR and microvascular resistance, and protocols have been introduced for testing the presence of coronary vasospasm.^{36,39}

3.3.3.1. Invasive coronary angiography

Invasive coronary angiography with available coronary pressure assessment^{49,308–311,313} is indicated in patients with a very high (>85%) clinical likelihood of obstructive CAD,¹ in particular those with severe symptoms refractory to antianginal treatment, or characteristic angina or dyspnoea at a low level of exercise^{1,47} or left ventricle dysfunction suggesting extensive obstructive CAD.^{47,182,314,315}

Invasive coronary angiography/coronary pressure assessment is also indicated if non-invasive assessment suggests high event risk—e.g. CCTA shows $\geq 50\%$ left main stenosis, or $\geq 70\%$ proximal LAD stenosis with single or two-vessel CAD, or $\geq 70\%$ proximal three-vessel CAD^{56,182,316,317}—or when any stress test shows moderate to severe inducible ischaemia³¹⁶ or when symptoms are highly suggestive for obstructive CAD. In all the above situations, ICA/coronary pressure assessment is performed for additional risk stratification^{318–320} and to determine a potential revascularization approach (see Section 4.4).^{49,308,309,313}

Invasive coronary angiography/coronary pressure assessment may also be indicated to confirm or exclude the diagnosis of obstructive CAD in patients with uncertain results on non-invasive testing.³¹⁶

Given the frequent mismatch between the angiographic and haemodynamic severities of coronary stenoses, coronary pressure assessment should be readily available to complement ICA investigation for clinical decision-making.^{321–326}

In patients with suspected ANOCA/INOCA and an ICA/coronary pressure assessment disclosing no significant epicardial CAD, additional invasive investigations including index of microcirculatory resistance (IMR), CFR and, if necessary, invasive vasoreactivity testing using Ach (or ergonovine)³⁶ as part of a complete 'invasive coronary functional testing' (ICFT) can be performed.

Performing ICA is not exempt from potential complications. Given that femoral diagnostic catheterization has been associated with a 0.5%–2.0% composite rate of major complications, mainly bleeding requiring blood transfusions,³²⁷ radial access is now the standard access when possible. Radial access has been associated with reduced mortality and reduced major bleeding while allowing rapid ambulation.³²⁷ Still, the composite ICA rate of death, MI, or stroke through radial access is of the order of 0.1%–0.2%.³²⁷ The decision to perform ICA should balance benefits and risks, as well as potential therapeutic consequences, of the investigation that should be part of the process of shared clinical decision-making. Patients should be adequately informed of these aspects ahead of the procedure.

Recommendation Table 11 — Recommendations for invasive coronary angiography in the diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 11)

Recommendations	Class ^a	Level ^b
When ICA is indicated, radial artery access is recommended as the preferred access site. ^{327–330}	I	A
When ICA is indicated, it is recommended to have coronary pressure assessment available and to use it to evaluate the functional severity of intermediate non-left main stem stenoses ^c prior to revascularization. ^{49,195,308,313,321,322,325,331–333}	I	A
Invasive coronary angiography is recommended to diagnose obstructive CAD in individuals with a very high (>85%) clinical likelihood of disease, severe symptoms refractory to guideline-directed medical therapy, angina at a low level of exercise, and/or high event risk.	I	C
In individuals with de novo symptoms highly suggestive of obstructive CAD that occur at a low level of exercise, ICA with a view towards revascularization is recommended as first diagnostic test after clinical assessment by a cardiologist.	I	C
When ICA is indicated, measurement of FFR/iFR should be considered to evaluate the functional severity of intermediate left main stem stenoses ^c prior to revascularization. ^{331,334,335}	IIa	A
When ICA is indicated, IVUS should be considered to evaluate the severity of intermediate stenoses of left main stem ^c prior to revascularization. ^{336,337}	IIa	B

© ESC 2024

CAD, coronary artery disease; FFR, fractional flow reserve; ICA, invasive coronary angiography; iFR, instantaneous wave-free ratio; IVUS, intravascular ultrasound.

^aClass of recommendation.

^bLevel of evidence.

^cTypically 40%–90% for non-left main stem stenoses and 40%–70% for left main stem stenoses by visual estimate. For ICA in the diagnostic management of individuals with suspected ANOCA/INOCA, see Section 5.3. (Specific groups).

3.3.3.2. Functional assessment of epicardial stenosis severity to guide coronary revascularization

When non-invasive stress tests are inconclusive or not performed, identifying the artery responsible for ischaemia during ICA can be challenging, especially in cases with multivessel CAD or coronary stenoses of intermediate severity (typically around 40%–90% for non-left main stem stenoses or 40%–70% for left main stem stenoses by visual estimate). In such cases, recording wire-based intracoronary pressure during maximal hyperaemia to calculate FFR or at rest to measure iFR is recommended to improve risk assessment and clinical decision-making and to reduce clinical events.^{318–320} This has been confirmed by large clinical outcome studies such as FAME 1,³⁰⁸ FAME 2,⁴⁹ DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation),³¹⁰ iFR-SWEDEHEART (Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome),³¹¹ R3F (French FFR Registry),³¹³ and RIPCORD (Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain trial).³⁰⁹ Haemodynamic relevance, as defined by FFR of ≤ 0.80 , or iFR of ≤ 0.89 , correlates poorly with diameter stenosis by visual assessment. In the PRIME-FFR [Insights From the POST-IT (Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease) and R3F Integrated Multicenter Registries—Implementation of FFR (Fractional Flow Reserve) in Routine Practice]³²² and FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) study,¹⁹⁵ 31% of the 40%–49% stenoses were haemodynamically significant while only 35% of the 50%–70% stenoses were haemodynamically relevant, and of the 71%–90% stenoses, 20% were not. Only an estimated diameter stenosis of >90% predicted haemodynamic relevance with high accuracy (96% correct classification). The discordance between angiographical and functional assessment of coronary stenosis severity varies with age, presence of CMD and lesion-specific factors.^{338,339} Lesions in the left main or proximal LAD are more likely to result in a significant FFR, as they supply a larger myocardial mass than those in smaller arteries. As a result, the optimal angiographic cut-off value for functionally non-significant stenosis is 43% for the left main and 55% for small vessels.³³⁹ This implies that the threshold for functional assessment for larger arteries should be set at 40% diameter stenosis.

Large management studies showed that integration of FFR to ICA is associated with treatment reclassification in 30%–50% of cases in the R3F, POST-IT, RIPCORD, and DEFINE-REAL studies.^{309,313,340,341} Subsequently, many other non-hyperaemic pressure parameters were introduced [distal coronary pressure to aortic pressure ratio (Pd/Pa), diastolic pressure ratio (dPR), relative flow reserve (RFR)], with good correlation with FFR or iFR, but without available clinical outcome data. It is interesting to note that both separate and pooled analyses of the patients included in those studies reveal that 'FFR/iFR-based reclassification' does not have any significant effect on the number of patients recommended for revascularization.³⁴²

Meta-analyses of the 5-year outcome of patients managed with iFR and FFR as part of the randomized DEFINE-FLAIR and DEFINE-SWEDEHEART studies have reported a 2% absolute increase in all-cause mortality in those managed with iFR.^{343,344} This was not associated with any unplanned revascularization or non-fatal MI rate increase.^{343,344} Although it was initially hypothesized that this mortality excess could be related to a higher proportion of 'inappropriate' revascularization deferral with iFR compared with FFR (50% vs. 45%),³⁴³ it is reassuring that iFR-based deferral is as safe as FFR-based deferral up to 5 years.³⁴⁵

In patients with multivessel CAD, systematic FFR measurement of all epicardial vessels has been proposed to select appropriate therapy, but

recent studies (RIPCORDER and FUTURE) did not demonstrate any clinical outcome improvement compared with angiography alone.^{346,347} Therefore, intracoronary pressure measurement in patients with multi-vessel CAD should only be performed on intermediate lesions.

Several recent studies using either FFR or iFR suggest that the pattern of pressure drop along the coronary artery (focal vs. progressive) recorded during a pullback is important to select patients who will benefit more from PCI.^{2,348–352} Longitudinal functional vessel interrogation can therefore be helpful in patients with serial lesions or diffuse CAD.

New 3D angiographically derived wireless coronary pressure parameters, such as quantitative flow ratio (QFR) or vessel fractional flow reserve (vFFR), are at different stages of clinical investigation^{325,353,354} (NCT03729739) and have important features that may help to increase the use of coronary pressure measurement during ICA significantly. These technologies have indeed the unique advantage of providing both distal coronary pressure measures and a coronary pressure map along the coronary vessel without requiring the use of any pressure wire. The lack of benefits shown in some recent FFR trials demonstrates that it is not sufficient to validate such new coronary pressure indexes against FFR alone to demonstrate their clinical value, and it is important to also show benefit in a direct comparative trial vs. angiography. In that context, the results of the FAVOR III China study³⁵⁵ are important, demonstrating an improved clinical outcome in the QFR-guided group compared with the angiography-guided group, driven by fewer MIs and ischaemia-driven revascularizations.

The combined measurements of pressure and flow (measured by Doppler or thermodilution) may further reduce the number of interventions. Patients with lesions and concordant normal FFR and CFR have an excellent prognosis. Patients with lesions and discordant results between FFR and CFR have a similar prognosis to that of patients with lesions and concordant abnormal FFR and CFR, treated with PCI. Lesions with an abnormal FFR but normal CFR pertain to a good clinical outcome up to 5 years of follow-up if left untreated.^{356–358} Moreover, hyperaemic stenosis resistance (HSR), by measuring the pressure gradient across a lesion divided by flow, is an excellent index for both diagnostic and prognostic purposes.^{359,360} The recently introduced continuous thermodilution technique for measuring absolute coronary flow presents an alternative method for determining CFR. Additionally, this method allows for evaluation of the microvascular resistance reserve (MRR), a novel index for assessing coronary microvascular function.^{361–364}

Coronary flow capacity (CFC) integrates hyperaemic flow and CFR and is useful for both diagnostic purposes as well as the evaluation of the result after PCI.^{365–368}

Intravascular imaging techniques [e.g. intravascular ultrasound (IVUS) or optical coherence tomography (OCT)] have demonstrated good diagnostic accuracy in predicting FFR, especially in stenoses located in the left main stem.^{369,370} They are reasonable options to assess left main stenosis severity and prognosis; increasing left main plaque burden was associated with long-term all-cause and cardiac mortality in patients not undergoing revascularization.³⁷¹

While coronary pressure thresholds, specifically 0.80 for FFR and 0.89 for iFR, are crucial in aiding clinical decision-making, particularly in the case of deferring revascularization when FFR/iFR exceeds the ischaemic threshold,^{310,372} they must be considered alongside other parameters. These include a careful assessment of the patient's symptoms and the results of non-invasive stress testing to determine the need for revascularization.

Recommendation Table 12 — Recommendations for functional assessment of epicardial artery stenosis severity during invasive coronary angiography to guide revascularization (see also Evidence Table 12)

Recommendations	Class ^a	Level ^b
During ICA, selective assessment of functional severity of intermediate ^c diameter stenoses is recommended to guide the decision to revascularize, using the following techniques:		
• FFR/iFR (significant ≤ 0.8 or ≤ 0.89 , respectively); ^{49,308,310,311,313,321–323,332,373}	I	A
• QFR (significant ≤ 0.8). ^{325,355,374,375}	I	B
In addition:		
• CFR/HSR/CFC should be considered as a complementary investigation; ^{359,360,366–368,376}	IIa	B
• resting invasive measurement of Pd/Pa, dPR, RFR, or angiography-derived vessel FFR may be considered as alternative parameters. ^{353,377}	IIb	C
Systematic and routine wire-based coronary pressure assessment of all coronary vessels is not recommended. ^{346,347}	III	A

CFC, coronary flow capacity; CFR, coronary flow reserve; dPR, diastolic pressure ratio; FFR, fractional flow reserve; HSR, hyperaemic stenosis resistance; ICA, invasive coronary angiography; iFR, instantaneous wave-free ratio; Pd/Pa, distal coronary pressure to aortic pressure ratio; QFR, quantitative flow ratio; RFR, relative flow reserve.

^aClass of recommendation.

^bLevel of evidence.

^cTypically around 40%–90% for non-left main stem or 40%–70% for left main stem by visual estimate.

3.3.3.3. Assessment of microvascular dysfunction

Detailed discussion of microvascular dysfunction by invasive coronary functional testing is provided in Section 5.2.5.2. After nitroglycerine, adenosine is administered to assess endothelium-independent vasodilation [CFR, IMR, and hyperaemic myocardial velocity resistance (HMR)]. Coronary flow reserve can be calculated using bolus thermodilution (as baseline transit time divided by hyperaemic transit time) or continuous thermodilution (as the ratio of hyperaemic and resting absolute coronary flow), or Doppler flow velocity (hyperaemic flow velocity divided by baseline flow velocity).^{307,378,379} The IMR is calculated as the product of distal coronary pressure at maximal hyperaemia multiplied by the hyperaemic mean transit time. Increased IMR (≥ 25 U) indicates microvascular dysfunction.^{380,381} It is important to note that continuous thermodilution-derived measurements have shown higher reproducibility than similar measurements derived from bolus thermodilution.³⁸²

Angiography-derived index of coronary microcirculatory resistance (angio-IMR) allows microcirculation assessment without using intracoronary wires.³⁸³

3.3.3.4. Testing for coronary vasospasm

Vasoreactivity testing explores endothelium-dependent mechanisms of CMD and epicardial and microvascular vasomotor tone disorders.^{36,73,384}

The most established approach for coronary vasoreactivity testing is by intracoronary infusion of Ach, although other substances like ergonovine have been proposed.^{384,385} The methodology is described in detail in Section 5.2.5.2.2.

3.3.4. Diagnostic algorithm and selection of appropriate tests

After estimation of the pre-test likelihood of obstructive epicardial CAD based on the RF-CL model (Figure 4 and Figure 5),¹³⁹ further diagnostic testing is dependent on the clinical scenario, general condition, QoL, presence of comorbidities, local availability and expertise for different diagnostic techniques, and importantly patient expectations and preferences (Figure 6; Table 6).

In patients with severe comorbidities or severe frailty or very low QoL that all contribute to a limited life expectancy, in whom

revascularization is judged to be futile, the diagnosis of CCS can be made clinically, and managed with medical therapy and lifestyle changes alone. If CCS diagnosis is uncertain in such patients, establishing a diagnosis using non-invasive functional imaging for myocardial ischaemia before treatment is reasonable.

Individual adjustment of the clinical likelihood should always be considered based on the clinical CCS scenario including ECG and echocardiography findings. Further diagnostic testing can be deferred in patients with a very low ($\leq 5\%$) likelihood of obstructive CAD. Based on the CACS-CL model, in patients with a low ($>5\%$ – 15%) likelihood of

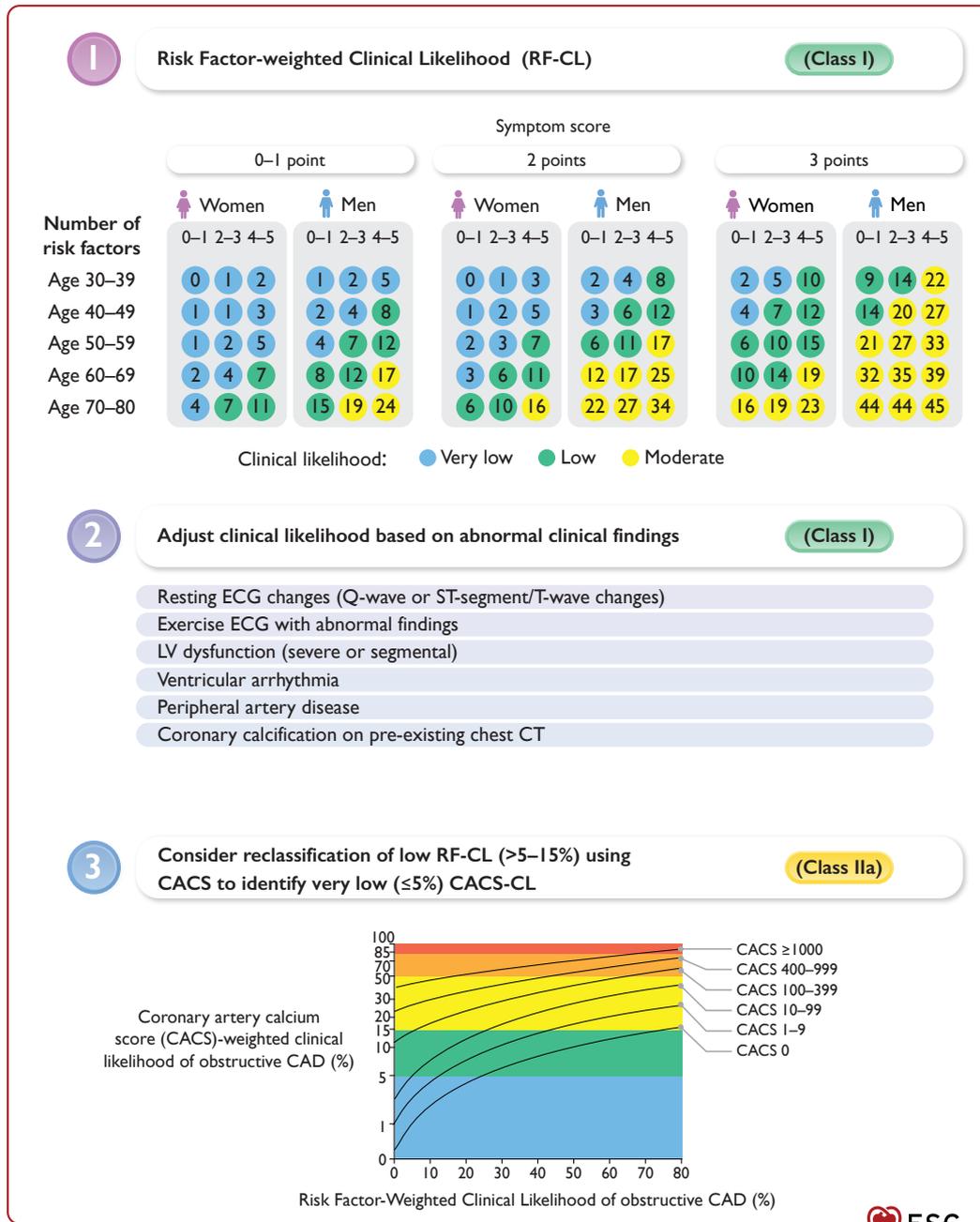


Figure 5 Adjustment and reclassification of the estimated clinical likelihood of obstructive coronary artery disease. CACS, coronary artery calcium score; CACS-CL, coronary artery calcium score + RF-CL model; CAD, coronary artery disease; CT, computed tomography; ECG, electrocardiogram; LV, left ventricular; RF-CL, risk factor-weighted clinical likelihood.

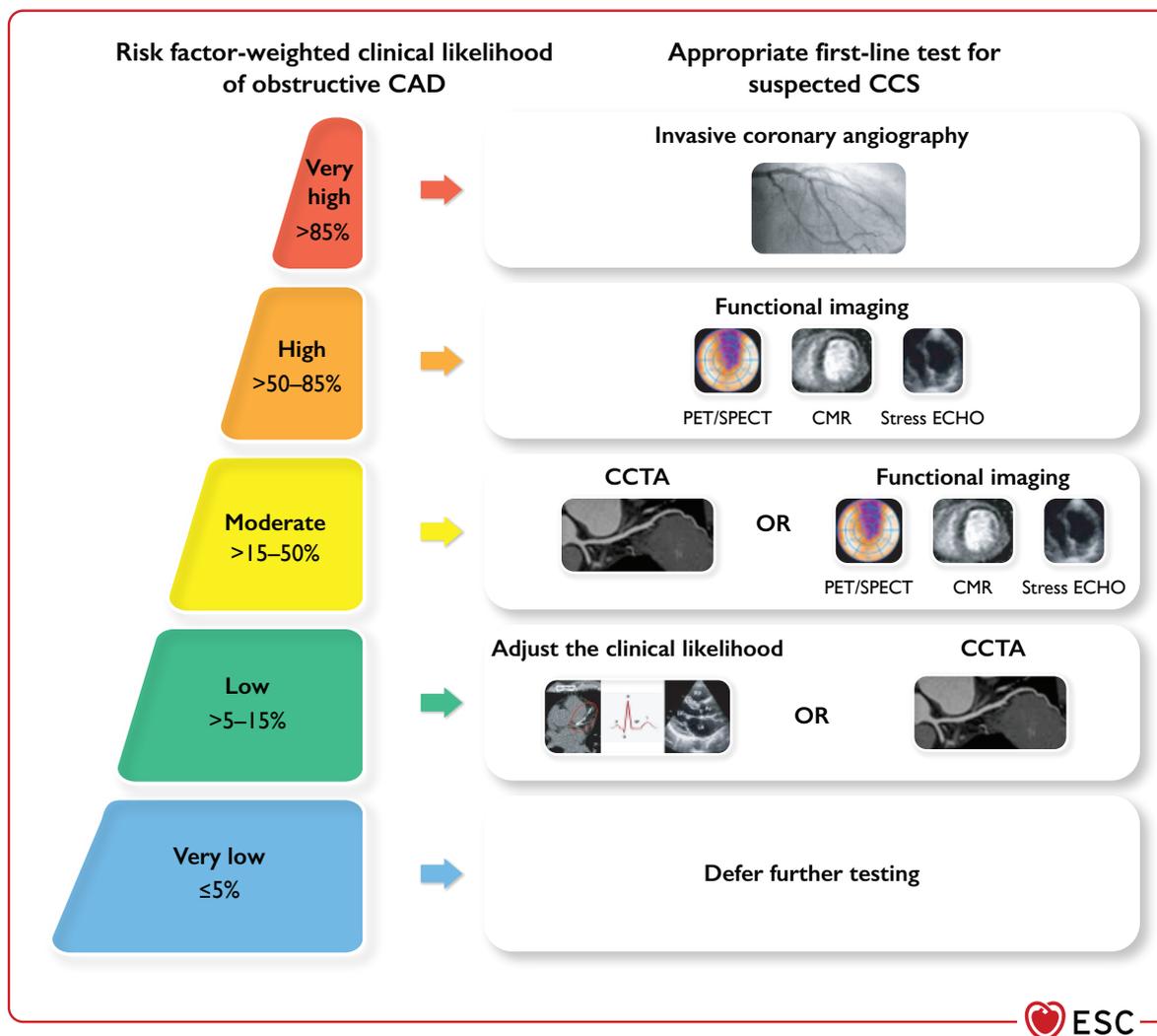


Figure 6 Appropriate first-line testing in symptomatic individuals with suspected chronic coronary syndrome. CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; ECHO, echocardiography; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

obstructive CAD, CACS can be considered to re-estimate the likelihood of obstructive CAD.^{139,165,141,154} Further diagnostic testing can also be deferred in patients reclassified based on CACS from a low to a very low (<5%) likelihood of obstructive CAD (Figure 5).¹⁴³ Conversely, if CACS is high and there are clinical findings indicating that the RF-CL model may be under-estimating the likelihood of obstructive CAD, further diagnostic testing should be selected based on the adjusted clinical likelihood and coronary calcium burden. It is important to note that patients with a very low and low (≤15%) likelihood of obstructive CAD constitute approximately 85% of individuals with *de novo* symptoms suspected of CCS.^{27,30,139} Most can be treated conservatively without the need for further testing as they have no stenoses or non-obstructive CAD with a very low incidence of events during long-term follow-up.^{27,139,143}

Individuals with a moderate or high (>15%–85%) likelihood of obstructive CAD should be referred for non-invasive anatomical or functional imaging to establish the diagnosis and assess the risk for future cardiac events. There is growing support for using CCTA as a

first-line test in the group with a low or moderate (15%–50%) likelihood.^{27,31,32,139,386} Given the low prevalence of CAD in this group of patients and its high negative predictive value, CCTA is the most effective diagnostic method to rule out obstructive CAD. Moreover, besides its strength in ruling out CAD, CCTA offers direct visualization of non-obstructive CAD, which may trigger intensification of preventive measures. The use of CCTA as a first-line test is supported by large, randomized trials showing equivalence in health outcomes with functional testing³³ and even superiority compared with usual care using exercise ECG.³⁴

In patients with a very high (≥85%) clinical likelihood of obstructive CAD, symptoms unresponsive to medical therapy, or angina at a low level of exercise, and an initial clinical evaluation (including echocardiogram and, in selected patients, exercise ECG) that indicates a high event risk, proceeding directly to ICA without further diagnostic testing is a reasonable option. Under such circumstances, the indication for revascularization of stenoses with a diameter reduction of <90% should be guided by coronary pressure assessment (Figure 6; Table 6).

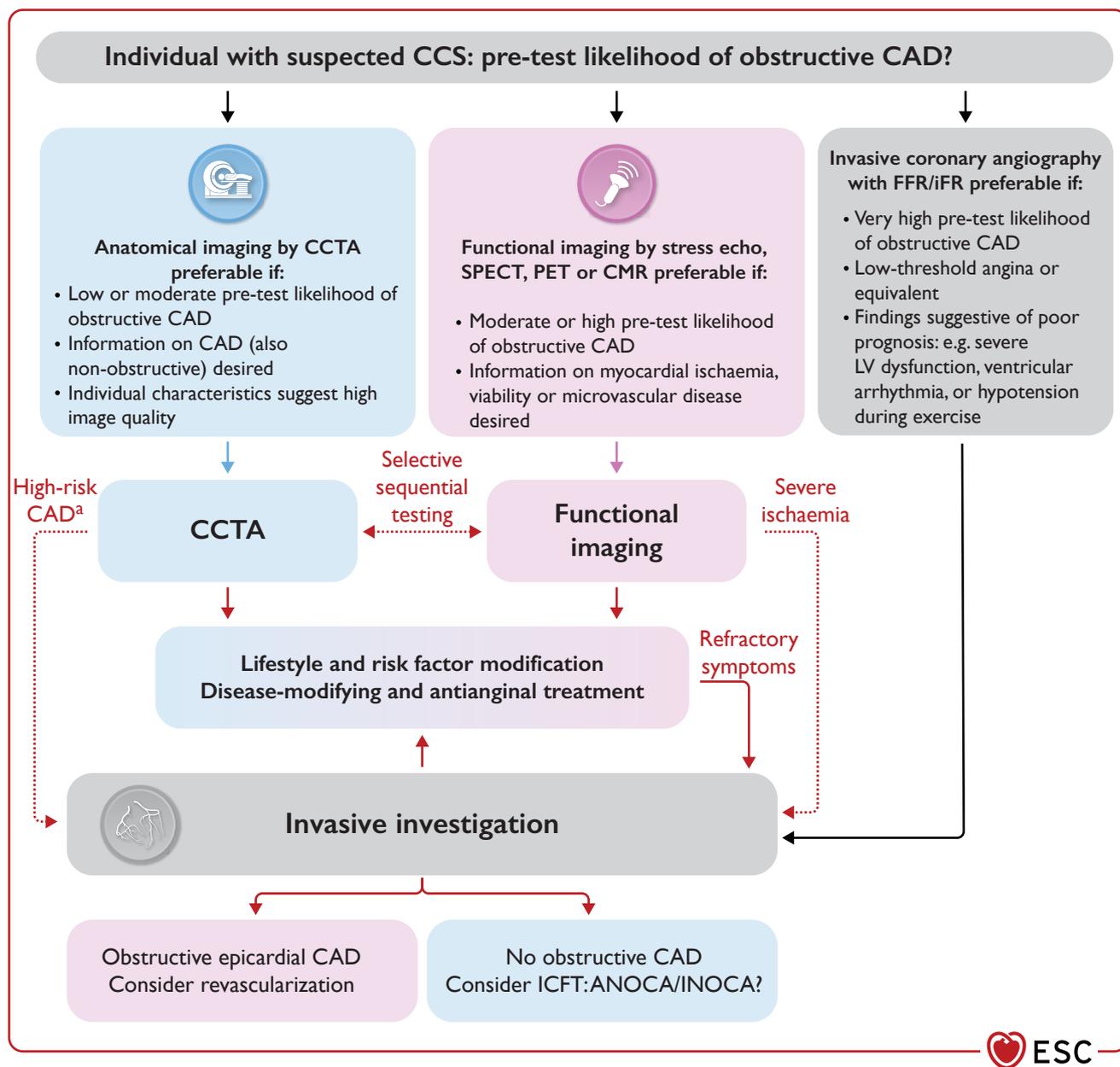


Figure 7 Initial management of symptomatic individuals with suspected chronic coronary syndrome. ANOCA, angina with non-obstructive coronary arteries; CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; Echo, echocardiography; FFR, fractional flow reserve; ICFT, invasive coronary functional testing; iFR, instantaneous wave-free ratio; INOCA, ischaemia with non-obstructed coronary arteries; LV, left ventricular; PET, positron emission tomography; SPECT, single-photon emission computed tomography. Consider local availability and expertise, and individual characteristics when choosing non-invasive testing. *Table 6* offers tips for selecting the first-line test in people with suspected CCS. ^aHigh-risk CAD: obstructive CAD at high risk of adverse events by CCTA: $\geq 50\%$ stenosis of the left main stem; three-vessel disease with severe stenoses ($\geq 70\%$ diameter stenosis); single- or two-vessel disease including the proximal LAD with severe stenoses. Consider functional imaging or invasive investigation.

Functional imaging should be selected as a first line test if information on myocardial ischaemia, viability, or microvascular disease is desired. Tests for detecting ischaemia have better rule-in power compared with CCTA and therefore should be selected if there is a moderate-high ($>15\text{--}85\%$) likelihood of obstructive CAD. Moreover, functional

imaging tests overcome the limitations of CCTA in certain groups (older patients with more extensive coronary calcifications, AF, and other situations with an irregular or fast heart rate, renal insufficiency, or iodinated contrast allergy), and avoid exposure to ionizing radiation in young individuals and in those suspected of ANOCA/INOCA (*Figure 7*).

Table 6 Overview of non-invasive tests used for first-line testing in individuals with suspected chronic coronary syndrome

	Main imaging target(s) in CCS	Requirements	Limitations
Anatomical imaging			
CCTA	Atherosclerosis (obstructive and non-obstructive) in epicardial coronary arteries	Iodinated contrast Radiation Premedication: • Beta-blockers or ivabradine for heart rate control • Nitroglycerine for adequate vasodilation	Severely impaired kidney function ^a Documented allergy to iodinated contrast Tachyarrhythmia refractory to beta-blockade Irradiation (especially young women)
SPECT/CT PET/CT	Atherosclerosis coronary artery calcium score	Radiation	Irradiation (especially young women)
Functional imaging			
Stress Echo	LVEF and volumes		Poor Echo windows
	Wall motion abnormalities Myocardial perfusion Coronary velocity flow reserve	Performed with exercise, dobutamine and vasodilators Echo contrast to improve image quality and assess perfusion	Poor Echo windows Contraindications to stressor
CMR	LVEF and volumes		Non-CMR-compatible metal devices Severe claustrophobia
	MI (scar)	Paramagnetic contrast	Non-CMR-compatible metal devices Severe claustrophobia Haemodialysis
	Ischaemia/blood flow	Vasodilator stress + paramagnetic contrast	Non-CMR-compatible metal devices Severe claustrophobia Contraindications to stressor Haemodialysis
	Wall motion abnormalities	Inotropic stress (dobutamine)	Non-CMR-compatible metal devices Severe claustrophobia Contraindication to stressor
SPECT	LVEF and volumes Ischaemia/viability	Vasodilator or exercise stress Radioactive tracer	Contraindication to stressor Irradiation (especially young women)
PET	LVEF Ischaemia/blood flow Viability	Vasodilator stress Radioactive tracer (¹³ N-ammonia, ¹⁵ O-water, ⁸² Rb)	Contraindication to stressor Irradiation (especially young women)

CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; CT, computed tomography; Echo, echocardiography; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

^aPreventive measures are recommended for patients with eGFR <30 mL/min/1.73 m².³⁸⁹

The discussion about which modality to use as a first-line test has been heavily focused on the detection of obstructive epicardial stenoses, neglecting the relatively high prevalence of non-obstructive coronary disease and ANOCA/INOCA, especially in female patients. The current rationale behind choosing a first-line test should be to assess the anatomical severity and functional consequences of coronary disease, whether obstructive or not. In this regard, PET-CT should be more frequently considered and its availability increased as it combines calcium scoring with accurate operator-independent detection of myocardial ischaemia and CMD with a low irradiation dose.⁴⁵

Individuals in the moderate likelihood group, except older men with all three CCS symptom characteristics, will have a likelihood of obstructive CAD around 20%. In these, anatomical and functional testing will each result in an intermediate positive predictive value with eventually many false positives, especially with CCTA easily overestimating stenosis severity. Sequential testing (i.e. functional testing after CCTA, or vice versa) will therefore be needed in many individuals to establish an accurate diagnosis of obstructive, ischaemia-inducing CAD (Figure 8). Sequential or combined anatomical and functional testing is also useful for the non-invasive diagnosis of ANOCA/INOCA.⁴¹ Moreover, combined testing, e.g. combining CCTA and PET, may result in improved prognostication of CCS patients.³⁸⁷

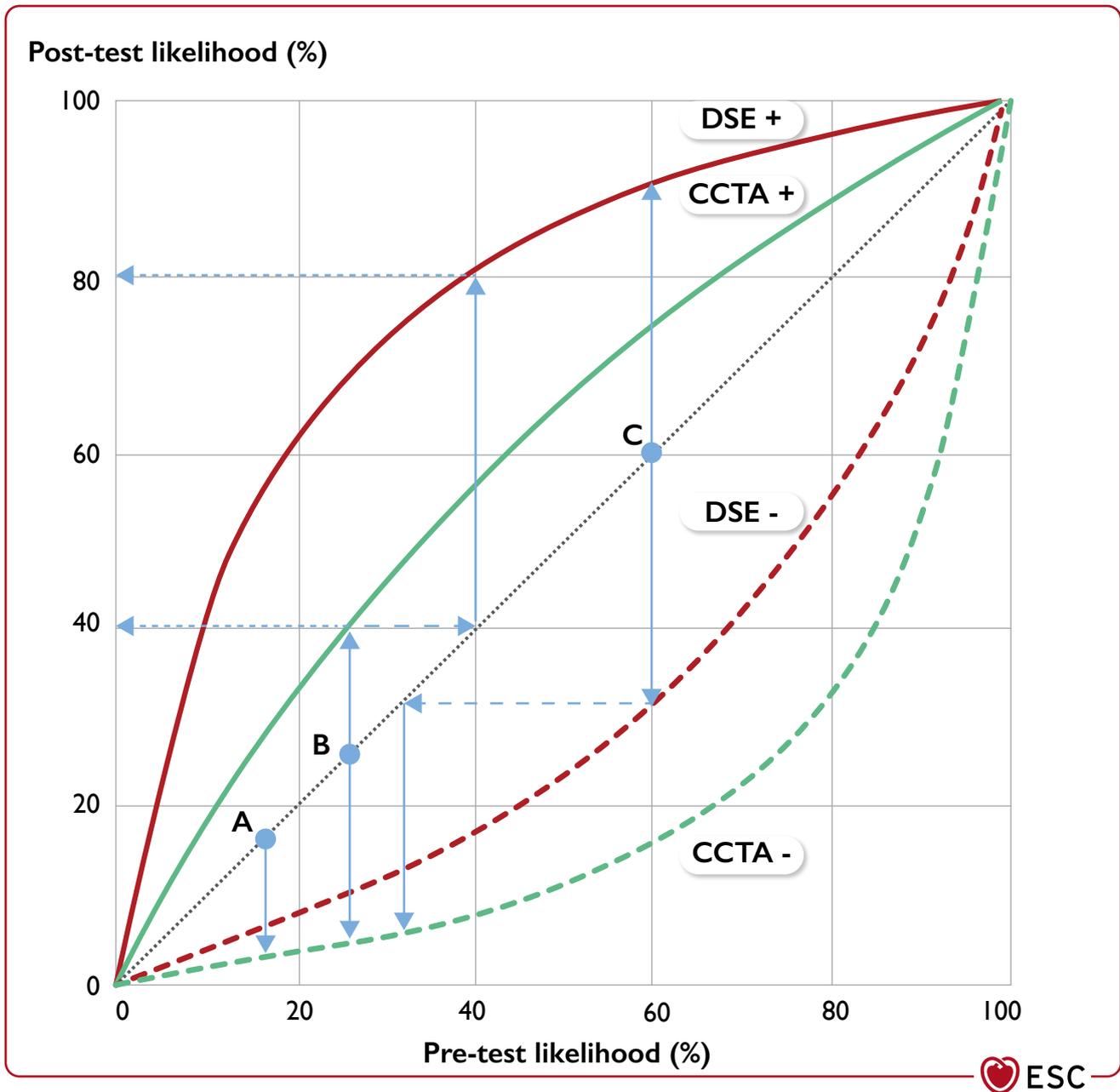


Figure 8 Ruling in and ruling out functionally significant obstructive coronary artery disease by sequential anatomical (coronary computed tomography angiography) and functional (dobutamine stress echocardiography) testing.^a CAD, coronary artery disease; CCTA, coronary computed tomography angiography; DSE, dobutamine stress echocardiography; ECG, electrocardiogram; FFR, fractional flow reserve. The curves display the post-test likelihood of obstructive CAD for a positive (+) and a negative (-) test result for CCTA and DSE, as the pre-test likelihood of obstructive CAD increases. The post-test likelihoods were calculated using the likelihood ratios taken from recent meta-analyses.^{148,388} ^aBased on invasive FFR measurement or diameter stenosis of $\geq 70\%$.

- A 70-year-old woman with four coronary risk factors and exertional dyspnoea has a pre-test likelihood of 16% (A). A normal CCTA almost completely rules out obstructive CAD with a very low negative post-test likelihood (2%).
- A 55-year-old man with two coronary risk factors and all three anginal symptom characteristics has a pre-test likelihood of 27% (B). An abnormal CCTA brings the post-test likelihood to 40%, insufficient to rule in obstructive CAD. Sequential testing with DSE performed after CCTA brings the post-test likelihood to 82%. A normal CCTA effectively rules out obstructive CAD.
- A 69-year-old man with four coronary risk factors and all three anginal symptom characteristics has an adjusted pre-test likelihood of 60% (C) (adjustment based on abnormalities on the resting ECG and on symptoms during exercise). A positive DSE alone has a high post-test likelihood ($\pm 90\%$). A negative DSE is associated with a 32% post-test likelihood. Sequential testing by CCTA would allow ruling out obstructive CAD (<5% post-test likelihood).

Recommendation Table 13 — Recommendations for selection of initial diagnostic tests in individuals with suspected chronic coronary syndrome (see also Evidence Table 13)

Recommendations	Class ^a	Level ^b
Selection of non-invasive testing		
It is recommended to select the initial non-invasive diagnostic test based on pre-test likelihood of obstructive CAD, other patient characteristics that influence the performance of non-invasive tests, ^c and local expertise and availability. ^{29,148}	I	C
In symptomatic patients in whom the pre-test likelihood of obstructive CAD by clinical assessment is >5%, CCTA or non-invasive functional imaging for myocardial ischaemia is recommended as the initial diagnostic test. ^{33,148,178,187,189,211,212,219,222,390}	I	B
To rule out obstructive CAD in individuals with low or moderate (>5%–50%) pre-test likelihood, CCTA is recommended as the preferred diagnostic modality. ^{29,148}	I	B
CCTA is recommended in individuals with low or moderate (>5%–50%) pre-test likelihood of obstructive CAD if functional imaging for myocardial ischaemia is not diagnostic. ³⁹¹	I	B
Functional imaging for myocardial ischaemia is recommended if CCTA has shown CAD of uncertain functional significance or is not diagnostic. ^{392–394}	I	B
In patients with a known intermediate coronary artery stenosis ^d in a proximal or mid coronary segment on CCTA, CT-based FFR may be considered. ^{395–401}	IIb	B
Subsequent invasive testing		
Invasive coronary angiography with the availability of invasive functional assessments is recommended to confirm or exclude the diagnosis of obstructive CAD or ANOCA/INOCA in individuals with an uncertain diagnosis on non-invasive testing. ^{36,49,308,384}	I	B

ANOCA, angina with non-obstructive coronary arteries; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CT, computed tomography; FFR, fractional flow reserve; INOCA, ischaemia with non-obstructive coronary arteries.

^aClass of recommendation.

^bLevel of evidence.

^cCharacteristics determining ability to exercise, likelihood of good image quality, expected radiation exposure, and risks or contraindications.

^dTypically around 40%–90% by visual estimate.

After confirmation of diagnosis with the first line of testing, all patients should receive lifestyle and risk-factor modification recommendations, and disease-modifying and antianginal therapy should be prescribed. The ISCHEMIA trial (Initial Invasive or Conservative Strategy for Stable Coronary Disease)⁴⁷ showed that an early revascularization strategy did not yield a short-term survival benefit in patients without left main disease nor reduced LVEF and with moderate-severe ischaemia at non-invasive testing, suggesting that most such patients should initially be treated conservatively with optimized GDMT. Patients can be referred for ICA if CCTA detects a $\geq 50\%$ stenosis of the left main stem,

three-vessel or two-vessel disease including the proximal LAD artery with $\geq 70\%$ stenosis, or if functional imaging shows moderate or severe ischaemia encompassing an extensive perfusion territory.

For patients with obstructive CAD and refractory symptoms despite optimized GDMT, a referral for ICA may be considered to improve symptoms through revascularization. Optimization of medical therapy by combining two or more antianginal drugs can safely be obtained over 6 weeks in almost all patients and should be awaited before referral to ICA.^{402,403} It is worth noting that in the Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) trial, PCI did not provide short-term advantages compared with GDMT in terms of reducing anginal frequency or physical limitations.⁴⁰² In the CLARIFY registry, anginal symptoms resolved in many CCS patients over time without requiring revascularization or changes in antianginal therapy.⁴⁰⁴

Combined anatomical and functional imaging before ICA facilitates its planning by orientating the invasive cardiologist to perform, in the same session, haemodynamic assessment of coronary stenoses and ICFT to detect microvascular disease or vasospasm in individuals suspected of ANOCA/INOCA, performing these tests in a single session rather than in staged procedures.

3.3.5. Adverse-event risk assessment

Chronic coronary syndromes can be complicated by cardiovascular death, ischaemic and haemorrhagic events, HF, arrhythmic events, the development of valvular heart disease, and other comorbidities, which are further discussed in the [Supplementary data](#), available at *European Heart Journal* online. It is recommended that all patients with newly diagnosed obstructive CAD or myocardial ischaemia undergo an adverse-risk event assessment to identify those at high risk of adverse outcomes who could benefit from revascularization beyond symptom relief. Based on large registries and historical RCTs, a high event risk has been defined as a cardiac mortality rate of $>3\%$ per year, intermediate event risk as between $\geq 1\%$ and $\leq 3\%$ per year, and low event risk as $<1\%$ per year.⁴⁰⁵

Adverse-event risk stratification is usually based on the same clinical, non-invasive and invasive investigations used to diagnose obstructive CAD (see [Table 14](#)).

Clinical history, physical examination, 12-lead ECG and laboratory tests can provide important prognostic information. Assessment of risk factors such as advanced age, diabetes mellitus (DM), or renal failure allows the identification of patients at high risk of events.^{406–408} Left ventricular function is the strongest predictor of long-term survival; a patient with an LVEF of $<50\%$ is already at high risk for all-cause and cardiovascular death.^{409,410}

Although the diagnostic value of an exercise ECG is limited, the occurrence of ST-segment depression at a low workload combined with exertional symptoms (angina or dyspnoea), low exercise capacity, complex ventricular ectopy, or other arrhythmias and abnormal BP response are markers of a high risk of cardiac mortality.^{411–414}

High plaque burden and coronary stenoses are well-known prognostic markers. The ISCHEMIA trial using a cut-off of 70% stenosis on CCTA³¹⁷ confirms the very old observations of the Coronary Artery Surgery Study¹⁸² that the prognosis of obstructive CAD-related CCS is mainly determined by the number of $>70\%$ obstructed coronary arteries or by the presence of a left main stenosis (using for the latter a cut-off of $>50\%$ diameter stenosis on coronary angiography).³¹⁷ More recently, the classical paradigm that the severity of stenoses and the number of diseased vessels are the main determinants of prognosis has been challenged by *post hoc* analyses of the SCOT-HEART trial and other CCTA-based

registries showing that plaque burden and presence of adverse plaque characteristics, especially low-attenuation plaque, are the strongest predictors of fatal and non-fatal MI above the classical risk factors, including stenosis severity.^{210,415–417} These findings emphasize a major advantage of anatomical imaging by CCTA as an initial test in selected patients, allowing the assessment of severity and extent of obstructive CAD as well as coronary plaque characteristics.

Regarding the prognostic impact of inducible myocardial ischaemia by functional stress imaging, the evidence remains conflicting. While there are extensive data from large observational studies^{315,418–425} consistently demonstrating a robust prognostic value conferred by the extent of inducible ischaemia as detected by functional imaging (e.g. $\geq 3/16$ abnormal segments at stress echocardiography, $\geq 10\%$ LV ischaemia at nuclear or magnetic resonance perfusion imaging, or decreased hyperaemic flow or flow reserve at quantitative PET imaging), *post hoc* analyses of the randomized COURAGE^{426,427} and ISCHEMIA³¹⁷ trials showed that only CAD severity, but not ischaemia severity, was independently predictive of long-term mortality and MI risk. These discrepancies may be explained by selection and entry biases between registries and RCTs.⁴²⁸ Registries typically report on all-comer populations with suspected CCS referred for diagnostic testing and/or revascularization, representing the real-life scenario. RCTs usually include only a very selected group of patients, and the external applicability of their findings is always open for debate. As COURAGE and ISCHEMIA selectively included only patients with functionally moderate or severe myocardial ischaemia but without any information on CAD anatomical severity, it becomes harder to demonstrate a prognostic effect of myocardial ischaemia, and the anatomical burden becomes the prominent prognostic factor. The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial, which included patients more representative of an all-comer population, demonstrated that CCTA, mainly by detecting non-obstructive CAD, outperformed functional testing in predicting outcomes, emphasizing the prognostic significance of imaging coronary atherosclerosis beyond myocardial ischaemia.²⁰⁸ However, adding the Framingham Risk Score to the functional test result improved its prognostic value, making the difference with anatomical testing insignificant. Both modalities are thus equivalent for detecting CCS symptoms and predicting outcomes when considering risk factors.

Besides imaging coronary atherosclerosis, the additional benefit of ICA is the ability to perform intracoronary pressure measurements. While FFR of ≤ 0.8 and iFR of ≤ 0.89 have been associated with a higher risk of vessel-related cardiovascular events, it is important to remember that a lower FFR/iFR reflects more profound ischaemia in the vessel territory and is associated with a progressive and proportional increase in risk.^{318,319} A similar observation has been made with FFR-CT.⁴⁰¹ It has also been shown that for any given FFR value, a more proximal lesion is associated with more extensive ischaemia and an increased risk of a clinical event.⁴²⁹ In addition, global FFR, summing the coronary pressure collected in each of the three main coronary vessel territories as a single patient-related index (normal value of global FFR = $1 + 1 + 1 = 3$), can appreciate overall cardiovascular risk; patients with a borderline FFR but with a global FFR of < 2.72 showed a significantly increased risk compared with higher global-FFR patients.^{430,431} One of the main limitations of such a global integrative approach based on invasive coronary pressure is that it requires advancing a pressure wire in each of the three coronary arteries, which is not often performed³⁴¹ and is not recommended as a routine, based on the RIPCORD2³⁴⁷ and FUTURE results.³⁴⁶ Recent methods using 3-dimensional image reconstruction and computational fluid dynamics enable FFR estimation with CCTA⁴³² or with 'wire-less' invasive coronary

angiography.^{433,434} This allows a less invasive, easier and more accurate global FFR calculation, provided imaging is of sufficiently good quality.^{369–371}

In summary, when assessing event risk, clinicians should choose an integrative approach, considering risk factors, comorbidities, LV dysfunction, the severity of myocardial ischaemia, the number of functionally significantly stenotic coronary arteries, and the coronary plaque burden and characteristics, as all of these are likely interrelated factors that affect overall prognosis.

Recommendation Table 14 — Recommendations for definition of high risk of adverse events (see also Evidence Table 14)

Recommendations	Class ^a	Level ^b
An initial stratification of risk of adverse events is recommended based on basic clinical assessment (e.g. age, ECG, anginal threshold, diabetes, CKD, LVEF). ^{406–408}	I	B
The use of one or more of the following test results is recommended to identify individuals at high risk of adverse events: ⁴⁰⁵ <ul style="list-style-type: none"> • exercise ECG: <ul style="list-style-type: none"> ◦ Duke Treadmill Score < -10,¹⁹¹ • stress SPECT or PET perfusion imaging: <ul style="list-style-type: none"> ◦ area of ischaemia $\geq 10\%$ of the LV myocardium,^{287,315,422,423,435} • stress echocardiography: <ul style="list-style-type: none"> ◦ ≥ 3 of 16 segments with stress-induced hypokinesia or akinesia;⁴³⁵ • stress CMR: <ul style="list-style-type: none"> ◦ ≥ 2 of 16 segments with stress perfusion defects or ≥ 3 dobutamine-induced dysfunctional segments;⁴³⁵ • CCTA: <ul style="list-style-type: none"> ◦ left main disease with $\geq 50\%$ stenosis, three-vessel disease with $\geq 70\%$ stenosis, or two-vessel disease with $\geq 70\%$ stenosis, including the proximal LAD or³¹⁷ one-vessel disease of the proximal LAD with $\geq 70\%$ stenosis and FFR-CT ≤ 0.8. 	I	B
In individuals at high risk of adverse events (regardless of symptoms), ICA—complemented by invasive coronary pressure (FFR/iFR) when appropriate—is recommended, with the aim of refining risk stratification and improving symptoms and cardiovascular outcomes by revascularization. ^{318,319}	I	A

CCTA, coronary computed tomography angiography; CKD, chronic kidney disease; CMR, cardiac magnetic resonance; CT, computed tomography; ECG, electrocardiogram; FFR, fractional flow reserve; FFR-CT, CCTA-derived FFR; ICA, invasive coronary angiography; iFR, instantaneous wave-free ratio; LAD, left anterior descending; LV, left ventricular; LVEF, left ventricular ejection fraction; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

^aClass of recommendation.

^bLevel of evidence.

3.4. STEP 4: Initial therapy

Initial therapy frequently starts during the diagnostic process. In individuals with a high suspicion of CCS, sublingual nitroglycerine is frequently prescribed to treat anginal pain symptoms. Rapid relief within 1 or 2

min of chest discomfort after sublingual nitroglycerine increases the likelihood of CCS. Patients may be advised to refrain from strenuous physical activities before the diagnostic process is completed and should be instructed what to do if prolonged anginal chest pain indicative of acute MI arises.

Guideline-directed management and therapy are started during or after the diagnostic process is concluded. The main goals of treating CCS are to improve both QoL and life expectancy. This involves various interventions to reduce the risk of (i) cardiac mortality, (ii) non-fatal ischaemic events, (iii) progression of epicardial and/or microvascular chronic coronary disease, and (iv) symptoms and limitations caused by CCS. When deciding on treatment options, it is important to consider patient preferences, possible complications of procedures or medications, and healthcare costs. In shared decision-making with patients, clinicians should clearly explain that certain treatments can alleviate symptoms, while others can reduce the likelihood of ischaemic events.

4. Guideline-directed therapy

4.1. Patient education, lifestyle optimization for risk-factor control, and exercise therapy

4.1.1. Patient education

In CCS patients, education on risk factors and symptom management is associated with improvements in knowledge, self-care, and patient empowerment, and may improve health-related QoL.⁴³⁶ In addition, education can facilitate long-term adherence to lifestyle interventions.^{437,438} Educational programmes—either alone or as a core component of multidisciplinary care management programmes—promote patients' awareness of their condition and the rationale for lifestyle interventions. However, awareness of CVD risk factors through education alone might be insufficient for adoption of healthy behaviour.⁴³⁹ Therefore, self-care programmes are needed to enable patients to have a major role in coping with their condition and accepting their prescribed treatment.^{440,441} Elements in patient education include (modifiable) risk factors in relation to individual cardiovascular risk, since risk perception is an integral part of many major health behaviour theories, ultimately leading to modification of human habits.^{441,442}

Information on benefits of risk-factor control on recurrence risk, disease progression, complications, and overall survival should be discussed. The format, time horizon, and outcome used for risk estimation influence patient perceptions and should be considered when designing risk communication tools.^{443–445}

Lifelong education for patient-centred information and problem-based learning is superior to home-sent information in improving risk-factor control in the long term.^{438,444} Refer to Section 6.2.1 for further guidance on patient education.

4.1.2. Key lifestyle interventions for risk-factor control

Reducing CVD risk at the individual level begins with effective information on risk and anticipated risk reduction by treatment. Risk algorithms are available for use in clinical practice by means of interactive tools online. The use of the Smart risk score (U-prevent.com) is suggested by the European Association of Preventive Cardiology for risk estimation in patients with previous CVD.⁴⁴⁶ Ideally, patients are made aware of

their individual risks and the potential benefit of prevention treatments and then actively engaged in managing their disease. Treatment goals are communicated using a patient-centred approach (Table 7).

Table 7 Practical advice on lifestyle counselling and interventions

Topic	Recommendation and treatment goals in patients with established CCS
Lifestyle counselling	
Immunization	<ul style="list-style-type: none"> Vaccination against influenza, pneumococcal disease and other widespread infections, e.g. COVID-19
Sleep quality	<ul style="list-style-type: none"> Treat sleep-related breathing disorders
Sexual activity	<ul style="list-style-type: none"> Males and females: low risk for stable patients who are not symptomatic at low-to-moderate activity levels Males: PDE-5 inhibitors are generally safe, not to be taken in combination with nitrate medications because of risk of severe hypotension
Psychosocial aspects	<ul style="list-style-type: none"> Avoid psychosocial stress Treat depression and anxiety by psychological or pharmacological interventions
Environment/pollution	<ul style="list-style-type: none"> Avoid passive smoking Reduce environmental noise Avoid exposure to air pollution
Lifestyle interventions for risk-factor control	
Smoking and substance abuse	<ul style="list-style-type: none"> Use pharmacological and behavioural strategies to assist in smoking cessation Avoid e-cigarettes Abstain from substance abuse
Obesity and being overweight	<ul style="list-style-type: none"> Obtain and maintain a healthy weight (BMI 18.5–25 kg/m²) Reduce weight through recommended energy intake and increased physical activity and through pharmacological/surgical interventions in selected patients
Hyperlipidaemia	<ul style="list-style-type: none"> Ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction in LDL-C vs. baseline is recommended
Diabetes	<ul style="list-style-type: none"> HbA1c < 7.0% (53 mmol/mol)
Arterial hypertension	<ul style="list-style-type: none"> SBP 120–129 mmHg, provided the antihypertensive treatment is well tolerated
Diet and alcohol consumption	<ul style="list-style-type: none"> Limit alcohol consumption to <100 g/week Diet high in vegetables, fruit, and wholegrains (Mediterranean diet) Limit saturated fat to <10% of total calorie intake
Physical activity and exercise	<ul style="list-style-type: none"> 30–60 min moderate activity, >5 days/week Reduce sedentary time and engage in at least light activity throughout the day

BMI, body mass index; CCS, chronic coronary syndrome; COVID-19, coronavirus disease 2019; HbA1c, glycated haemoglobin; LDL-C, low-density lipoprotein cholesterol; PDE-5, phosphodiesterase-5; SBP, systolic blood pressure.

4.1.2.1. Smoking and substance abuse

Smoking cessation in CCS patients improves prognosis, with a reported 36% risk reduction of premature death in those who quit compared with those who continue to smoke.⁴⁴⁷ Measures to promote smoking cessation include brief advice, counselling and behavioural interventions, and pharmacological therapy.^{448,449} Patients should also avoid passive smoking.

Drug support to assist in smoking cessation should be considered in all smokers who are ready to undertake this action. Nicotine-replacement therapy, bupropion, or varenicline are effective,^{450,451} and are not linked to an increase in MACE.⁴⁵²

The use of electronic cigarettes (e-cigarettes), as an alternative to conventional cigarettes, should be discouraged because they are not harm-free.⁴⁵³ Newer devices deliver higher nicotine contents, and e-cigarettes emit other constituents, such as carbonyls, and fine and ultrafine particulates.⁴⁵⁴ Evidence from several studies indicates that acute inhalation of e-cigarettes leads to negative changes in vascular endothelial function.^{453,454} E-cigarettes should only be considered to aid tobacco cessation alongside a formal tobacco cessation programme.^{453,455,456}

Various substances, including cocaine, opioids, and marijuana can have adverse effects on the cardiovascular system and have a potential for drug–drug interactions with cardiovascular medication.^{457–459} Single-question screening for unhealthy drug use has been validated in primary care and can identify individuals requiring counselling on adverse cardiovascular effects.⁴⁶⁰

4.1.2.2. Weight management

In a population-based study, lifetime risk of incident CVD, and cardiovascular morbidity and mortality, were higher in those who were overweight or obese compared with those with a normal BMI (18.5–24.9 kg/m²).⁴⁶¹

Compared with normal BMI, among middle-aged men and women, competing hazard ratios (HR) for incident CVD were 1.21 [95% confidence interval (CI), 1.14–1.28] and 1.32 (95% CI, 1.24–1.40), respectively, for overweight (BMI of 25.0–29.9 kg/m²), 1.67 (95% CI, 1.55–1.79) and 1.85 (95% CI, 1.72–1.99) for obesity (BMI of 30.0–39.9 kg/m²), and 3.14 (95% CI, 2.48–3.97) and 2.53 (95% CI, 2.20–2.91) for morbid obesity (BMI of ≥40.0 kg/m²). Obesity was associated with a shorter overall lifespan, and being overweight was associated with developing CVD at an earlier age.⁴⁶¹ In subjects with CAD, intentional weight loss is associated with a significantly lower risk of adverse clinical outcomes,⁴⁶² and has beneficial effects on risk-factor control and QoL.⁴⁶³ Healthy diets with energy intake limited to the amount needed to obtain and maintain a healthy weight (BMI of 18.5–25 kg/m²), and combined with increasing physical activity, are recommended for weight management.¹⁶ If weight targets are not reached, pharmacological treatment with glucagon-like peptide-1 (GLP-1) receptor agonists may be considered for further weight reduction (Section 4.3.4). In patients without diabetes, the STEP8 trial showed a significant reduction in weight after 68 weeks with either semaglutide (mean weight change of –15.8%; 95% CI, –17.6% to –13.9%) or liraglutide (mean weight change of –6.4%; 95% CI, –8.2% to –4.6%) compared with placebo (–1.9%; 95% CI, –4.0% to 0.2%).⁴⁶⁴ The double-blind, placebo-controlled Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial showed a significant reduction in the incidence of cardiovascular death, MI, or stroke (HR 0.80; 95% CI, 0.72–0.90) in patients with pre-existing CVD who were overweight or obese, but without diabetes, treated with weekly subcutaneous semaglutide.⁴⁶⁵

The SURMOUNT-1 (Efficacy and Safety of Tirzepatide Once Weekly in Participants Without Type 2 Diabetes Who Have Obesity or Are Overweight With Weight-Related Comorbidities: A Randomized,

Double-Blind, Placebo-Controlled Trial) trial showed a dose-dependent weight-loss benefit (mean weight change of up to –20.9%; 95% CI, –21.8% to –19.9%) with tirzepatide, a combined glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, compared with placebo in obese adults without diabetes over 72 weeks,⁴⁶⁶ a dose effect that was confirmed in the SURMOUNT-2 trial.⁴⁶⁷ Bariatric surgery in severe obesity appears to be a safe and effective intervention for further weight loss in CCS patients.⁴⁶⁸

Cardiac rehabilitation programmes should include weight-loss interventions to reach a healthy weight as a specific component. The incremental value of telehealth interventions and pharmacological interventions need full consideration in secondary prevention.⁴⁶⁹

4.1.2.3. Diet and alcohol

Dietary habits influence cardiovascular risk, mainly through risk factors such as lipids, BP, body weight, and DM. It is recommended to adopt a Mediterranean or similar diet to lower the risk of CVD, as described in the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice.¹⁶ If alcohol is consumed, it should be limited to <100 g/week or 15 g/day, since alcohol intake of >100 g/week is associated with higher all-cause and other CVD mortality in large individual-data meta-analyses.⁴⁷⁰ A recent genetic analysis showed that the causal association between light-to-moderate levels of alcohol intake and lower cardiovascular risk is possibly mediated by confounding lifestyle factors, therefore questioning the previously observed cardioprotective role of light alcohol use.⁴⁷¹

4.1.2.4. Mental health

Psychosocial stress, depression, and anxiety are associated with worse cardiovascular outcomes, and make it difficult for patients to make positive changes to their lifestyles or adhere to a therapeutic regimen. Therefore, assessment for psychosocial risk factors is recommended in secondary prevention.¹⁶ Clinical trials have shown that psychological (e.g. counselling and/or cognitive behavioural therapy) and pharmacological interventions have a beneficial effect on depression, anxiety, and stress, with some evidence of a reduction in cardiac mortality and events compared with placebo (see Section 6.1.2).⁴⁷²

4.1.2.5. Physical activity and sedentary behaviour

Physical activity reduces the risk of many adverse health outcomes and risk factors in all ages and both sexes. There is an inverse relationship between moderate-to-vigorous physical activity and all-cause mortality, cardiovascular mortality, and atherosclerotic cardiovascular disease (ASCVD).⁴⁷³ The reduction in risk continues across the full range of physical activity volumes, and the slope of risk decline is steepest for the least active individuals.⁴⁷⁴ Adults are recommended to perform at least 150–300 min per week of moderate-intensity physical activity, or 75–150 min of vigorous-intensity physical activity, or an equivalent combination of both, spread throughout the week.⁴⁷³ Additional benefits are gained with even more physical activity.⁴⁷⁵ Practising physical activity should still be encouraged in individuals unable to meet the minimum. In sedentary individuals, a gradual increase in activity level is recommended.⁴⁷⁶ Physical activity can be incorporated flexibly, either daily or limited to specific days. Activity patterns limited to 1–2 sessions per week but meeting recommended levels of physical activity have been shown to reduce all-cause mortality (HR 0.66; 95% CI, 0.62–0.72), CVD mortality (HR 0.60; 95% CI, 0.52–0.69), and cancer mortality (HR 0.83; 95% CI, 0.73–0.94) when compared with inactive participants.⁴⁷⁷ Physical activity accumulated in bouts of even <10 min is associated with favourable outcomes, including mortality.⁴⁷⁸

High levels of time spent sedentary is associated with an increased risk for several major chronic diseases and mortality.⁴⁷⁹ For physically

inactive adults, light-intensity physical activity, even as little as 15 min a day, is likely to produce benefits.⁴⁷⁹

4.1.3. Exercise therapy

Exercise training, either alone or in the context of multidisciplinary, exercise-based cardiac rehabilitation, leads to reduction in hospitalizations, adverse cardiovascular events, mortality rates, and improved CVD risk profile in patients with ASCVD.^{480–483} Therefore, exercise is a therapy that should be offered to every CCS patient in the setting of secondary disease prevention.¹⁶

Exercise training should be individually prescribed according to the FITT (frequency, intensity, time, type) model for aerobic and resistance training.⁴⁸⁴

For aerobic training (walking, jogging, cycling, swimming, etc.), an exercise frequency of at least 3 days/week, preferably 6–7 days/week, at moderate or moderate-to-high intensity is recommended. Relative intensity is determined based on an individual's maximum (peak) effort, e.g. percentage of cardiorespiratory fitness (%VO₂ max), percentage of maximum (peak) heart rate (%HRmax) or ventilatory thresholds (VT1 and VT2).⁴⁸⁵ To date, there is insufficient evidence to promote high-intensity interval training over moderate-intensity continuous training; nevertheless, optimizing total energy expenditure (either by increasing intensity or total exercise volume) is related to greater favourable changes in cardiovascular risk and physical fitness.⁴⁸⁶ Moderate-intensity continuous training is the most feasible and cost-effective aerobic training modality for patients with CCS. High-intensity interval training can be prescribed in selected patients for specific targets of intervention (e.g. to increase VO₂ peak).⁴⁸⁵

Resistance exercise in addition to aerobic training is associated with lower risks of total cardiovascular events and all-cause mortality.¹⁶ The suggested prescription is one to three sets of 8–12 repetitions, at the intensity of 6%–80% of the individual's one-repetition maximum, at a frequency of at least 2 days per week, using a variety of 8–10 different exercises involving each major muscle group.^{16,484}

Exercise is contraindicated in patients with refractory/unstable angina and other high-risk cardiovascular conditions (e.g. high-grade arrhythmias, decompensated HF, severe aortic dilatation, active thromboembolic disease). In non-cardiac unstable conditions (e.g. active infection, uncontrolled diabetes, end-stage cancer, chronic obstructive pulmonary disease exacerbation), exercise is contraindicated. Maintenance of the prescribed exercise regimen is crucial. According to a meta-regression analysis, no single exercise component predicts mortality outcomes, whereas the largest reductions in total and cardiovascular mortality were seen in post-cardiac rehabilitation patients with the highest adherence rate.⁴⁸⁷ In addition, continuation of the exercise therapy (Phase III cardiac rehabilitation) is recommended as it will result in increased/maintained functional capacity, QoL, and physical activity levels.⁴⁸⁸

Sharing decision-making and offering a personalized prescription, based on the patient's preferences (self-selected training) and abilities (age, concomitant diseases, leisure and working habits, logistical restraints), is recommended to increase long-term adherence.⁴⁸⁹ In addition, smartphone applications⁴⁹⁰ and wearable activity trackers⁴⁹¹ may assist in long-term adherence to physical activity goals and exercise therapy (see Section 6.2.1.3).⁴⁹²

Home-based cardiac rehabilitation with or without telemonitoring may increase participation and be as effective as centre-based cardiac rehabilitation.⁴⁹³ Telehealth interventions are more effective than no intervention and may also complement conventional cardiac rehabilitation.^{494,495} Also, mobile device-based healthcare (mHealth) delivery

through smartphones may be as effective as traditional centre-based cardiac rehabilitation, showing significant improvements in health-related QoL.⁴⁹⁶

Small, single-centre studies on exercise training in patients with INOCA show that it is feasible and improves cardiorespiratory function and QoL.⁴⁹⁷ Larger trials are needed to determine the optimal rehabilitation protocols and define its long-term benefits.

Recommendation Table 15 — Recommendations for cardiovascular risk reduction, lifestyle changes, and exercise interventions in patients with established chronic coronary syndrome (see also Evidence Table 15)

Recommendations	Class ^a	Level ^b
An informed discussion on CVD risk and treatment benefits tailored to individual patient needs is recommended. ¹⁶	I	C
Multidisciplinary behavioural approaches to help patients achieve healthy lifestyles, in addition to appropriate pharmacological management, are recommended. ^{484,498–503}	I	A
A multidisciplinary exercise-based programme to improve cardiovascular risk profile and reduce cardiovascular mortality is recommended. ^{480–482}	I	A
Aerobic physical activity of at least 150–300 min per week of moderate intensity or 75–150 min per week of vigorous intensity and reduction in sedentary time are recommended. ^{16,473,478,479}	I	B
Home-based cardiac rehabilitation and mobile health interventions should be considered to increase patients' long-term adherence to healthy behaviours, and to reduce hospitalizations or cardiac events. ^{480,493,494}	IIa	B

CVD, cardiovascular disease.

^aClass of recommendation.

^bLevel of evidence.

4.2. Antianginal/anti-ischaemic medication

4.2.1. General strategy

In patients with CCS, antianginal medical therapy aims to control symptoms while ensuring acceptable tolerability and patient adherence. Several factors should be considered for the selection of antianginal medical therapy. First, there is no robust evidence from direct comparisons that some antianginal drugs are more effective than others for improving symptoms.^{504,505} There have been no large randomized trials comparing head-to-head the historically first approved antianginal medications [i.e. beta-blockers or calcium channel blockers (CCBs)] vs. newer anti-ischaemic drugs (ivabradine, nicorandil, ranolazine, trimetazidine);^{504,506} the latter have been tested in smaller trials assessing non-inferiority compared with beta-blockers⁵⁰⁷ or CCBs,⁵⁰⁸ or in a larger trial as add-on therapy with a background of beta-blockers and/or CCBs.^{508,509} Moreover, there is no evidence that any antianginal medication may improve long-term cardiovascular outcomes, except beta-blockers if administered within 1 year after an acute MI.⁵¹⁰ Second, many patients require a combination of anti-ischaemic drugs to adequately control symptoms.⁵¹¹ It remains unclear whether upfront combination therapy with two antianginal drugs is preferable to monotherapy, or which combinations of antianginal classes may be better

than others for improving angina symptoms. Third, in any given patient, myocardial ischaemia and angina symptoms may be caused by various underlying pathophysiological mechanisms, alone or in combination;^{6,512} these may include obstruction of epicardial coronary arteries, vasospasm, and endothelial/microvascular dysfunction. Based on their mechanisms of action, different classes of antianginal drugs may be preferable (as initial therapy or as part of combination therapy) for patients with myocardial ischaemia of predominantly obstructive, vasospastic, or microvascular origin.⁵¹³

The current empirical paradigm for the selection of antianginal medical therapy has consisted of a hierarchical, stepwise approach including first-line (beta-blockers, CCBs) and second-line drugs (long-acting nitrates, nicorandil, ranolazine, ivabradine, trimetazidine).^{1,514} This task force reinforces the concept that medical therapy for symptom control in CCS should be tailored to each patient's haemodynamic profile (BP, heart rate), comorbidities (particularly presence of HF), concomitant medications with potential drug interactions, and preferences, also taking into account the pathophysiological basis of myocardial ischaemia in each patient, as well as local availability of different drugs.^{515,516} For many patients with CCS, initial drug therapy should include a beta-blocker and/or a CCB. Other antianginal drugs (long-acting nitrates, ivabradine, nicorandil, ranolazine, trimetazidine) can be added on top

of a beta-blocker and/or a CCB, or as a part of initial combination therapy in appropriately selected patients (Figure 9).

Regardless of the initial strategy, response to initial antianginal therapy should be reassessed, and treatment should be adapted if adequate angina control is not achieved or if the initial treatment is poorly tolerated.

A review of the antianginal agents that can be used in the medical treatment of CCS can be found in the [Supplementary data](#).

4.2.2. Beta blockers

Beta-blockers can be used for symptomatic relief of angina, or to improve prognosis in some patients with CCS. If used for antianginal purposes, the aim should be to lower resting heart rate to 55–60 beats per minute (b.p.m.).^{517,518}

Beyond improving symptoms, the clinical benefit of beta-blockers in patients with CAD without prior MI and with normal LVEF is largely unknown in the absence of evidence from RCTs. The main findings of some observational studies addressing this issue are summarized in the [Supplementary data](#).

The clinical benefit of beta-blockers in post-ACS patients with reduced LVEF is supported by solid evidence.^{519–521} However, there are no large RCTs supporting the prescription of beta-blockers after uncomplicated ACS in patients with LVEF >40%.⁵²² The evidence provided by

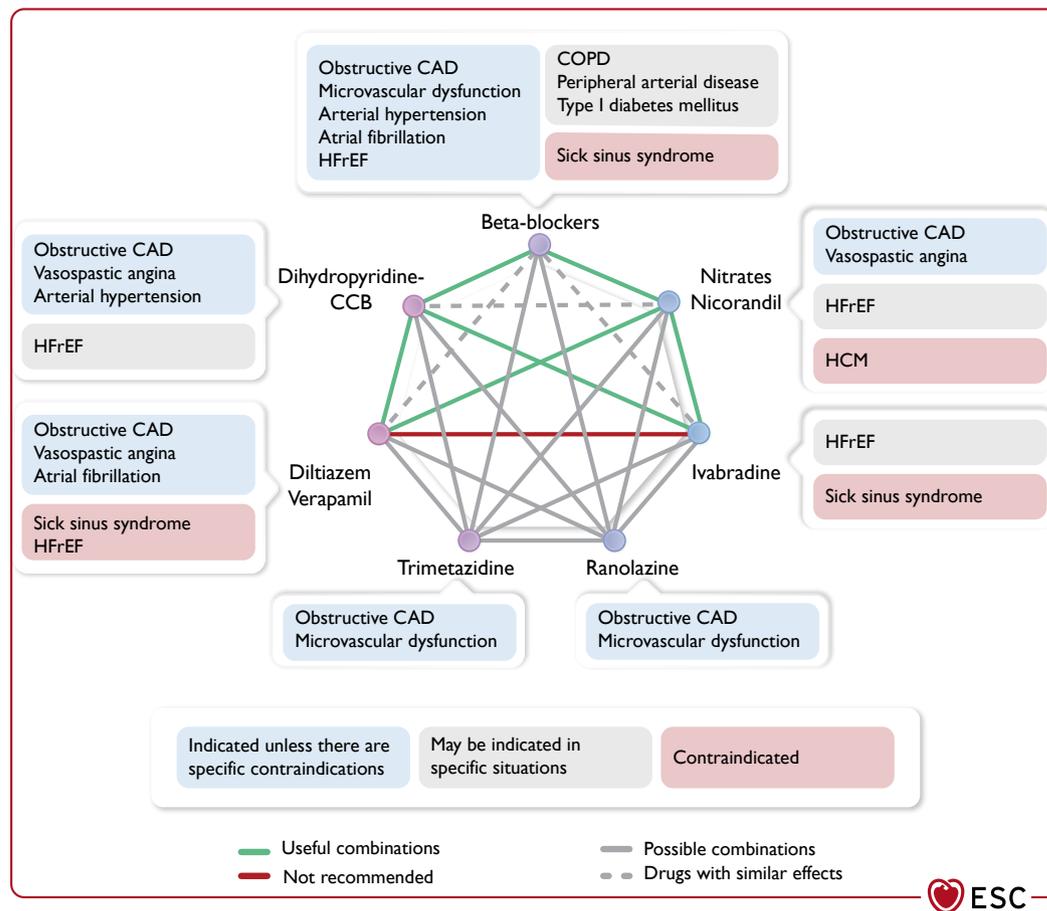


Figure 9 Possible combinations of antianginal drugs. CAD, coronary artery disease; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; HCM, hypertrophic cardiomyopathy; HFrEF, heart failure with reduced ejection fraction. The schematic shows useful combinations (green lines), combinations that are not recommended (red lines), possible combinations (solid blue lines), and drugs with similar effects (blue dashed lines), which can be combined in selected indications: HFrEF (ivabradine and beta-blocker), atrial fibrillation (diltiazem/verapamil and beta-blocker), vasospastic angina (dihydropyridine CCB and nitrates). Modified from Davies *et al.*⁵⁵⁵.

observational studies and meta-analyses is conflicting (some suggest an association between beta-blockers and better clinical outcomes, whereas others show a lack of association).^{521,523–526} There have been only two open-label trials testing the efficacy of beta blockers in post-MI patients (NCT03278509 and NCT01155635), though both trials were underpowered to yield solid conclusions.⁵²⁷ To further elucidate the benefit of beta-blockers in this clinical scenario, three European pragmatic, prospective, large-scale RCTs recruiting post-ACS patients with preserved LVEF to receive beta-blockers or control treatment are currently underway.^{522,528–530}

The duration of beta-blocker therapy, in the long run, is a matter of debate, particularly in patients with prior MI and preserved LVEF.⁵³¹ Evidence from RCTs assessing beta-blockers rarely goes beyond a few years of follow-up, but patients are often given continuous treatment up to old age.⁵³¹ Observational data are also conflicting in this regard. One study has suggested that the clinical benefit of beta-blockers might be restricted to the first year after the index event, showing that their discontinuation at 1 year was not associated with higher 5-year mortality.⁵³² In contrast, a Swedish study starting the follow-up 1 year after the ACS episode has shown a lack of association between the use of beta-blockers and a composite of all-cause mortality, MI, unscheduled revascularization, or hospitalization for HF.⁵³³ Another study has shown that the discontinuation of beta-blockers beyond 1 year after acute MI was associated with an increased risk of a composite of death or readmission for ACS, but not of all-cause mortality.⁵³⁴ The impact of beta-blocker withdrawal 6–12 months after uncomplicated ACS in patients with LVEF ≥40% is being tested in two large-scale RCTs (NCT03498066, NCT04769362).⁵³⁵

Recommendation Table 16 — Recommendations for antianginal drugs in patients with chronic coronary syndrome (see also Evidence Table 16)

Recommendations	Class ^a	Level ^b
General strategy		
It is recommended to tailor the selection of antianginal drugs to the patient’s characteristics, comorbidities, concomitant medications, treatment tolerability, and underlying pathophysiology of angina, also considering local drug availability and cost.	I	C
Selection of antianginal medication		
Short-acting nitrates are recommended for immediate relief of angina. ^{536,537}	I	B
Initial treatment with beta-blockers and/or CCBs to control heart rate and symptoms is recommended for most patients with CCS. ^{c 518,538}	I	B
If anginal symptoms are not successfully controlled by initial treatment with a beta-blocker or a CCB alone, the combination of a beta-blocker and a DHP-CCB should be considered, unless contraindicated. ^{505,538,539}	IIa	B
Long-acting nitrates or ranolazine should be considered as add-on therapy in patients with inadequate control of symptoms while on treatment with beta-blockers and/or CCBs, or as part of initial treatment in properly selected patients. ^{d 513,540}	IIa	B

Continued

When long-acting nitrates are prescribed, a nitrate-free or low-nitrate interval should be considered to reduce tolerance. ⁵⁴⁰	IIa	B
Ivabradine should be considered as add-on antianginal therapy in patients with left ventricular systolic dysfunction (LVEF <40%) and inadequate control of symptoms, or as part of initial treatment in properly selected patients. ^{541,542}	IIa	B
Nicorandil or trimetazidine may be considered as add-on therapy in patients with inadequate control of symptoms while on treatment with beta-blockers and/or CCBs, or as part of initial treatment in properly selected patients. ^{543–550}	IIb	B
Ivabradine is not recommended as add-on therapy in patients with CCS, LVEF >40%, and no clinical heart failure. ⁵⁰⁹	III	B
Combination of ivabradine with non-DHP-CCB or other strong CYP3A4 inhibitors is not recommended. ⁵⁵¹	III	B
Nitrates are not recommended in patients with hypertrophic cardiomyopathy or in co-administration with phosphodiesterase inhibitors. ^{552,553}	III	B

CCB, calcium channel blocker; CCS, chronic coronary syndrome; CYP3A4, cytochrome P450 3A4; DHP, dihydropyridine; DM, diabetes mellitus; LVEF, left ventricular ejection fraction.

^aClass of recommendation.

^bLevel of evidence.

^cThese drugs may require caution or may be contraindicated in certain patients with low BP (beta-blockers and DHP-CCB), DM (beta-blockers), atrioventricular conduction disorders (beta-blockers and non-DHP-CCB), chronic obstructive pulmonary disease (non-cardioselective beta-blockers).

^dConsideration for initial therapy: ivabradine, nicorandil, long-acting nitrates, ranolazine, or trimetazidine for patients with intolerance or contraindications to beta-blockers and/or CCBs; ranolazine and trimetazidine for patients with microvascular angina; nicorandil or nitrates for patients with coronary artery spasm. The drugs are listed in alphabetical order.

4.2.3. Combination therapy

The aim of antianginal medications is to ensure adequate relief of angina symptoms in patients with CCS, in part independently of their effect or lack of effect on MACE. Initiation of monotherapy, with subsequent escalation to a combination of antianginal drugs in the case of inadequate relief of symptoms, is a reasonable approach. In this context, the empirical approach of starting with a beta-blocker can be recommended in many patients with CCS, unless there are contraindications or other drugs are more suitable instead of beta-blockers (e.g. patients with low heart rate and/or BP). If a combination of antianginal drugs is required, the selection of the most appropriate drugs should be individualized and determined by the haemodynamic profile, comorbidities, and tolerability. The combination of a beta-blocker with a dihydropyridine CCB is appropriate for most patients, whereas the addition of other antianginal drugs (long-acting nitrates, ranolazine, nicorandil, trimetazidine, or ivabradine in patients with LV systolic dysfunction) can be considered when treatment with a beta-blocker and/or CCB is contraindicated or poorly tolerated, or when angina symptoms are inadequately controlled.

The following points should additionally be kept in mind: (i) beta-blockers are not indicated in the presence of sick sinus syndrome or

atrioventricular conduction disorders,⁵⁵⁴ and should be used with caution in patients with PAD and chronic obstructive pulmonary disease; (ii) CCBs require caution in patients with heart failure with reduced ejection fraction (HFrEF);⁵²⁶ (iii) ivabradine should not be combined with non-dihydropyridine CCBs (verapamil or diltiazem); and (iv) ranolazine and trimetazidine are reasonable options as part of antianginal combination therapy in patients with low heart rate and/or BP.

4.3. Medical therapy for event prevention

Prevention of coronary ischaemic events is based on lowering the risk of coronary artery occlusion and consequent ACS. Medical event-preventing therapies include antithrombotic, lipid-lowering, anti-RAAS (renin–angiotensin–aldosterone system), anti-inflammatory, and metabolic-acting agents.

4.3.1. Antithrombotic drugs

The standard antithrombotic treatment of patients with epicardial atherosclerotic CAD is single antiplatelet therapy (SAPT), typically with aspirin. In patients with ACS or post-PCI, standard treatment is dual antiplatelet therapy (DAPT) with aspirin and an oral P2Y₁₂ inhibitor, for a duration of 12 months after ACS (with or without PCI)⁶⁵ or 6 months after CCS-PCI.^{1,556} Thus, in ACS or CCS-PCI patients, DAPT is usually replaced by SAPT at some point. Several recent trials have investigated shortened DAPT durations and P2Y₁₂ inhibitor monotherapy post-PCI to reduce the risk of bleeding. On the other hand, in CCS patients with persistently high ischaemic risk and low bleeding risk, extended intensified antithrombotic therapy should be considered. Ultimately, the choice and duration of antithrombotic regimens largely depend on the delicate balance between each individual's ischaemic and bleeding risks.

The mechanisms of action of the most commonly used antithrombotic drugs in CCS patients are depicted in [Figure 10](#).

4.3.1.1. Antiplatelet drugs

For details on antiplatelet drugs, please see [Supplementary data, Table S1](#).

4.3.1.1.1. Aspirin monotherapy. Low-dose aspirin (75–100 mg once daily) is the traditional drug of choice in patients with CCS, with or without prior MI.^{557,558} In an individual-patient data meta-analysis of secondary prevention trials (43 000 patient-years), aspirin vs. no aspirin significantly reduced the combined risk of non-fatal MI, non-fatal ischaemic stroke, or death from vascular causes [from 8.2% to 6.7% per year ($P < .0001$), with relative risk (RR) reductions of 31%, 22%, and 9%, respectively], translating into 15 fewer fatal and non-fatal serious vascular events for every 1000 patients treated for 1 year.⁵⁵⁸ Aspirin allocation increased major gastrointestinal (GI) and extracranial bleeds, from 0.07% to 0.10% per year ($P < .0001$), with a non-significant increase in haemorrhagic stroke but reductions of about a fifth in total stroke (from 2.54% to 2.08% per year, $P = .002$) and in coronary events (from 5.3% to 4.3% per year, $P < .0001$).

Thus, for secondary prevention, the reduction of ischaemic events with aspirin outweighs serious bleeding events.^{557,558} There is no evidence of different aspirin effects in women and men.^{558,559} Daily aspirin doses of 75–100 mg seem to be as effective as higher doses for long-term treatments.^{558–561}

4.3.1.1.2. Oral P2Y₁₂ inhibitor monotherapy.

4.3.1.1.2.1. Clopidogrel monotherapy. In addition to the cyclooxygenase-I pathway inhibited by aspirin, the platelet P2Y₁₂ receptor also plays a pivotal role in arterial thrombus formation and is the target for three oral platelet inhibitors: clopidogrel, prasugrel, and ticagrelor. The relative efficacy and safety of clopidogrel compared with aspirin for secondary prevention in CCS patients has been tested in multiple randomized trials that, taken together, have involved over 29 000 patient-years.^{562,563}

In an overall population of 19 185 patients with either previous MI (within 35 days), stroke (within 6 months), or PAD, followed for a mean of 1.9 years, the CAPRIE trial (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) demonstrated a small benefit in ischaemic events (RR reduction of 8.7%) with clopidogrel 75 mg/day vs. aspirin 325 mg/day.⁵⁶⁴

In the recent, open-label, South Korean, non-inferiority HOST-EXAM (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-EXtended Antiplatelet Monotherapy) trial, clopidogrel was compared with low-dose aspirin in 5530 patients after 6–18 months of uneventful DAPT post-PCI (72% initial ACS, 28% initial CCS).⁵⁶⁵ Relative to aspirin, clopidogrel reduced the composite of all-cause death, non-fatal MI, readmission attributable to ACS, stroke, and BARC (Bleeding Academic Research Consortium) ≥ 3 bleeding from 7.7% to 5.7% at the end of the 2-year follow-up; the results were maintained at 5.8 years, in a *post hoc*, per-protocol, post-trial analysis.⁵⁶⁶

A very recent individual patient-level meta-analysis examined seven trials involving 24 325 patients (including recent ACS, post-CABG, or initial CCS patients) randomized to either aspirin monotherapy (12 147 patients) or P2Y₁₂ inhibitor monotherapy [clopidogrel in 7545 (62.0%), ticagrelor in 4633 (38.0%)] and followed for 6–36 months.⁵⁶² P2Y₁₂ inhibitors reduced the combined ischaemic outcome of cardiovascular death, MI, and stroke compared with aspirin (in doses of 100 or 325 mg daily), mainly through reduction of infarction. The risk of major bleeding was similar, whereas GI bleeding and haemorrhagic stroke occurred less frequently with a P2Y₁₂ inhibitor. The treatment effect was consistent across pre-specified subgroups (ACS or CCS) and type of P2Y₁₂ inhibitor.⁵⁶²

The above overall evidence supports clopidogrel monotherapy as an effective and safe alternative to aspirin monotherapy for long-term secondary prevention in patients with CCS.

4.3.1.1.2.2. Ticagrelor monotherapy. Since ticagrelor compared with clopidogrel is more effective and displays less variable platelet inhibition,^{567,568} although with greater bleeding potential,⁵⁶⁹ ticagrelor monotherapy has been compared with aspirin monotherapy for secondary prevention in CCS patients treated with PCI.

The RCT GLOBAL LEADERS trial [Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs. aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent (DES): a multicentre, open-label, randomized superiority trial]⁵⁷⁰ of 15 968 patients (53% with initial CCS) did not show superiority of ticagrelor monotherapy vs. standard of care in terms of survival or new Q-wave MI.⁵⁷⁰ A pre-specified GLOBAL LEADERS ancillary analysis of independently adjudicated outcomes in 7585 patients reported non-inferiority for ischaemic events and no difference in BARC major bleeding between the two strategies.⁵⁷¹ A *post hoc* landmark analysis of the GLOBAL LEADERS trial, conducted in 11 121 uneventful patients at 1 year (53% CCS from trial onset, 47% transitioning to CCS from

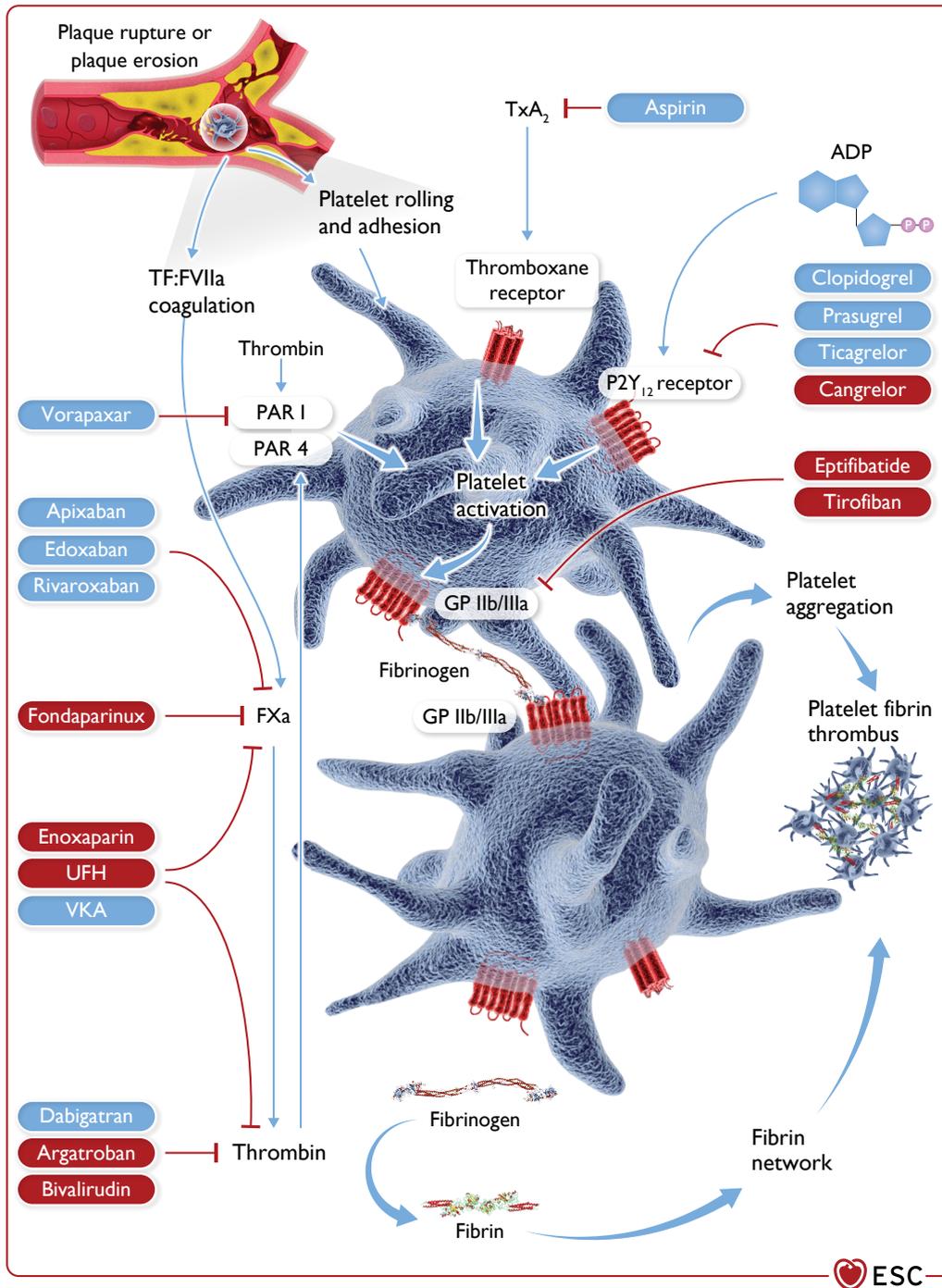


Figure 10 Antithrombotic drugs for chronic coronary syndromes: pharmacological targets. ADP, adenosine diphosphate; FVIIa, activated factor VII; FXa, activated factor X; GP, glycoprotein; PAR, protease-activated receptor; TF, tissue factor; TxA_2 , thromboxane A2; UFH, unfractionated heparin; VKA, vitamin K antagonist. Orally administered drugs are shown on a blue background, parenterally administered ones on red. Aspirin prevents TxA_2 formation by acetylating platelet cyclooxygenase-1.

ACS), showed reduced ischaemic events, but increased BARC 3 and 5 major bleeding, during ticagrelor monotherapy compared with aspirin monotherapy from 1 to 2 years after PCI.⁵⁷²

The double-blind, non-inferiority TWILIGHT trial, conducted in 7119 patients [35% CCS, 65% NSTEMI (non-ST-segment elevation)-ACS] undergoing high-risk PCI (defined as multivessel, stenting of >30 mm, thrombotic, two-stent bifurcation, left main, proximal LAD, or

atherectomy-treated calcified lesions) and uneventfully receiving 3 months of ticagrelor-based DAPT after PCI, showed that ticagrelor monotherapy 90 mg b.i.d. (twice daily) compared with ticagrelor-based DAPT for an additional 12 months significantly reduced the primary endpoint of clinically relevant bleeds (BARC 2, 3, and 5, or BARC 3 and 5), with no significant increase in the composite of any death, MI, or stroke (3.9% in both groups).⁵⁷³

The above trial data^{570–573} and meta-analytical data^{562,563,574} suggest that ticagrelor monotherapy may be an option for selected CCS or stabilized post-ACS patients treated with PCI. However, the overall evidence is weaker than for other recommended antithrombotic strategies. Moreover, the optimal timing and duration (longest tested duration 23 months) are unclear. Only the 90 mg b.i.d. regimen has been tested as monotherapy.^{573,575} Data on prasugrel monotherapy for CCS patients are limited to a single-armed, open-label study with 3 months of follow-up.⁵⁷⁶

In summary, for long-term secondary prevention in CCS patients without an indication for oral anticoagulant (OAC), aspirin or, as an alternative, clopidogrel monotherapy are generally recommended. In selected patients at high ischaemic risk without high bleeding risk (HBR), ticagrelor monotherapy may be considered [at the time of writing not contemplated by the European Medicines Agency (EMA) (<https://www.ema.europa.eu/en/medicines/human/EPAR/brilique>)] with a lower level of evidence than for aspirin or clopidogrel (Figure 11). Details on the pharmacology of antiplatelet drugs^{567,577–582} and on the randomized evidence (including trial limitations) can be found in the [Supplementary data, Table S1](#) and in the evidence tables.

4.3.1.1.3. Dual antiplatelet therapy post-percutaneous coronary intervention. After PCI for CCS, DAPT consisting of aspirin and clopidogrel is recommended to reduce the risk of stent thrombosis and MI compared with aspirin alone.⁵⁵⁶ With few exceptions, there is no reason to replace clopidogrel with ticagrelor, based on the ALPHEUS (Assessment of Loading with the P2Y₁₂ Inhibitor Ticagrelor or Clopidogrel to Halt Ischemic Events in Patients Undergoing Elective Coronary Stenting) trial results demonstrating, in 1883 patients followed for 30 days, that ticagrelor did not significantly reduce PCI-related MI or major myocardial injury, while minor bleeding was significantly increased compared with clopidogrel.⁵⁸³

In the THEMIS trial (The Effect of Ticagrelor on Health Outcomes in diabEtes Mellitus patients Intervention Study) of 19 220 CCS patients aged ≥ 50 years, with type 2 DM and no previous MI or stroke (58% with prior PCI), ticagrelor plus low-dose aspirin marginally reduced ischaemic events compared with placebo plus aspirin at a median follow-up of 40 months, but increased major bleeding, including intracranial haemorrhage.⁵⁸⁴

A default DAPT duration of 6 months is recommended for CCS patients undergoing PCI.⁵⁵⁶ However, multiple RCTs have investigated shorter DAPT durations (1 or 3 months) to decrease the risk of bleeding.^{570,573,585–588} The combined evidence indeed shows a decrease in—mostly minor—bleeding, without an increase in ischaemic events, indicating that a shorter duration of DAPT of 1–3 months post-PCI may benefit CCS patients who are not at high ischaemic risk or who are at HBR.

This concept was tested in the MASTER-DAPT trial (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen), randomizing 4579 PCI patients (~50% CCS) with HBR, after 1-month uneventful DAPT, to immediate DAPT discontinuation or to DAPT continuation for at least 2 additional months.⁵⁸⁷ After 335 days, the trial demonstrated that discontinuation was non-inferior for ischaemic events compared with standard duration of DAPT, but major and clinically relevant non-major bleeding was reduced.⁵⁸⁷

A meta-analysis, including 11 RCTs and 9006 patients (42% CCS) at HBR [defined by a PREdicting bleeding Complications In patients undergoing Stent implantation and subSequent Dual AntiPlatelet Therapy (PRECISE-DAPT) score of ≥ 25 or by Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria, listed in [Supplementary data, Table S2](#)]^{589–591} showed at 12 months of follow-up

that an abbreviated DAPT of 1–3 months reduced both major bleeding and ischaemic events, as well as cardiovascular mortality, compared with standard DAPT, irrespective of CCS or ACS presentation.⁵⁹¹

The overall data indicate that, in CCS patients with HBR, DAPT discontinuation 1–3 months after PCI is recommended, while in patients without HBR, DAPT duration may be reduced only in the absence of high ischaemic risk (Figure 11). For patients at high ischaemic risk without HBR, see below.

4.3.1.1.4. Extended intensified antithrombotic therapy. In patients at high ischaemic risk without HBR, there are three options for intensifying antithrombotic therapy to prevent ischaemic events, albeit at the cost of increased bleeding: (i) continue DAPT, consisting of aspirin and clopidogrel or of aspirin and prasugrel after PCI, based on the results of the DAPT Study;⁵⁹² (ii) add ticagrelor to aspirin in post-MI patients, based on the PEGASUS-TIMI (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin - Thrombolysis In Myocardial Infarction) 54 trial;⁵⁹³ or (iii) add very low-dose rivaroxaban to aspirin in CCS patients, based on the COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulant Strategies).⁵⁹⁴

The randomized DAPT Study demonstrated, in patients at 1-year post-PCI, that an additional 18 months of DAPT reduced ischaemic events compared with aspirin alone, but moderate and severe GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries) or BARC bleeding rates were higher, and all-cause death tended to be increased.⁵⁹² Of note, in the DAPT Study, first-generation DES were used with an increased risk of stent thrombosis.

The PEGASUS-TIMI 54 trial showed that in aspirin-treated patients with a history of MI 1–3 years previously and at least one high-risk characteristic (i.e. aged >65 years, DM, second MI, multivessel CAD, or CKD), ticagrelor (90 or 60 mg b.i.d.) vs. placebo reduced ischaemic events at 3 years, while it increased TIMI (Thrombolysis In Myocardial Infarction) major, but not fatal, bleeding.⁵⁹³ The 60 mg dose was safer and better tolerated than the 90 mg dose^{584,593} and therefore approved. The subgroups of patients with (compared with those without) DM, multivessel CAD, and PAD benefited more from ticagrelor.^{595–597}

The COMPASS trial demonstrated that the combination of aspirin plus rivaroxaban 2.5 mg b.i.d., but not rivaroxaban 5.0 mg b.i.d. monotherapy, reduced ischaemic events, but increased modified-ISTH (International Society on Thrombosis and Haemostasis) major bleeding, compared with aspirin alone in patients with stable atherosclerotic disease (mostly CAD, with additional risk conditions if younger than 65 years).⁵⁹⁴ There was no significant difference in intracranial or fatal bleeding between the two treatment arms, and death rates were lower in the aspirin plus rivaroxaban 2.5 mg b.i.d. group. Subgroups of patients with (compared with those without) DM, PAD, mild CKD, and active smoking habit benefited more from aspirin plus rivaroxaban.^{594,598}

Patient eligibility for extended intensified antithrombotic therapy must be defined taking into account individual patient characteristics (see [Supplementary data, Table S2](#)), as well as study inclusion and exclusion criteria. The different options are described in [Table 8](#).

In summary, in high ischaemic risk CCS patients without HBR, either aspirin plus ticagrelor 60 mg b.i.d. or aspirin plus rivaroxaban 2.5 mg b.i.d. should be considered, based on patient characteristics (Figure 11). DAPT prolongation with clopidogrel or prasugrel may also be an option, although the evidence for this choice suffers limitations. In patients with extended intensified antithrombotic therapy, re-evaluation of bleeding and ischaemic risk at regular intervals is essential. Randomized evidence beyond study follow-up times is unavailable.

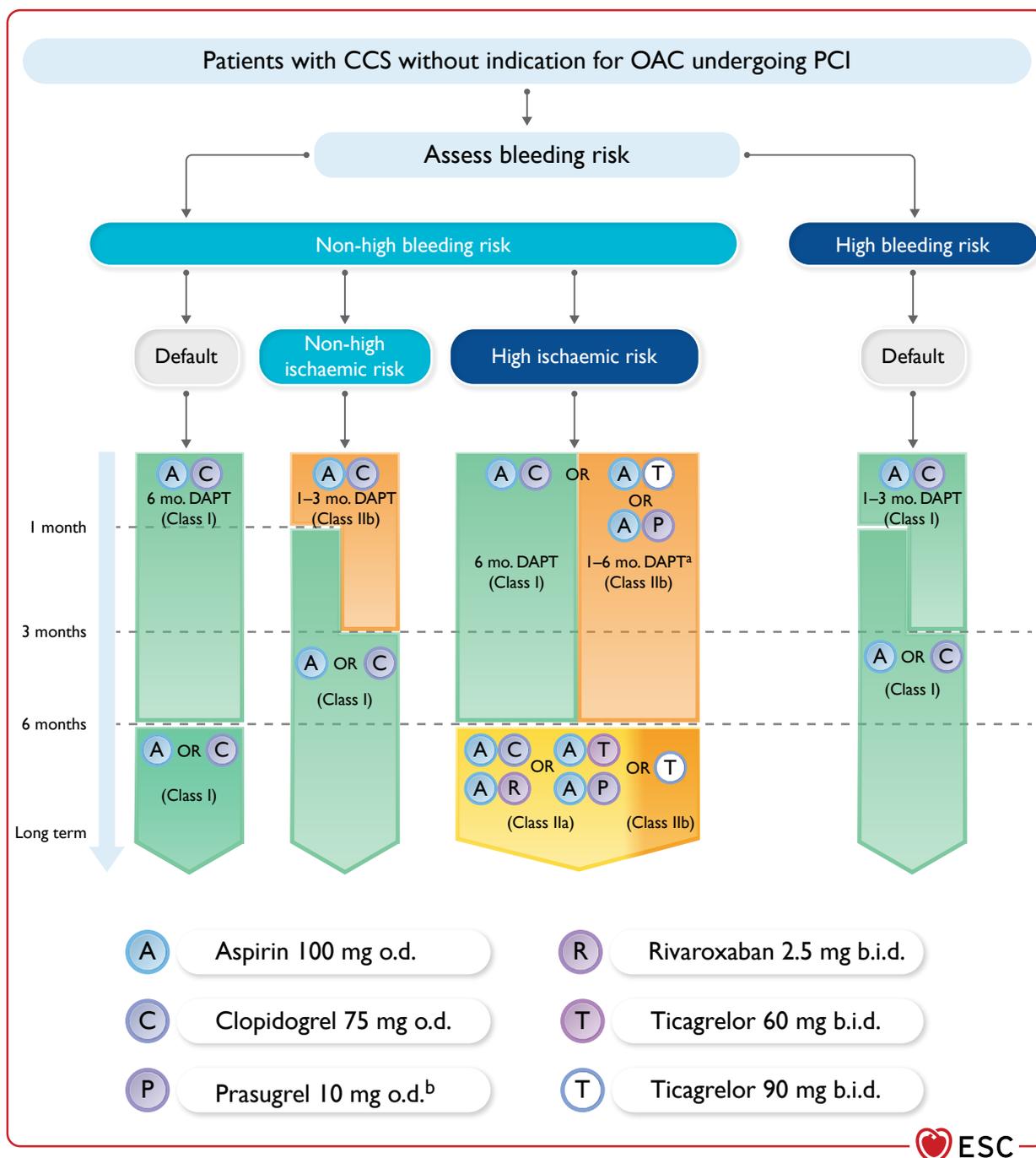


Figure 11 Antithrombotic treatment in chronic coronary syndrome patients undergoing percutaneous coronary intervention. ARC-HBR, Academic Research Consortium for High Bleeding Risk; b.i.d., bis in die (twice daily); CCS, chronic coronary syndrome; CYP2C19, cytochrome P450 2C19; DAPT, dual antiplatelet therapy; mo., months; OAC, oral anticoagulant; o.d., once daily; PCI, percutaneous coronary intervention; PRECISE-DAPT, PREDicting bleeding Complications In patients undergoing Stent implantation and subSequent Dual Anti Platelet Therapy. ^aIn CCS patients undergoing high-thrombotic risk stenting (e.g. complex left main stem, 2-stent bifurcation, suboptimal stenting result, prior stent thrombosis, previously known CYP2C19*2/*3 polymorphisms), prasugrel or ticagrelor (in addition to aspirin) may be considered instead of clopidogrel for the first month, and up to 3-6 months. ^bPrasugrel 5 mg o.d. for patients aged ≥ 75 years or with a body weight < 60 kg. Bleeding risk criteria according to PRECISE-DAPT or ARC-HBR.

4.3.1.1.5. Genotype- and phenotype-guided dual antiplatelet therapy. There is high laboratory interindividual variability in patients treated with clopidogrel, with patients who carry a cytochrome P450 2C19 (CYP2C19) loss-of-function allele having less platelet inhibition and a higher risk of ischaemic events post-PCI compared

with non-carriers.^{599,600} In ST-segment elevation myocardial infarction (STEMI) patients, early de-escalation from aspirin plus ticagrelor or aspirin plus prasugrel to aspirin plus clopidogrel based on genotyping or platelet function testing was non-inferior for net adverse clinical events (ischaemic endpoints and bleeding combined) compared with routine

Table 8 Options for extended intensified antithrombotic therapy

Drug	Dose	Clinical setting	NNT (ischaemic outcomes)	NNH (bleeding outcomes)
<i>Co-administered with aspirin 100 mg o.d.</i>				
Rivaroxaban (COMPASS trial; vs. placebo)	2.5 mg b.i.d.	Patients with CAD or symptomatic PAD at high risk of ischaemic events	77	84 (modified-ISTH major bleeding)
<i>Co-administered with low-dose aspirin 75–162 mg o.d.</i>				
Clopidogrel, (6505/9961 of DAPT trial; vs. placebo)	75 mg/day	Post MI in patients who have tolerated DAPT for 1 year (25% ACS, 22% previous MI)	63	105 (moderate and severe GUSTO bleeds, or BARC 2, 3, and 5 bleeds)
Prasugrel, (3456/9961 of DAPT trial; vs. placebo)	10 mg/day (5 mg/day if body weight <60 kg or age ≥75 years)	Post PCI for MI in patients who have tolerated DAPT for 1 year	63	105 (as above)
Ticagrelor (PEGASUS-TIMI 54; vs. placebo)	60/90 mg b.i.d.	Post-MI in patients who have tolerated DAPT for 1 year	84	81 (TIMI major bleeds)

ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; b.i.d., bis in die (twice daily); CAD, coronary artery disease; DAPT, dual antiplatelet therapy; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; NNH, number needed to cause a harmful event; NNT, number needed to treat to prevent an adverse event; o.d., once daily; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction. Drugs (in addition to aspirin 75–100 mg/day) for extended DAPT options are listed in alphabetical order. For definitions of highly/moderately increased ischaemic and bleeding risk see [Supplementary data, Tables S2 and S3](#). NNT refers to the primary ischaemic endpoints and NNH refers to the key safety endpoints of the respective trials. NNT and NNH from the DAPT trial are pooled numbers for clopidogrel and prasugrel.

treatment with ticagrelor or prasugrel.^{601,602} In patients with CCS, current evidence does not support the routine use of genotype or platelet function testing.^{602–607} However, in patients undergoing high-risk PCI who are known carriers of a CYP2C19 loss-of-function allele, replacing aspirin plus clopidogrel with aspirin plus ticagrelor or prasugrel is a reasonable option.^{600,607,608}

4.3.1.2. Anticoagulant therapy

4.3.1.2.1. Monotherapy with oral anticoagulant. Historical randomized data from patients with recent MI not undergoing PCI, followed for up to 4 years, showed that OAC monotherapy with a vitamin K antagonist (VKA) targeted to an international normalized ratio (INR) of about 3.0–4.0 was at least as effective as low-dose aspirin in preventing MACE, but with a significant increase in major bleeding.^{609,610} Moreover, given the obsoletely high INR target and the cumbersome management, VKA has not gained popularity for secondary prevention in patients with CCS. Successful introduction of the direct oral anticoagulants (DOACs) for stroke prevention in AF and for prevention and treatment of venous thrombo-embolism (VTE) has renewed the interest in OAC for patients with CAD. The COMPASS trial in CCS and/or PAD patients at high ischaemic risk, however, reported no significant ischaemic benefit of rivaroxaban monotherapy 5 mg twice daily over aspirin alone, with a significantly higher incidence of modified-ISTH major bleeding, although not of fatal bleeding.⁵⁹⁴

Thus, in CCS patients without a concomitant long-term indication for OAC, OAC monotherapy with either VKA or rivaroxaban (the only DOAC currently tested in this context) is not recommended. OAC may be considered, however, when antiplatelet agents are not tolerated, if the risk of bleeding is not high,^{594,611} or in CCS patients with a concomitant long-term indication for OAC (see below).

4.3.1.2.2. Combination of anticoagulant and antiplatelet therapy after percutaneous coronary intervention in chronic coronary syndrome patients with AF or other indication for oral anticoagulant. Approximately one in five patients with AF need to undergo

PCI, with a theoretical indication for both OAC for stroke prevention (for which DOACs are preferred to VKA) and DAPT for stent thrombosis and MI prevention, leading to triple antithrombotic therapy.^{612,613} The combination of an OAC plus DAPT, however, leads to an increased bleeding risk, and major bleeding is associated with earlier mortality and should therefore be avoided when possible.⁶¹⁴ In this setting, the results of five RCTs have shown that double compared with triple antithrombotic therapy reduced major or clinically relevant non-major bleeding, without a significant increase of ischaemic events, leading to the recommended use of double antithrombotic therapy (OAC plus P2Y₁₂ receptor inhibitor, mostly clopidogrel) after a 1–4 week period of triple antithrombotic therapy in CCS patients with AF undergoing PCI.^{615–620}

The AUGUSTUS trial (Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban versus Vitamin K Antagonist and Aspirin versus Aspirin Placebo in Patients with AF and Acute Coronary Syndrome or Percutaneous Coronary Intervention) additionally demonstrated that the DOAC apixaban reduced major or clinically relevant non-major bleeding compared with VKA, independently of a double or triple antithrombotic regimen.⁶¹⁹ The AUGUSTUS trial and several meta-analyses demonstrated that aspirin compared with placebo reduced stent thrombosis events, which occurred mainly during the first 30 days after PCI and not thereafter, while increasing bleeding risk.^{620–622}

Thus, based on the combined evidence, double antithrombotic therapy with a DOAC and clopidogrel for up to 12 months should be standard care for CCS patients with AF undergoing PCI, with additional aspirin only for a limited initial period (from during PCI up to a maximum of 30 days in patients at high ischaemic risk). In patients with the highest bleeding risk, clopidogrel discontinuation at 6 (or even 3) months post-PCI and continuation of OAC alone may be considered when ischaemic risk is not high [Class IIb/level of evidence (LOE) C]. Ticagrelor or prasugrel should generally not be used as part of triple antithrombotic therapy, while ticagrelor, and possibly prasugrel (although specific data are not available), may be considered as part of double

antithrombotic therapy when there is a very high risk of stent thrombosis and a low bleeding risk.^{619,623,624}

After a 6- to 12-month period of double antithrombotic therapy, in most AF-PCI CCS patients, OAC alone is preferred over continuation of double antithrombotic therapy.^{625,626} An open-label randomized trial, conducted in 2236 Japanese AF patients who had undergone PCI (71% of patients) or CABG (11% of patients) >1 year before or had known CAD not requiring revascularization, compared rivaroxaban monotherapy (15 or 10 mg once daily based on creatinine clearance) with rivaroxaban plus SAPT (mostly aspirin).⁶²⁷ At a median follow-up of 23 months, the occurrence of ISTH major bleeding and of all-cause deaths were each significantly lower with rivaroxaban monotherapy, whereas MACE occurrence did not differ significantly in the two treatment arms.⁶²⁷

Whether the above considerations remain valid when the indication for OAC is other than AF, e.g. mechanical heart valves (where DOACs are not indicated) or VTE, is uncertain given limited available evidence. In the absence of data regarding the efficacy for MACE prevention of rivaroxaban 10 mg once daily and apixaban 2.5 mg twice daily, which should be used for extended OAC after the first 6 months of therapeutic anticoagulation in patients with VTE,⁶²⁸ it is recommended to resume full doses of these anticoagulants in case of concomitant CCS.

4.3.1.3. Coronary artery bypass grafting and antithrombotic therapy

Low-dose aspirin is recommended lifelong in patients undergoing CABG.^{629,630} Aspirin should be continued until the day of CABG and restarted as soon as there is no concern over bleeding, possibly within 24 h of CABG.^{631,632} In general, other antithrombotic drugs should be stopped at intervals related to their duration of action (prasugrel stopped ≥ 7 days before; clopidogrel ≥ 5 days before; ticagrelor ≥ 3 days before; and rivaroxaban, apixaban, edoxaban, and dabigatran 1–2 days before, depending on drug and renal function).^{633,634} Although not consistent, there is evidence that DAPT with a P2Y₁₂ receptor inhibitor compared with aspirin monotherapy provides higher graft patency rates after CABG.^{635,636,637} A meta-analysis of four RCTs, involving 1316 patients (with 3079 grafts) followed for 3 to 12 months after CABG, reported superior vein graft patency with ticagrelor-based DAPT vs. aspirin alone, but with increased rates of BARC 2–5 (but not BARC 3–5) bleeds, and no significant differences in cardiovascular death, or the composite of cardiovascular death, MI, and stroke, or the composite of all-cause death, MI, stroke, and

revascularization.⁶³⁵ Therefore, in patients undergoing CABG for CCS, DAPT is not routinely indicated; however, it may be considered in selected cases at increased risk of graft occlusion who are not at high bleeding risk (defined in [Supplementary data, Tables S2 and S3](#)).

Transient new-onset AF is common 2 to 3 days after CABG, occurring in approximately one-third of patients.⁶³⁸ AF after CABG is associated with a higher stroke risk,⁶³⁹ which is, however, lower than that with AF unrelated to surgery.⁶⁴⁰ The impact of early OAC initiation on patient outcomes remains unclear.^{641,642} In a Danish cohort study, early OAC initiation was associated with a lower risk of thrombo-embolic events,⁶⁴¹ while in a Swedish cohort study, OAC was associated with no reduction of thrombo-embolic complications but an increased risk of major bleeding.⁶⁴²

Decisions on OAC should consider thrombo-embolic and bleeding risks, timing, and duration of post-operative AF. Longer AF durations and delayed-onset post-CABG have higher risks. We refer to the 2024 ESC Guidelines for the management of AF regarding recommendations for OAC in this context. It is unknown whether, in such patients, the combination of aspirin and OAC may be more effective compared with OAC alone in preventing ischaemic events post-CABG.

4.3.1.4. Proton pump inhibitors

Antithrombotic therapy may provoke GI bleeding, especially in patients at increased risk, such as the elderly, those with a history of GI bleeding or peptic disease, high alcohol consumption, chronic use of steroids or non-steroidal anti-inflammatory drugs (NSAIDs), or receiving a combination of antithrombotic drugs.^{643–645} In patients on various types of antithrombotic therapy, proton pump inhibitors may be effective in reducing the risk of GI bleeding, in particular from gastroduodenal lesions.^{646–648} In general, gastric protection with proton pump inhibitors is recommended in patients at increased risk of GI bleeding for as long as any antithrombotic therapy is administered.^{65,86} Because the proton pump inhibitors omeprazole and esomeprazole inhibit CYP2C19, when administered with clopidogrel, they reduce exposure to clopidogrel's active metabolite; while their use is discouraged in combination with clopidogrel, univocal effects of these combinations on the risk of ischaemic events or stent thrombosis have not been demonstrated (<https://www.ema.europa.eu/en/medicines/human/EPAR/plavix>).^{643,646} Of note, proton pump inhibitors do not increase MACE vs. placebo in patients with CVD.⁶⁴⁶

Recommendation Table 17 — Recommendations for antithrombotic therapy in patients with chronic coronary syndrome (see also Evidence Table 17)

Recommendations	Class ^a	Level ^b
Long-term antithrombotic therapy in patients with chronic coronary syndrome and no clear indication for oral anticoagulation		
In CCS patients with a prior MI or remote PCI, aspirin 75–100 mg daily is recommended lifelong after an initial period of DAPT. ^{558,559}	I	A
In CCS patients with a prior MI or remote PCI, clopidogrel 75 mg daily is recommended as a safe and effective alternative to aspirin monotherapy. ^{562,564–566,649}	I	A
After CABG, aspirin 75–100 mg daily is recommended lifelong. ^{558,559,629}	I	A
In patients <i>without</i> prior MI or revascularization but with evidence of significant obstructive CAD, aspirin 75–100 mg daily is recommended lifelong. ^{557–559}	I	B
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients at enhanced ischaemic risk ^c and without high bleeding risk ^d (options and definitions in Table 8 and in the Supplementary data online, Tables S2 and S3). ^{592–594}	IIa	A
In CCS or stabilized post-ACS patients who underwent PCI and were initially treated with ticagrelor-based DAPT, who remain at high ischaemic risk and are not at high bleeding risk, ticagrelor monotherapy 90 mg b.i.d. may be considered as an alternative to dual or other single antiplatelet therapy. ^{563,570–573}	IIb	C

Continued

Antithrombotic therapy post-percutaneous coronary intervention in patients with chronic coronary syndrome and no indication for oral anticoagulation		
In CCS patients with no indication for oral anticoagulation, DAPT consisting of aspirin 75–100 mg and clopidogrel 75 mg daily for up to 6 months is recommended as the default antithrombotic strategy after PCI-stenting. ^{650–654}	I	A
In patients at high bleeding risk ^d but not at high ischaemic risk, ^c it is recommended to discontinue DAPT 1–3 months after PCI and to continue with single antiplatelet therapy. ^{587,591}	I	A
Stopping DAPT after 1–3 months from PCI-stenting may be considered in patients who are not at high bleeding risk nor at high risk of ischaemic events. ^{588,655–657,c,d}	IIb	B
In CCS patients undergoing high-thrombotic risk stenting (e.g. complex left main stem, 2-stent bifurcation, suboptimal stenting result, prior stent thrombosis, previously known CYP2C19 *2/*3 polymorphisms), prasugrel or ticagrelor (in addition to aspirin) may be considered instead of clopidogrel, for the first month, and up to 3–6 months.	IIb	C
Long-term antithrombotic therapy in patients with chronic coronary syndrome and an indication for oral anticoagulation		
In CCS patients with a long-term indication for OAC, an AF therapeutic dose of VKA alone or, preferably, of DOAC alone (unless contraindicated) is recommended lifelong. ^{609,627}	I	B
Antithrombotic therapy post-percutaneous coronary intervention in chronic coronary syndrome patients with an indication for oral anticoagulation		
In patients with an indication for OAC who undergo PCI, initial low-dose aspirin once daily is recommended (loading dose when not on maintenance dose) in addition to OAC and clopidogrel.	I	C
In patients who are eligible for OAC, DOAC (unless contraindicated) is recommended in preference to VKA. ^{619,658}	I	A
After uncomplicated PCI in CCS patients with concomitant indication for OAC: <ul style="list-style-type: none"> • early cessation of aspirin (≤1 week); • followed by continuation of OAC and clopidogrel: <ul style="list-style-type: none"> ◦ up to 6 months in patients not at high ischaemic risk;^c or ◦ up to 12 months in patients at high ischaemic risk;^c • followed by OAC alone; is recommended. ^{616–619,622,627,659}	I	A
Continuation of aspirin up to 1 month after PCI, in addition to OAC and clopidogrel, should be considered in patients at high ischaemic risk ^c or with anatomical/procedural characteristics judged to outweigh the bleeding risk. ^{620–622,e}	IIa	B
When concerns about high bleeding risk prevail over concerns about stent thrombosis or ischaemic stroke: rivaroxaban 15 mg daily should be considered in preference to rivaroxaban 20 mg daily for the duration of concomitant antiplatelet therapy; ⁶¹⁶	IIa	B
dabigatran 110 mg twice daily should be considered in preference to dabigatran 150 mg twice daily for the duration of concomitant antiplatelet therapy. ⁶¹⁷	IIa	B
In patients with an indication for VKA in combination with single or dual antiplatelet therapy, targeting VKA intensity to an INR in the lower part of the recommended range and to a time in therapeutic range >70% should be considered. ^{615,660–663}	IIa	B
The use of ticagrelor or prasugrel is generally not recommended as part of triple antithrombotic therapy with aspirin and an OAC.	III	C
Antithrombotic therapy post-coronary artery bypass grafting		
It is recommended to initiate aspirin post-operatively as soon as there is no concern over bleeding. ^{629,630}	I	B
DAPT may be considered after CABG in selected patients at greater risk of graft occlusion ^f and at low risk of bleeding. ⁶³⁵	IIb	B
Use of proton pump inhibitors		
A proton pump inhibitor is recommended in patients at increased risk of gastrointestinal bleeding for the duration of combined antithrombotic therapy (antiplatelet therapy and/or OAC). ^{646–648,664}	I	A
A proton pump inhibitor should be considered when a single antithrombotic (antiplatelet or anticoagulant) drug is used, considering the gastrointestinal bleeding risk of the individual patient. ^{646,665–668}	IIa	A

ACS, acute coronary syndrome; AF, atrial fibrillation; ARC-HBR, Academic Research Consortium for High Bleeding Risk; b.i.d., bis in die (twice daily); CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, chronic coronary syndrome; CKD, chronic kidney disease; CYP2C19, cytochrome P450 2C19; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; INR, international normalized ratio; LAD, left anterior descending; MI, myocardial infarction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; PRECISE-DAPT, PREdicting bleeding Complications In patients undergoing Stent implantation and subSequent Dual AntiPlatelet Therapy; VKA, vitamin K antagonist.

^aClass of recommendation.

^bLevel of evidence.

^cEnhanced thrombotic/ischaemic risk criteria for extended treatment with a second antithrombotic agent (Supplementary data, Table S3). Thrombotic risk encompasses (i) the risk of thrombosis occurring, and (ii) the risk of death should a thrombotic event occur, both of which relate to anatomical, procedural, and clinical characteristics. Thrombotic/ischaemic risk factors for CCS (that may also apply to CABG) patients include stenting of left main stem, proximal LAD, or last remaining patent artery; suboptimal stent deployment; stent length of >60 mm; diabetes mellitus; CKD; bifurcation with two stents implanted; treatment of chronic total occlusion; and previous stent thrombosis on adequate antithrombotic therapy.

^dBleeding-risk criteria according to PRECISE-DAPT or ARC-HBR (Supplementary data, Table S2).

^eAnatomical/procedural thrombotic risk characteristics: stenting of left main, proximal LAD, or last remaining patent artery; suboptimal stent deployment; stent length of >60 mm; bifurcation with two stents implanted; treatment of chronic total occlusions.

^fFor example, stentectomy, endarterectomy, poor venous graft quality.

4.3.2. Lipid-lowering drugs

Evidence from genetic, epidemiological, and randomized clinical studies has established the key causal role of LDL-C and other apo-B-containing lipoproteins in the development of atherosclerotic disease.⁶⁶⁹ In patients with established ASCVD, lowering of LDL-C levels reduces the risk of recurrent MACE.^{128,670,671} Elevated lipid levels should be managed according to the 2019 ESC/EAS Guidelines for the management of dyslipidaemias⁶⁴ and the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice.¹⁶

Because patients with CCS are considered at very high cardiovascular risk, the treatment goal is to lower LDL-C levels to <1.4 mmol/L (<55 mg/dL) and achieve a reduction by at least 50% from baseline. For patients who experience a second vascular event within 2 years while taking maximum tolerated statin-based therapy, an even lower LDL-C goal of <1.0 mmol/L (40 mg/dL) may be considered.

In addition to exercise, diet, and weight control, which favourably affect blood lipid levels and are recommended for all patients with CCS (see Section 5.1), pharmacological treatment with a maximally tolerated dose of a potent statin is the first-line therapy recommended for all CCS patients.^{128,670,671} In a landmark meta-analysis involving patients with and without ASCVD, statin treatment was shown to reduce the risk of major vascular events by 22%, all-cause mortality by 10%, and mortality due to coronary heart disease by 20% per 1.0 mmol/L of achieved reduction in LDL-C levels.⁶⁷⁰ High-intensity statin treatment (i.e. atorvastatin ≥40 mg or rosuvastatin ≥20 mg daily) reduces LDL-C levels by 45%–50% on average, although interindividual variability exists.⁶⁷² Statins should not be given when pregnancy is planned, during pregnancy, or during the breastfeeding period.⁶⁴

In many patients with CCS, statin therapy alone will not suffice to achieve the recommended LDL-C goals;⁶⁷³ hence, a combination of lipid-lowering drug therapy is required. In a trial of patients with recent ACS, the combination of statin with ezetimibe resulted in additional reduction of LDL-C levels by 20%–25% compared with simvastatin monotherapy. This LDL-C reduction translated into a modest reduction of a composite endpoint involving fatal and non-fatal events (6.4% RR reduction, 2.0% absolute risk reduction).⁶⁷⁴ Ezetimibe should be used as second-line therapy when the treatment goal is not achieved with maximally tolerated statin therapy, or as first-line therapy in the case of intolerance to any statin regimen. Proprotein convertase subtilisin/kexin type 9 inhibitors (alirocumab or evolocumab), administered subcutaneously every 2 or 4 weeks, lower LDL-C levels by 60% when added to statin therapy.⁶⁷⁵ In cardiovascular outcomes trials, these monoclonal antibodies resulted in significant reduction of non-fatal cardiovascular events, with no impact on cardiovascular mortality.^{675,676} Their favourable safety profile was recently confirmed for longer follow-up (median 5 years) in open-label extension studies of the outcomes trials.⁶⁷⁷ The high cost of PCSK9 inhibitors is still a limitation for broader implementation.

Bempedoic acid is an oral cholesterol synthesis inhibitor that lowers LDL-C by approximately 18% in monotherapy and 38% when combined with ezetimibe.^{678,679} In a recent cardiovascular outcomes trial including statin-intolerant patients, bempedoic acid significantly reduced MACE.⁶⁸⁰ Inclisiran, a small interfering ribonucleic acid molecule, is administered subcutaneously every 3–6 months and reduces LDL-C by approximately 50% either in combination with statin or without statin therapy.⁶⁸¹ A cardiovascular outcomes trial for inclisiran is currently underway (ClinicalTrials.gov identifier: NCT03705234).

In patients scheduled to undergo elective PCI, pre-treatment with a high-dose statin in statin-naïve patients or loading with high-dose statin in statin-treated patients has been shown to reduce the risk of

periprocedural events.⁶⁸² Routine pre-treatment or loading (in the context of pre-existing statin treatment) with a high-dose statin can be considered in patients with CCS undergoing PCI.

Recommendation Table 18 — Recommendations for lipid-lowering drugs in patients with chronic coronary syndrome (see also Evidence Table 18)

Recommendations	Class ^a	Level ^b
Lipid-lowering treatment with an LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction in LDL-C vs. baseline is recommended. ^{64,670,671}	I	A
A high-intensity statin up to the highest tolerated dose to reach the LDL-C goals is recommended for all patients with CCS. ^{670,671}	I	A
If a patient's goal is not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended. ⁶⁷⁴	I	B
For patients who are statin intolerant and do not achieve their goal on ezetimibe, combination with bempedoic acid is recommended. ⁶⁸⁰	I	B
For patients who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with a PCSK9 inhibitor is recommended. ^{675,676}	I	A
For patients who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with bempedoic acid should be considered.	IIa	C
For patients with a recurrent atherothrombotic event (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered. ^{675,676}	IIb	B

CCS, chronic coronary syndrome; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

^aClass of recommendation.

^bLevel of evidence.

4.3.3. Renin–angiotensin–aldosterone blockers/angiotensin receptor neprilysin inhibitor

Modulation of the RAAS and the neprilysin inhibitor sacubitril in combination with a RAS blocker has proved beneficial in patients with HF post-MI and in patients with hypertension. In these clinical syndromes, RAAS inhibition has greatly improved morbidity and mortality. Angiotensin-converting enzyme inhibitors (ACE-Is) can reduce mortality, MI, stroke, and HF among patients with LV dysfunction,^{683–685} previous vascular disease,^{686–688} and high-risk DM.⁶⁸⁹ These data bring strong evidence to recommend ACE-Is [or angiotensin receptor blockers (ARBs) in cases of intolerance] for the treatment of patients with CCS with co-existing hypertension, LVEF ≤40%, DM, or CKD, unless contraindicated (e.g. severe renal impairment, hyperkalaemia, etc.). In trials that include patients with mildly reduced and preserved LV function >40%, the effect of ACE-Is to reduce all-cause death, cardiovascular death, non-fatal MI, stroke, or HF in patients with atherosclerosis is not uniform.^{686,687,690} A meta-analysis, including 24 trials and 61 961 patients, documented that, in CCS patients without HF, RAAS inhibitors reduced cardiovascular events and death only when compared

with placebo, but not when compared with active control treatment.⁶⁹¹ For this reason ACE-I therapy in CCS patients without HF or high cardiovascular risk is not generally recommended, unless required to meet BP targets. However, a new observational study showed that ACE-I/ARB therapy was associated with significant long-term survival benefit in patients post-PCI for STEMI/non-ST-segment elevation myocardial infarction (NSTEMI). This survival benefit is apparent in patients with both preserved and reduced LV function. These findings provide contemporary evidence to support the use of these agents in coronary patients who underwent PCI for STEMI/NSTEMI, irrespective of their baseline LV function.⁶⁹²

Sacubitril/valsartan contains an ARB and a prodrug of neprilysin inhibitor, which inhibits the degradation of endogenous natriuretic peptides. In patients with LVEF $\leq 35\%$ (of ischaemic aetiology in 60%), sacubitril/valsartan proved to reduce HF hospitalization and cardiovascular death compared with ACE-I.⁶⁹³ Moreover, sacubitril/valsartan may decrease myocardial ischaemia because of its effect in reducing LV wall stress and improving coronary circulation. The risk of coronary events using sacubitril/valsartan compared with ACE-I was also significantly reduced on post-hoc analyses.⁶⁹⁴

4.3.4. Sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists

Sodium–glucose cotransporter 2 (SGLT2) inhibitors and GLP-1 receptor agonists were initially intended as glucose-lowering medications for patients with type 2 DM; however, a growing body of evidence has established that these drugs lower ASCVD risk and confer cardiovascular benefits beyond their glucose-lowering potential.^{688,695–697} Among patients with DM, SGLT2 inhibitor use was associated with a reduced risk of MACE, especially in patients with established ASCVD.⁶⁹⁸ The exact mechanism(s) by which SGLT2 inhibitors improve CVD outcomes remain largely unknown, but several hypotheses have been proposed.^{695,696,699–702} The benefits of SGLT2 inhibitors may relate more to cardiorenal haemodynamic effects than to atherosclerosis.¹⁶ The cardiovascular benefits of GLP-1 receptor agonists is driven by reduced risk of ASCVD-related events.⁷⁰³ Overall, the results of cardiovascular outcome trials of SGLT2 inhibitors and GLP-1 receptor agonists support their recommendation as first-line treatment for all patients with type 2 DM and ASCVD including CCS, independently of decisions about glycaemic management (*Recommendation Table 19*).

In patients with HF with reduced (HFrEF) or preserved EF (HFpEF), dapagliflozin and empagliflozin lowered the risk of worsening HF or cardiovascular death in the presence or absence of type 2 DM.^{704–707} Recent results indicate benefits of SGLT2 inhibitors on hospitalization for HF and cardiovascular death in patients at high cardiovascular risk, irrespective of HF history.⁷⁰⁸ Recommendations for the use of SGLT2 inhibitors in patients with diabetes and patients with HF are detailed in the 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes⁸⁶ and the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure⁵²⁶ and its 2023 Focused Update.⁷⁰⁹ Recommendations on the use of these medications in patients with HF are given in *Section 4.3.4* and *Recommendation Table 24*.

In patients with pre-existing CVD, the SELECT trial assessed the effect of weekly subcutaneous administration of the GLP-1 receptor agonist semaglutide at a dose of 2.4 mg on MACE reduction in overweight or obese adults without type 2 DM. The trial involved 17 604 patients with established CVD and a BMI ≥ 27 kg/m². Patients lost a mean of 9.4% of body weight over the first 2 years with semaglutide vs. 0.88% with placebo. The primary cardiovascular endpoint—a

composite of death from cardiovascular causes, non-fatal MI, or non-fatal stroke—was reduced significantly, with an HR of 0.80 (95% CI, 0.72–0.90; $P < .001$).⁴⁶⁵

Recommendation Table 19 — Recommendations for sodium–glucose cotransporter 2 inhibitors and/or glucagon-like peptide-1 receptor agonists in patients with chronic coronary syndrome (see also Evidence Table 19)

Recommendations	Class ^a	Level ^b
CCS patients with type 2 diabetes		
SGLT2 inhibitors with proven CV benefit ^c are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication. ^{86,688,695,697,700}	I	A
GLP-1 receptor agonists with proven CV benefit ^d are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication. ^{710,711}	I	A
CCS patients without type 2 diabetes		
The GLP-1 receptor agonist semaglutide should be considered in overweight (BMI >27 kg/m ²) or obese CCS patients without diabetes to reduce CV mortality, MI, or stroke. ⁴⁶⁵	IIa	B

BMI, body mass index; CCS, chronic coronary syndrome; CV, cardiovascular; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; MI, myocardial infarction; SGLT2, sodium–glucose cotransporter 2; T2DM, type 2 diabetes mellitus.

^aClass of recommendation.

^bLevel of evidence.

^cCanagliflozin, dapagliflozin, empagliflozin, sotagliflozin (listed in alphabetical order).

^dDulaglutide, epeglatide, liraglutide, semaglutide (listed in alphabetical order).

4.3.5. Anti-inflammatory agents for event prevention

Four large double-blind trials have compared the effects of anti-inflammatory agents vs. placebo in patients with atherothrombotic CAD. The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) tested three doses of the anti-interleukin-1-beta monoclonal antibody canakinumab against placebo in over 10 000 patients with previous MI and plasma C-reactive protein ≥ 2 mg/L.⁷¹² The highest dose (300 mg every 3 months) reduced plasma interleukin-6 and C-reactive protein and the combined endpoint of cardiovascular death, non-fatal MI, and non-fatal stroke over a mean of 3.7 years: 3.90 vs. 4.50 events per 100 person-years (HR 0.86; 95% CI, 0.75–0.99; $P = .031$). The other doses did not provide favourable results. Despite efficacy, the drug was not developed further for this indication because of the risk of fatal infections and high costs.

Low-dose methotrexate (target dose 15–20 mg once weekly) did not reduce the composite of cardiovascular death, non-fatal MI, non-fatal stroke, or unstable angina-driven revascularization in 4786 patients with previous MI or multivessel coronary atherosclerosis and additional DM or metabolic syndrome.⁷¹³ The trial was stopped early (median 2.3 year follow-up) for futility.

The COLCOT (Colchicine Cardiovascular Outcomes Trial) tested low-dose colchicine (0.5 mg daily) vs. placebo in 4745 patients with recent MI (<30 days) regardless of C-reactive protein values.⁷¹⁴ During a median of 2.3 years, the composite of cardiovascular death, resuscitated

cardiac arrest, non-fatal MI, non-fatal stroke, or unstable angina-driven revascularization occurred in 5.5% on colchicine vs. 7.1% on placebo (HR 0.77; 95% CI, 0.61–0.96; $P = .02$). Colchicine had favourable effects on each outcome component. All-cause mortality did not differ (43 vs. 44 events). Diarrhoea was reported in 9.7% vs. 8.9% (statistically non-significant); pneumonia, although not frequent, was recorded more often with colchicine than placebo (0.9% vs. 0.4%; $P = .03$).

The LODOCO2 trial (Low-Dose Colchicine 2) randomized 5500 patients with atherosclerotic CAD who had been stable for at least 6 months to low-dose colchicine (0.5 mg daily) or placebo for a median of 2.4 years.⁷¹⁵ The primary endpoint (cardiovascular death, spontaneous MI, ischaemic stroke, or ischaemia-driven revascularization) occurred in 6.8% on colchicine vs. 9.6% on placebo (HR 0.69; 95% CI, 0.57–0.83; $P < .001$). The main secondary endpoint (cardiovascular death, non-fatal MI, or non-fatal stroke) was reduced by 28% (4.2% on colchicine vs. 5.7% on placebo; HR 0.72; 95% CI, 0.57–0.92; $P = .007$). There were no significant differences in rates of pneumonia or GI disorders. The incidence of non-cardiovascular death was nominally higher, but not statistically significant (0.7 vs. 0.5 events per 100 person-years; HR 1.51; 95% CI, 0.99–2.31).

A recent meta-analysis including over 12 000 patients with atherothrombotic CAD⁷¹⁶ has estimated the treatment effects of colchicine vs. placebo for individual outcome components. Significantly lower risks were found for MI (RR, 0.76; 95% CI, 0.61–0.96), stroke (RR, 0.48; 95% CI, 0.30–0.77) and unstable angina-driven revascularization (RR, 0.61; 95% CI, 0.42–0.89), with no significant difference for cardiovascular death (RR, 0.73; 95% CI, 0.45–1.21), all-cause death (RR, 1.01; 95% CI, 0.71–1.43), or GI events (provided colchicine daily dose did not exceed 0.5 mg; RR, 1.02; 95% CI, 0.92–1.14).

Recommendation Table 20 — Recommendations for anti-inflammatory drugs in patients with chronic coronary syndrome (see also Evidence Table 20)

Recommendation	Class ^a	Level ^b
In CCS patients with atherosclerotic CAD, low-dose colchicine (0.5 mg daily) should be considered to reduce myocardial infarction, stroke, and need for revascularization. ^{714–716}	IIa	A

© ESC 2024

CAD, coronary artery disease; CCS, chronic coronary syndrome.

^aClass of recommendation.

^bLevel of evidence.

Recommendation Table 21 — Recommendations for angiotensin-converting enzyme inhibitors in patients with chronic coronary syndrome (see also Evidence Table 21)

Recommendations	Class ^a	Level ^b
In CCS patients, ACE-Is (or ARBs) are recommended in the presence of specific comorbidities, such as hypertension, diabetes, or heart failure. ^{683–685}	I	A
ACE-Is should be considered in CCS patients at very high risk of cardiovascular events. ^{686,687,690,691}	IIa	A

© ESC 2024

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCS, chronic coronary syndrome.

^aClass of recommendation.

^bLevel of evidence.

4.4. Revascularization for chronic coronary syndromes

Invasive treatment of CAD with either CABG or PCI is historically described under the term revascularization. Although both procedures increase CFC^{365,366} and prevent myocardial ischaemia during exercise or emotional stress, they do not heal coronary atherosclerosis. Revascularization by both modalities improves angina-related health status.^{50,52,717} Randomized and meta-analytical evidence supports a survival benefit above medical therapy for CABG in patients with left main disease,^{718–721} as well as three-vessel disease,⁷²² particularly in patients with LV dysfunction.^{719,723,724} Most of this evidence was obtained prior to the introduction of disease-modifying therapies such as ACE-Is/ARBs and statins. Meta-analytical evidence suggests a potential benefit of PCI on cardiovascular survival,^{55,725,726} which, similarly to CABG, appears to be related to the prevention of MI.^{55,727} In general, among surgically eligible patients with multivessel disease, CABG is superior to PCI and to medical therapy, particularly in those with diabetes and higher coronary complexity.^{727,728} Recent evidence has generated controversy on (i) the value of routine early revascularization compared with optimal medical therapy alone,^{47,56,314,729} (ii) the value of PCI vs. CABG for complex CAD,^{326,730} and (iii) the value of ischaemia testing for decision-making in revascularization.^{315,317,726} At the same time, advances in interventional technologies and medications have expanded the application of PCI to more complex forms of CAD.⁷³¹

4.4.1. Appropriate indication for myocardial revascularization

In CAD patients with moderate or severe inducible ischaemia but no left main disease nor LVEF of <35%, the largest-to-date ISCHEMIA trial, up to 5 years, did not show significant benefit of an initial invasive strategy over an initial conservative strategy for the primary endpoint of ischaemic cardiovascular events or death from any cause,⁴⁷ triggering discussion about the role of initial angiography followed by revascularization when feasible, in this type of CCS patients, once optimal medical therapy has been established. The CLARIFY registry found that many CCS patients with angina experience a resolution of symptoms over time, often without changes in treatment or revascularization, and experience good outcomes.⁴⁰⁴ While these findings suggest that this type of CCS patients should initially receive conservative medical management, it is worth noting that patients who were randomly assigned to the invasive strategy in the ISCHEMIA trial experienced significantly lower rates of spontaneous MI and greater improvement in angina-related health status compared with those assigned to the conservative strategy.^{47,50} Furthermore, the ORBITA 2 trial demonstrated that patients with stable angina, who were receiving minimal or no anti-anginal medication and had objective evidence of ischaemia, experienced a lower angina symptom score following PCI treatment compared with a placebo procedure, indicating a better health status with respect to angina.⁵² Although initial conservative medical management of CCS patients is generally preferred, symptom improvement by revascularization should therefore not be neglected if patients remain symptomatic despite antianginal treatment.

After publication of the ISCHEMIA trial results, several meta-analyses have reported similar overall survival and inevitably higher rates of procedural MI with routine revascularization, while confirming consistently greater freedom from spontaneous MI, unstable angina, and anginal symptoms after revascularization compared with GDMT alone.^{732–734} Of note, these meta-analyses showed some differences in methodology, in selected trials, and follow-up duration.

Furthermore, the importance of 'any myocardial infarction' as an endpoint is complicated by a debate over the prognostic importance of procedural infarctions as well as how various MI definitions affect the prediction of long-term outcomes.^{735,736} A more recent meta-analysis of RCTs that included the longest available follow-up showed that adding revascularization to GDMT reduced cardiac mortality compared with GDMT alone. The cardiac survival benefit improved with the duration of follow-up and was linearly related to a lower rate of spontaneous MI.⁵⁵

In ISCHEMIA, patients randomized to initial medical therapy alone had significantly more spontaneous MIs during the 5-year follow-up, which were associated with subsequent cardiovascular death.⁷³⁷ An early invasive strategy was associated with lower long-term risks of cardiovascular events, mainly spontaneous MIs, compared with a conservative strategy, at the cost of a higher risk of procedural MIs.⁷³⁸

Extended follow-up of the ISCHEMIA trial population up to 7 years (ISCHEMIA-EXTEND) revealed a significant 2.2% absolute decrease in cardiovascular mortality (adjusted HR 0.78; 95% CI, 0.63–0.96) favouring the initial invasive strategy.⁵⁶ The benefit was most marked in patients with multivessel CAD ($\geq 70\%$ diameter stenosis on CCTA; adjusted HR 0.68; 95% CI, 0.48–0.97) but was offset by a significant 1.2% absolute increase in non-cardiac mortality, without a significant difference (absolute decrease of -0.7%) in all-cause mortality.⁵⁶ In a recent meta-analysis of 18 trials, on the other hand, non-cardiac mortality did not differ significantly by initial invasive or conservative strategy in CCS patients with preserved or slightly impaired LVEF.⁷³⁹ In a *post hoc* analysis of the ISCHEMIA trial, CAD severity was associated with a higher risk of all-cause death, MI, and the primary endpoint of the trial.³¹⁷ This effect appeared to be most noticeable in patients with multivessel disease and/or proximal LAD stenosis ($\geq 70\%$ diameter stenosis on CCTA).

4.4.2. Additional considerations on reduced systolic left ventricular function: myocardial viability, revascularization, and its modality

Ischaemic cardiomyopathy is the leading cause of HFrEF, and new ischaemic events are the main drivers of worsening LV function, strongly impacting long-term survival.⁷⁴⁰ Ischaemic HFrEF is characterized by irreversibly damaged and scarred myocardium alternating with 'viable' myocardium that may be dysfunctional owing to repetitive ischaemic episodes (stunning) or chronic hypoperfusion (hibernation).⁷⁴¹ According to classical concepts, revascularization combined with GDMT synergistically improves systolic LV function and overall prognosis in patients with ischaemic HFrEF by restoring sufficient perfusion to dysfunctional yet viable myocardial segments and preventing new ischaemic events.⁷⁴² However, it carries increased periprocedural risk, especially in patients with severe LV dysfunction (LVEF $\leq 35\%$). A meta-analysis of 26 observational studies, including 4119 patients, showed that CABG can be performed with acceptable operative mortality (5.4%; 95% CI, 4.5%–6.4%) and 5-year actuarial survival (75%) in patients with severe LV dysfunction (mean pre-operative EF of 24.7%).⁷⁴³

In the 1990s, observational studies reported improved survival after revascularization in patients with severe CAD, significant LV dysfunction, and evidence of myocardial viability on imaging tests.⁷⁴⁴ The PARR-2 trial (PET and Recovery Following Revascularization) randomized 430 patients with suspected ischaemic cardiomyopathy to an F-18-fluorodeoxyglucose PET-assisted strategy or standard care. While there was a non-significant trend towards lower risk of cardiac events at 1 year with PET assistance,⁷⁴⁵ the 5-year follow-up showed

no overall reduction in cardiac events.⁷⁴⁶ However, significant benefits were observed when adhering to PET recommendations (after excluding 25% protocol violations).⁷⁴⁶ *Post hoc* analyses and substudies confirmed the positive outcomes of a PET-guided strategy.^{747,748}

The Surgical Treatment for Ischemic Heart Failure (STICH) trial randomized 1212 patients with CAD without left main diseases eligible for CABG and LVEF $\leq 35\%$ to receive either CABG and GDMT, or GDMT alone. The trial failed to achieve its primary endpoint of all-cause mortality at a median follow-up of 4 years (HR with CABG, 0.86; 95% CI, 0.72–1.04; $P = .12$).⁵³ However, at a median follow-up of 9.8 years, both all-cause and cardiovascular mortality were significantly reduced with CABG compared with GDMT alone (from 66.1% to 58.9%; HR 0.84; 95% CI, 0.73–0.97; $P = .02$; and from 49.3% to 40.5%; HR 0.79; 95% CI, 0.66–0.93; $P = .006$, respectively).⁵⁴ The reduction of cardiovascular mortality by CABG was greater in patients with three-vessel disease⁵⁴ and the reduction of all-cause mortality was greater in younger patients, in whom cardiovascular deaths accounted for a larger proportion of deaths vs. older patients ($P = .004$ for interaction).⁷⁴⁹ Viability was assessed by SPECT, dobutamine echocardiography, or both in 50% of STICH patients (298 randomized to CABG and 303 randomized to GDMT alone).⁷⁵⁰ There were no significant interactions between presence or absence of myocardial viability and improved LV function or long-term survival benefit for CABG above GDMT.^{747,748,750}

There have been no RCTs directly comparing CABG and PCI in patients with ischaemic HF. A meta-analysis of 21 studies, mostly observational except three including STICH, published between 1983 and 2016, supported CABG and PCI on a background of GDMT in appropriate patients with multivessel disease and LV systolic dysfunction; revascularization with either CABG or PCI improved long-term survival compared with GDMT, but compared with PCI, CABG provided a survival benefit and a lower risk of MI or repeat revascularization, with a slightly higher incidence of stroke.⁷⁵¹

PCI is increasingly used over CABG for treating patients with ischaemic HF and multivessel disease, as shown by two large registries.^{752,753} While these registries suggest that CABG is associated with a lower risk of long-term all-cause and cardiovascular mortality and lower MACE compared with PCI in patients with CAD and LVEF $\leq 35\%$,^{752,753} it is important to interpret these observational studies with great caution, given significant differences in baseline characteristics, including age, history of previous MI, severity of CAD, and completeness of revascularization.⁷⁵⁴ For the comparison of CABG with PCI in managing ischaemic HF with severely impaired LV dysfunction and multivessel CAD, the results of ongoing trials (NCT05427370 and NCT05329285) are awaited.

The Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction (REVIVED-BCIS2) trial randomized 700 patients with impaired LV function (EF $\leq 35\%$), extensive CAD amenable to PCI, and evidence of myocardial viability in at least four dysfunctional myocardial segments to a strategy of PCI plus GDMT or GDMT alone.⁷²⁹ After a 3.4-year follow-up, PCI showed no significant reduction in the composite primary endpoint of all-cause death or HF rehospitalization (HR 0.99; 95% CI, 0.78–1.27; $P = .96$). Patients treated by PCI showed slight and temporary improvements in their symptoms and no incremental improvement of overall LV function compared with GDMT.

A pre-specified secondary analysis of REVIVED-BCIS2, conducted in 87% of patients, failed to establish significant correlations between viability extent (assessed by CMR or dobutamine stress echocardiography) and outcomes, thereby challenging the traditional concept of myocardial hibernation, which can be reversed by revascularization.⁷⁵⁵ However, the analysis did find that larger amounts of non-viable myocardium were linked to an increased risk of the primary outcome,

regardless of whether PCI was performed, suggesting that viability assessment may be useful for risk stratification.

The two main RCTs, STICH and REVIVED-BCIS2, differ in various aspects. The REVIVED-BCIS2 trial patients were, on average, 10 years older than those in the STICH trial, had a less frequent history of MI (50% vs. 78%) and were more likely to be angina-free at baseline (67% vs. 36%). REVIVED-BCIS2 included fewer patients with three-vessel disease (38% vs. 60%). Additionally, patients in REVIVED-BCIS2 received more modern HF therapy and were more commonly treated with an ICD/CRT (cardiac resynchronization therapy) (21%/53% vs. 2%/19%). Finally, the duration of follow-up was shorter compared with the STICH trials. All these factors may have contributed to the absence of any PCI effect on survival.

In conclusion, the heterogeneous designs of the above studies, the statistical underpower of subgroup analyses, the heterogeneous methods of viability assessments (e.g. based on metabolism, contractile reserve, or scar extent) and variable quantification (dichotomous vs. continuous) leave many open questions on how viability should be defined,⁷⁵⁶ and when and why it should be assessed in ischaemic HFrEF patients. For instance, the classical binary definition of myocardial viability may benefit from more contemporary paradigms and from greater focus on anatomic alignment between viable myocardial regions and feasible revascularization of corresponding perfusing arteries.⁷⁴¹ Moreover, therapeutic aims should go beyond enhancing local and overall LV function to include safeguarding against new ischaemic events⁷²⁷ and their ensuing possibly lethal arrhythmias. Therefore, an integrative approach, including highly specialized imaging, HF, arrhythmia, and revascularization specialists, is needed for optimal patient management and improved outcomes.

4.4.3. Additional considerations—complete vs. partial revascularization

Complete revascularization treating all vessels and lesions causing ischaemia is preferable to incomplete revascularization.⁷⁵⁷ However, various factors may influence the implementation of complete revascularization, including clinical setting, comorbidities, anatomical and procedural features, advanced age, or frailty.^{758,759} Furthermore, whether the focus of complete revascularization should be anatomical or functional is still unclear. In the PCI group of the SYNTAX (SYnergy Between PCI with TAXUS and Cardiac Surgery) trial, a higher residual SYNTAX score, indicating incomplete anatomical revascularization, was associated with a higher mortality rate.⁷⁶⁰ However, the outcomes of anatomically incomplete but functionally complete revascularization by PCI were superior to those of anatomically complete revascularization.^{49,308,761} Of note, recent studies suggest that significant levels of residual ischaemia can persist despite good angiographic results after complex coronary stenting.

Individual reports suggest that incomplete revascularization is associated with increased mortality compared with complete revascularization.⁷⁶² In addition, unintended incomplete revascularization appears to be a surrogate marker of anatomic complexity and comorbidities, predisposing to more rapid native CAD progression.^{760,763} An important predictor of anatomical incomplete revascularization by PCI is the presence of chronic total occlusion. Randomized trials have shown improvements of angina and QoL with PCI for chronic total occlusion lesions,^{764,765} but failed to show any reduction of mortality risk and MI rates.^{764–767}

Among patients with high-risk multivessel CAD, incomplete anatomical revascularization is reported more frequently among those treated

with PCI compared with those treated with CABG. The rate ranges from 32% to 56% for PCI and 30% to 37% for CABG.^{759,762,768} However, interpreting these data is challenging due to several factors. Firstly, there is no uniform definition of complete revascularization.^{769,770} Secondly, although completeness of revascularization with PCI can be evaluated immediately after the procedure, many patients require staged procedures to achieve complete revascularization. Thirdly, within the first year after CABG, 20% to 40% of patients may experience asymptomatic graft failure as determined by CCTA.^{771–773} Therefore, selecting a revascularization modality cannot be based solely on completeness of revascularization but rather should be determined through shared decision-making and a risk–benefit assessment.

4.4.4. Assessment of clinical risk and anatomical complexity

While both CABG and PCI have shown continuous technical improvements and better clinical outcomes over time,^{774,775} the potential benefit of revascularization must be carefully evaluated against the procedural risk. The Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) risk model has proved to be more effective than the EuroSCORE II risk model in predicting peri-operative mortality and complications in CABG patients due to its continuous calibration.⁷⁷⁶ It has also shown satisfactory discrimination for all-cause death at 30 days in patients undergoing CABG, allowing differentiation of high (>8%) and intermediate (4% to 8%) from low (<4%) surgical mortality risk. Although primarily designed for surgical risk assessment, the STS-PROM score can also be used to evaluate the risk of revascularization through PCI in patients with multivessel disease, as recent studies³²⁶ have shown similar mortality rates between PCI and CABG. However, in patients with left main coronary artery disease (LMCAD) participating in the EXCEL trial (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization), the STS risk models were effective in predicting outcomes for CABG but not for PCI regarding peri-operative mortality and renal failure.⁷⁷⁷ Interestingly, the STS stroke risk model was more successful in predicting outcomes for PCI compared with CABG. More accurate risk prediction tools are needed to precisely estimate adverse events following LMCAD revascularization through both CABG and PCI. Other clinical factors, such as frailty or liver cirrhosis,^{778,779} have been found to increase post-operative mortality and should be taken into consideration during the decision-making process.⁷⁸⁰

The SYNTAX score was prospectively developed as an angiographic stratification tool to quantify the complexity of coronary lesions in patients with left main coronary artery (LMCA) or multivessel CAD and aid clinicians in deciding the most appropriate revascularization procedure during Heart Team discussions.⁷⁸¹ However, there are limitations to the SYNTAX score. Firstly, it is a time-consuming score requiring a detailed angiographic evaluation of each lesion. Secondly, there is considerable inter-observer variability in its calculation, with a poor correlation between core lab and operator-calculated SYNTAX score being reported.⁷⁷⁹ Thirdly, it is an anatomical score that quantifies obstruction but not plaque burden. Fourthly, it does not take physiological and clinical variables into account.⁷⁸² Machine learning may streamline this process, generating prognostic information that is superior to clinical risk scores⁷⁸³ and relevant to clinical decision-making.

The SYNTAX II score was developed by combining clinical and anatomical features to better guide decision-making between CABG and PCI than the anatomical SYNTAX score.^{784,785} Although the usefulness of the SYNTAX II score was demonstrated in several studies,^{785–787} it

overestimated 4-year all-cause mortality in the EXCEL trial.⁷⁸⁸ The updated version, SYNTAX score II 2020, using the SYNTAX Extended Survival (SYNTAXES) data and external validation in the population of the FREEDOM, BEST, and PRECOMBAT trials,⁷⁸⁹ showed modest discrimination for predicting 5-year MACE (c-index for PCI and CABG of 0.62 and 0.67, respectively) and acceptable discrimination for predicting 10-year mortality. Another validation study indicated that the score displayed acceptable discrimination for all-cause mortality at 5 years in a Japanese cohort with LMCAD and/or multivessel CAD,⁷⁸⁷ but external validation in a prospective setting is lacking.⁷⁸³

The British Cardiovascular Intervention Society myocardial jeopardy score (BCIS-JS) is an alternative to the SYNTAX score, enabling the assessment of the severity and extent of CAD. It has been proven effective in predicting mortality after PCI and assessing the completeness of revascularization,⁷⁹⁰ but it is not as commonly used as the SYNTAX score.

4.4.5. Choice of myocardial revascularization modality

Both myocardial revascularization modalities—PCI and CABG—can achieve excellent outcomes, although through different mechanisms, in appropriately selected patients when GDMT alone fails.

4.4.5.1. Patients with single- or two-vessel coronary artery disease

Randomized evidence and subgroup analyses of trials enrolling a broader spectrum of CAD patients showed similar performance of PCI and CABG in patients with one- or two-vessel CAD, with or without the involvement of the proximal LAD in terms of death, stroke, or MI.^{791–797} In patients with complex LAD lesions, the need for late repeat revascularization is higher after PCI than CABG,⁷⁹⁷ but CABG is a more invasive procedure with inherent risks, longer hospital stay and healing.⁷⁵⁸

4.4.5.2. Patients with unprotected left main coronary artery disease

Over the past two decades, several trials have compared PCI and CABG in patients with multivessel CAD, with or without unprotected LMCAD.^{326,728,730,798–801} (Table 9). The patients who were included in these trials had to meet the eligibility criteria for both CABG or PCI at an acceptable risk level, and their coronary anatomy had to allow complete revascularization through both procedures. However, due to the strict inclusion criteria, only a small percentage of eligible patients (ranging from 6% to 40%) were enrolled in these trials.^{798,801} The strict inclusion criteria resulted in enrolling a relatively young population with a lower burden of comorbidities (mean age <66 years).^{728,730,798,801}

Meta-analyses of RCTs have shown that the risk of death is similar for both CABG and PCI for LMCAD, even for patients with a high SYNTAX score, up to 5–10 years after the intervention. However, the risk of stroke is higher with CABG, while the risk of spontaneous MI is higher with PCI.^{728,730,800,802–804} In the individual-patient data meta-analysis of four randomized trials,⁷³⁰ mortality over 5 years was not statistically different between patients treated with PCI or with CABG [11.2% vs. 10.2%; HR 1.10 (95% CI, 0.91–1.32); $P = .33$; absolute risk difference of 0.9%]. A similar treatment effect was observed for 10-year mortality [22.4% vs. 20.4%; HR 1.10 (95% CI, 0.93–1.29); $P = .25$; absolute risk difference 2.0%]. Spontaneous MI was lower in the CABG arm [6.2% vs. 2.6%; HR 2.35 (95% CI, 1.71–3.23); $P < .0001$; absolute risk difference 3.5%], while the results of periprocedural MI differed according to whether the analysis used the protocol definition or the universal definition of MI (available for only two

studies). Stroke was not statistically different overall [2.7% vs. 3.1%; HR 0.84 (95% CI, 0.59–1.21); $P = .36$; absolute risk difference of -0.4%]. However, in a pre-specified analysis of the first 12 months of follow-up, stroke was lower after PCI than after CABG [0.6% vs. 1.6%; HR 0.37 (95% CI, 0.19–0.69); $P = .002$; absolute risk difference of -1.0%].⁷⁸² Subgroup analysis based on the SYNTAX score and the number of additionally involved coronary vessels revealed no difference in all-cause mortality between CABG and PCI for SYNTAX score ≤ 32 or LMCA stenosis with 0/1 vessel disease. However, a trend for higher all-cause mortality was noted with PCI for SYNTAX score > 32 (HR 1.30; 95% CI, 0.92–1.84) and/or LMCA stenosis with 2/3 vessel disease (HR 1.25; 95% CI, 0.97–1.60).⁷⁸² Of note, the LMCA stenosis involved distal bifurcation in 75% of the patients, and the absence of a bifurcation lesion had no impact on mortality.⁷³⁰ True bifurcation left main lesions (defined as Medina type 1,1,1 or 0,1,1 both main vessel and side vessel $> 50\%$ narrowed with reference diameters ≥ 2.75 mm),⁸⁰⁵ which frequently require 2-stent techniques, have worse clinical outcomes than non-bifurcation lesions.^{806–808} Despite excellent results after LMCA bifurcation stenting on angiography, 13% of patients still experience residual ischaemia in turn associated with higher long-term cardiovascular mortality.⁸⁰⁹ Using intracoronary imaging guidance to optimize stent expansion and prevent side-branch jailing may improve outcomes after PCI of bifurcation LMCA lesions.⁸¹⁰

Operator experience may significantly affect the outcomes after interventional procedures. A single-centre study from China found that operators with a higher volume of procedures performed (> 15 per year) had better outcomes for unprotected LMCA PCI.⁸¹¹ An analysis of the outcome data from the British Cardiovascular Intervention Society's national PCI database on 6724 patients who underwent PCI for unprotected LMCA between 2012 and 2014 revealed that the volume of procedures performed by the operator plays a significant role in determining the outcome after PCI of unprotected LMCA.⁸¹² Although high-volume operators undertook PCIs on patients with greater comorbid burden and CAD complexity compared with low-volume operators, 12-month survival was lower in high-volume operators [odds ratio (OR) 0.54; 95% CI, 0.39–0.73]. A close association between operator volume and superior 12-month survival was observed ($P < .001$).

A 2022 Joint ESC/EACTS (European Association for Cardio-Thoracic Surgery) task force recently reviewed the 2018 guideline recommendations on the revascularization of LMCAD in low-risk surgical patients with suitable anatomy for PCI or CABG.⁷⁸² The review was mainly based on the recent individual-patient data meta-analysis⁷³⁰ of the long-term outcomes after CABG or PCI for LMCAD from four randomized clinical trials that included 4394 patients between March 2005 and January 2015. The review confirmed that for stable CCS patients with left main stem disease requiring revascularization, both treatment options are clinically reasonable based on patient preference, expertise availability, and local operator volumes. It was proposed that revascularization with CABG be the recommended option, with suggested class I and LOE A, while PCI be overall recommended with a suggested class IIa and LOE A. The present guidelines confirm that, among patients suitable for both revascularization modalities, CABG is recommended as the overall preferred revascularization mode over PCI, given the lower risk of spontaneous MI and repeat revascularization.^{730,782} The present guidelines also acknowledge that in patients with significant LMCA stenosis of low complexity (SYNTAX score ≤ 22), in whom PCI can provide equivalent completeness of revascularization to that of CABG, PCI is recommended as an alternative to CABG, given its lower invasiveness and non-inferior survival.^{718,728,730,802,813}

Table 9 Summary of trial-based evidence for the comparison of percutaneous coronary intervention and coronary artery bypass grafting in patients with left main coronary artery disease

Study	Study population	Primary endpoint	Follow-up	Findings
PRECOMBAT (non-inferiority) ⁸¹⁴	600 patients with newly diagnosed LMCAD who had stable angina, unstable angina, silent ischaemia, or non-ST-segment elevation MI	All-cause death, MI, stroke, or ischaemia-driven target vessel revascularization	2 years	1-year follow-up: 8.7% and 6.7% primary endpoints for PCI and CABG, respectively, absolute risk difference 2% (95% CI, -1.6% to 5.6%), $P = .01$ for non-inferiority 2-year follow-up: 12.2% and 8.1% primary endpoints for PCI and CABG, respectively, HR 1.50 (95% CI, 0.90–2.52), $P = .12$
PRECOMBAT (extended follow-up) ⁸¹⁵			5 years	17.5% and 14.3% primary endpoints for PCI and CABG, respectively, HR 1.27 (95% CI, 0.84–1.90), $P = .26$
PRECOMBAT (extended follow-up) ⁸¹⁶			11.3 years (median)	29.8% and 24.7% primary endpoints for PCI and CABG, respectively, HR 1.25 (95% CI, 0.93–1.69)
SYNTAX ⁸¹⁷	1800 patients with <i>de novo</i> three-vessel (n = 1095) and LMCAD (n = 795)	All-cause death, stroke, MI, and repeat revascularization	1 year	For the LMCAD group: 15.8% and 13.7% primary endpoints for PCI and CABG, respectively; $P = .44$
SYNTAX ⁸¹⁸			3 years	For the LMCAD group: 26.8% and 22.3%, primary endpoints for PCI and CABG, respectively; $P = .20$
SYNTAX ⁸¹³			5 years	For the LMCAD group: 36.9% and 31.0% primary endpoints for PCI and CABG, respectively, HR 1.25 (95% CI, 0.93–1.69), $P = .12$
SYNTAX (extended follow-up) ⁷⁹⁵		All-cause death	10 years	For the LMCAD group: 27% and 28% primary endpoints for PCI and CABG, respectively, HR 0.92 (95% CI, 0.69–1.22)
NOBLE (non-inferiority hypothesis) ⁸¹⁹	1201 patients with LMCAD who had stable angina pectoris, unstable angina pectoris, or non-ST-segment elevation myocardial infarction	All-cause death, non-procedural MI, any repeat coronary revascularization, or stroke	3.1 years (mean)	28% and 18% primary endpoints for PCI and CABG, HR 1.51 (95% CI, 1.13–2.00), $P = .004$ for superiority
NOBLE (extended follow-up) ⁸²⁰			4.9 years (median)	28% and 19% primary endpoints for PCI and CABG, HR 1.58 (95% CI, 1.24–2.01), $P < .001$ for superiority
EXCEL (non-inferiority hypothesis) ⁸²¹	1905 patients with LMCAD of low or intermediate anatomical complexity (SYNTAX score ≤ 32)	All-cause death, stroke, or MI	3 years (median)	15.4% and 14.7% primary endpoints for PCI and CABG, absolute risk difference 0.7% (upper 97.5% confidence limit: 4%), $P = .02$ for non-inferiority; HR 1.00 (95% CI, 0.79–1.26), $P = .98$ for superiority
EXCEL (extended follow-up) ⁸²²			5 years	22.0% and 19.2% primary endpoints for PCI and CABG, absolute risk difference 2.8% (95% CI, -0.9 to 6.5), $P = .13$; OR 1.19 (95% CI, 0.95–1.50)

CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; LMCAD, left main coronary artery disease; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention.

4.4.5.3. Patients with multivessel coronary artery disease

The SYNTAX and SYNTAXES randomized trials, comparing PCI and CABG for multivessel CAD with or without unprotected LMCAD, reported differences in terms of survival and freedom from cardiovascular events dependent on SYNTAX score.^{795,798,823} The recently published 10-year follow-up results of the SYNTAX trial (SYNTAXES trial) reported similar all-cause death rates with both revascularization modalities,⁷⁹⁵ while there was significantly higher mortality in patients with SYNTAX scores ≥ 33 who were randomized for PCI (HR 1.41; 95% CI, 1.05–1.89).⁷⁹⁵ A significant 5-year mortality gap between PCI and CABG has been reported among patients with complex multivessel CAD in the presence of DM (15.7% after PCI vs. 10.7% after CABG; HR 1.44; 95% CI, 1.20–1.77; $P = .0001$).⁷²⁸

In the FREEDOM trial (Strategies for Multivessel Revascularization in Patients with Diabetes), 1900 patients with diabetes and multivessel disease without LMCAD were randomized to CABG vs. PCI (using first-generation DES). Long-term results at a median follow-up duration of 3.8 years [interquartile range (IQR) 2.5–4.9 years] showed higher all-cause mortality in the PCI group vs. CABG group (24.3% vs. 18.3%; $P = .01$).⁸⁰¹ Out of all the centres that participated in the study, only 25 agreed to participate in the FREEDOM extended follow-up, and therefore, only 49.6% of patients in the study were followed up for up to 8 years thus limiting statistical power. The all-cause mortality rate among the FREEDOM follow-up patients was not significantly different between those who underwent PCI and CABG procedures (23.7% vs. 18.7%; HR 1.32; 95% CI, 0.97–1.79; $P = .076$). In multivariable analysis, a significant interaction emerged between patient age and long-term survival benefit of CABG surgery. Patients younger than the median age at study entry (63.3 years) preferentially derived benefit from CABG; mortality among patients ≤ 63.3 years old was 20.7% (PCI) vs. 10.2% (CABG); mortality among patients > 63.3 years old was 26.3% vs. 27.6% ($P = .01$ for interaction).⁸²⁴

4.4.5.4. Impact of coronary pressure guidance on multivessel coronary artery disease patients undergoing percutaneous coronary intervention

Consistently higher rates of repeat revascularizations following PCI compared with CABG have been shown in clinical trials involving multivessel CAD patients, with significant impacts on outcomes.⁸²⁵ With the use of modern DESs, the rate of repeat revascularization after PCI has declined.^{725,795,802,820} FFR guidance during PCI leads to lower revascularization rates compared with angiography-guided PCI, with fewer stents placed in the FFR group.⁸²⁶

In the FAME 3 trial, 1500 patients with three-vessel CAD not involving the LMCA were randomly assigned to PCI with second-generation DESs (durable polymer zotarolimus-eluting stents) guided by FFR, or to CABG.³²⁶ At 1-year follow-up, the incidence of the composite primary endpoint, MACCE [major adverse cardiac (death from any cause, MI, stroke, or repeat revascularization) or cerebrovascular events], was 10.6% among patients assigned to FFR-guided PCI and 6.9% among patients assigned to CABG surgery (HR 1.5; 95% CI, 1.1–2.2), findings that were not consistent with non-inferiority ($P = .35$ for non-inferiority).³²⁶ At 3-year follow-up, there still was a significantly higher rate of MACCE for PCI than for CABG (18.6% vs. 12.5%; HR 1.5; 95% CI, 1.2–2.0; $P = .002$), consistent with the 1-year follow-up results. However, there was no difference in the incidence of the composite of death, MI, or stroke after FFR-guided PCI compared with CABG (12.0% vs. 9.2%; HR 1.3; 95% CI, 0.98–1.83; $P = .07$). The rates of death (4.1% vs. 3.9%; HR 1.0; 95% CI, 0.6–1.7; $P = .88$) and stroke (1.6% vs.

2.0%; HR 0.8; 95% CI, 0.4–1.7; $P = .56$) were not different, while MI again occurred more frequently after PCI (7.0% vs. 4.2%; HR 1.7; 95% CI, 1.1–2.7; $P = .02$).⁸²⁷ Repeat revascularization was also more frequent after PCI (11.1% vs. 5.9%; HR 1.9; 95% CI, 1.3–2.7; $P = .001$). Of note, after both PCI and CABG, event rates were lower (about half for mortality) than in the SYNTAX cohort of patients with three-vessel CAD. There was a narrower difference for MI rates between the two modalities, probably owing to procedural advances with PCI and CABG and improvements in GDMT. In patients with less complex CAD (SYNTAX score ≤ 22), outcomes were as favourable as after CABG.

4.4.5.5. Virtual percutaneous coronary intervention: combination of coronary pressure mapping with coronary anatomy for percutaneous coronary intervention planning

There is increasing evidence on the impact of post-PCI FFR/iFR/QFR on outcomes after PCI.^{828–833} A quarter of these patients have residual ischaemia (FFR < 0.80 or iFR ≤ 0.89) after angiographically successful PCI, with circa 80% of cases attributable to focal lesions not identified by angiography alone.⁸³⁰ One randomized trial reported that post-PCI iFR/FFR can be improved by additional intracoronary intervention, including post-dilatation or additional stent implantation, but remains ≤ 0.80 in 18% of cases.⁸²⁹ Preliminary results demonstrate that the combination of invasive coronary pressure mapping by iFR pullback or QFR mapping superimposed on the anatomical information of ICA accurately predict the post-PCI coronary pressure for any combination of stent location and stent length, as part of a 'virtual PCI' approach,^{348,834} and allows modification of the procedural planning in about 30% of cases.⁸³⁵ The AQVA (Angio-based Quantitative Flow Ratio Virtual PCI Versus Conventional Angio-guided PCI in the Achievement of an Optimal Post-PCI QFR) trial ($n = 300$) demonstrated that a strategy of QFR/ICA-based virtual PCI was associated with a higher rate of post-PCI QFR ≥ 0.90 compared with angiography-based PCI (93.4% vs. 84.9%, $P = .009$).⁸³⁶ The DEFINE GPS trial (NCT04451044) is currently investigating the clinical benefit of pre-procedural coronary pressure mapping with iFR pullback and 'virtual PCI' to clarify this issue further and improve post-PCI clinical outcomes.

Virtual PCI can be conducted by combining anatomical information from CCTA with that of FFR-CT. FFR-CT/CCTA-based virtual PCI has two theoretical advantages over ICA-based virtual PCI: (i) it does not require invasive investigation, and (ii) it provides information on vessel wall/plaque composition.⁸³⁷ FFR-CT/CCTA-based virtual PCI has been shown to accurately predict post-PCI FFR⁸³⁸ and to modify PCI procedural planning in 31% of lesions and 45% of patients.⁸³⁹ The Precise Procedural and PCI Plan (P4) trial (NCT05253677) is currently investigating the clinical benefit of iFR-based virtual PCI to clarify this issue further and improve post-PCI clinical outcomes.

4.4.5.6. Impact of intracoronary imaging guidance on multivessel coronary artery disease patients undergoing percutaneous coronary intervention

Three large randomized trials have recently investigated the clinical benefit of intracoronary imaging during 'complex' PCI. One trial, RENOVATE-COMPLEX PCI,⁸⁴⁰ mainly investigated the benefit of IVUS (74% IVUS, 26% OCT), while the two others, OCTOBER⁸¹⁰ and ILUMIEN IV,⁸⁴¹ investigated the benefit of OCT. Importantly, while OCTOBER (true bifurcation lesions) and RENOVATE-COMPLEX PCI (including true bifurcation lesions, long lesions,

chronic total occlusion lesions) focused on ‘anatomically’ complex lesions, ILUMIEN IV made the choice to define ‘complexity’ by the clinical context (DM and STEMI/NSTEMI) and/or by the anatomical characteristics of the lesions.

In RENOVATE-COMPLEX PCI, intravascular imaging-guided PCI led to a lower risk of a composite of death from a cardiac cause, target vessel-related MI, or clinically driven target-vessel revascularization than angiography-guided PCI by 2 years (7.7% vs. 12.3%; HR 0.64; 95% CI, 0.45–0.89; $P = .008$).⁸⁴⁰

In OCTOBER, OCT-guided PCI led to a lower risk of a composite of death from a cardiac cause, target-lesion MI, or ischaemia-driven target-lesion revascularization than angiography-guided PCI by 2 years (10.1% vs. 14.1%; HR 0.70; 95% CI, 0.50–0.98; $P = .035$).⁸¹⁰ In ILUMIEN IV, OCT-guided PCI failed to decrease the rate of the primary efficacy endpoint of target-vessel failure, defined as death from cardiac causes, target-vessel MI, or ischaemia-driven target-vessel revascularization (7.4% vs. 8.2%; HR 0.90; 95% CI, 0.67–1.19; $P = .45$), while the incidence of definite/probable stent thrombosis was significantly reduced by OCT guidance vs. angiography guidance (0.5% vs. 1.4%; HR 0.36; 95% CI, 0.14–0.91; $P = .02$).⁸⁴¹

4.4.5.7. Hybrid revascularization in multivessel coronary artery disease patients

Arterial grafting with left internal mammary artery (LIMA) to the LAD system and multiple arterial grafting reduces the risk of graft occlusion, thus increasing the longevity of revascularization efficacy after CABG.^{842,843} Hybrid revascularization of multivessel CAD with minimally invasive direct coronary artery bypass (MIDCAB)-LAD plus PCI of the remaining arteries may represent an alternative option. Hybrid off-pump revascularization seems a suitable option for patients at moderate-to-high risk for surgery by avoiding the use of cardiopulmonary bypass. Despite this attractive concept, the frequency of hybrid revascularizations remains extremely modest, with about 0.1% of surgical revascularizations.⁸⁴⁴ Few data are available comparing hybrid revascularization vs. conventional CABG or PCI. Large registry data report higher rates of bleeding, renal failure, MI, and HF with hybrid revascularization compared with PCI alone,⁸⁴⁴ while a very small randomized trial reported similar clinical outcomes at long-term follow-up.⁸⁴⁵ It seems challenging to perform larger RCTs to investigate this question. The recent National Heart, Lung, and Blood Institute-funded Hybrid Trial (Hybrid Coronary Revascularization Trial; NCT03089398) was prematurely discontinued due to slow enrolment, with only 200 patients in 5 years.

4.4.6. Patient–physician shared decision-making to perform and select revascularization modality

Shared decision-making between patients and healthcare professionals, based on patient-centred care, is considered a paramount process in defining the appropriate therapeutic pathway. Essential aspects of shared decision-making are: a complete and accurate explanation of the disease; presentation and description of therapeutic options; discussion of potential risks, benefits, and impact on QoL for each procedure; considering patient preferences and goals; and carefully explaining each step of the post-procedural course and follow-up. Poor shared decision-making is associated with worse physical and mental outcomes, lower adherence to therapy, and an increased number of emergency department visits.^{846–848} Shared decision-making and family

meetings involving relatives increase patient trust in the physicians, with greater adherence to therapeutic decisions. Shared decision-making and patient medical education, considering the patient’s characteristics, mental status, cultural beliefs, and educational level, are therefore associated with increased patient knowledge and better QoL and with lower levels of anxiety and depression.^{849–851}

Using lay language and discussion with patients and relatives of short-term procedure-related and long-term risks and benefits—such as survival, relief of angina, QoL, the potential need for late reintervention, the need for prevention measures, and uncertainties associated with different treatment strategies—are of great importance. Although current recommendations are primarily based on the ability of treatments to reduce adverse events, including improved survival, there is growing interest in PROMs.⁸⁵² Patients are not only interested in knowing how recommended treatment impacts prognosis but also their QoL in the way they perceive it.⁸⁵³ The patient’s right to decline the treatment option recommended by the Heart Team must be respected. Patient refusal of a recommended treatment should be acknowledged in a written document after the patient has received the necessary information. In this case, the Heart Team may offer the patient an alternative treatment option.

The multidisciplinary Heart Team, on site or with partner institutions (Hub-Spoke institutions)—comprising clinical or non-invasive cardiologists, cardiac surgeons and interventional cardiologists, as well as anaesthetists or other specialists and healthcare professionals, if deemed necessary—should provide a balanced multidisciplinary decision-making process.

Transparency in informed consent is critical, particularly when treatment options are debated. Complex cases, such as patients with CAD of high anatomic complexity and significant non-cardiac comorbidities, should be discussed in the Heart Team, taking into consideration other characteristics not always included in traditional databases, such as frailty. Heart Team/guideline discordance is common in complex CAD patients undergoing revascularization, especially in elderly patients, those with complex coronary disease, and those treated at centres without cardiac surgery service. These patients have a higher risk of mid-term mortality.⁸⁵⁴

In all cases, it is necessary to allow sufficient time to assess all available information and clearly explain and discuss the findings with each patient. The rationale for a decision and consensus on the optimal revascularization treatment should be documented on the patient’s chart. While the Heart Team decision is mainly driven by long-term survival benefits with a certain modality of revascularization, patient’s preferences must be respected.^{853,855,856}

4.4.7. Institutional protocols, clinical pathways, and quality of care

Institutional protocols, developed by the Heart Team and aligned with the current guidelines, should delineate specific anatomical and functional criteria of disease complexity and specific clinical subsets of patient’ risk for cardiac surgery or intervention that may or may not be treated *ad hoc*. These protocols should be incorporated into clinical pathways, with regular meetings to assess the applied indications for myocardial revascularization and monitor the safety and effectiveness of the procedures, ensuring the quality of delivered patient care. Collaborative protocols are necessary when cardiac surgery isn’t available on site, and remote Heart Team meetings should be established.

Recommendation Table 22 — Recommendations for revascularization in patients with chronic coronary syndrome (see also Evidence Table 22)

Recommendations	Class ^a	Level ^b
Informed and shared decisions		
It is recommended that patients scheduled for percutaneous or surgical revascularization receive complete information about the benefits, risks, therapeutic consequences, and alternatives to revascularization, as part of shared clinical decision-making. ^{847,848,857}	I	C
For complex clinical cases, to define the optimal treatment strategy, in particular when CABG and PCI hold the same level of recommendation, a Heart Team discussion is recommended, including representatives from interventional cardiology, cardiac surgery, non-interventional cardiology, and other specialties if indicated, aimed at selecting the most appropriate treatment to improve patient outcomes and quality of life.	I	C
It is recommended to communicate the proposal of the Heart Team in a balanced way using language that the patient can understand.	I	C
It is recommended that the decision for revascularization and its modality be patient-centred, considering patient preferences, health literacy, cultural circumstances, and social support. ^{849–851}	I	C
It is recommended that the Heart Team (on site or with a partner institution) develop institutional protocols to implement the appropriate revascularization strategy in accordance with current guidelines. ^{855,856,858}	I	C
Revascularization to improve outcomes		
In chronic coronary syndrome patients with left ventricular ejection fraction >35%		
In CCS patients with LVEF >35%, myocardial revascularization is recommended, in addition to guideline-directed medical therapy, for patients with functionally significant left main stem stenosis to improve survival. ^{718,719,859,860}	I	A
In CCS patients with LVEF >35%, myocardial revascularization is recommended, in addition to guideline-directed medical therapy, for patients with functionally significant three-vessel disease to improve long-term survival and to reduce long-term cardiovascular mortality and the risk of spontaneous myocardial infarction. ^{55,56,317,732–734}	I	A
In CCS patients with LVEF >35%, myocardial revascularization is recommended, in addition to guideline-directed medical therapy, for patients with functionally significant single- or two-vessel disease involving the proximal LAD, to reduce long-term cardiovascular mortality and the risk of spontaneous myocardial infarction. ^{55,56,317,719,732–734}	I	B
In chronic coronary syndrome patients with left ventricular ejection fraction ≤35%		
In CCS patients with LVEF ≤35%, it is recommended to choose between revascularization or medical therapy alone, after careful evaluation, preferably by the Heart Team, of coronary anatomy, correlation between coronary artery disease and LV dysfunction, comorbidities, life expectancy, individual risk-to-benefit ratio, and patient perspectives.	I	C
In surgically eligible CCS patients with multivessel CAD and LVEF ≤35%, myocardial revascularization with CABG is recommended over medical therapy alone to improve long-term survival. ^{53,54,749,861}	I	B
In selected CCS patients with functionally significant MVD and LVEF ≤35% who are at high surgical risk or not operable, PCI may be considered as an alternative to CABG. ^{526,729}	IIb	B
Revascularization to improve symptoms		
In CCS patients with persistent angina or anginal equivalent, despite guideline-directed medical treatment, myocardial revascularization of functionally significant obstructive CAD is recommended to improve symptoms. ^{50,321,402,732,734,757}	I	A
Assessment of procedural risks and post-procedural outcomes		
In patients with complex CAD in whom revascularization is being considered, it is recommended to assess procedural risks and post-procedural outcomes to guide shared clinical decision-making.	I	C
Calculation of the STS score is recommended to estimate in-hospital morbidity and 30-day mortality after CABG. ^{777,862–864}	I	B
In patients with multivessel obstructive CAD, calculation of the SYNTAX score is recommended to assess the anatomical complexity of disease. ^{786,865}	I	B
Intracoronary imaging guidance by IVUS or OCT is recommended when performing PCI on anatomically complex lesions, in particular left main stem, true bifurcations, and long lesions. ^{866,337,810,840,841}	I	A
Intracoronary pressure measurement (FFR or iFR) or computation (QFR) :		
• is recommended to guide lesion selection for intervention in patients with multivessel disease; ^{308,826,866,867}	I	A
• should be considered at the end of the procedure to identify patients at high risk of persistent angina and subsequent clinical events; ^{828,830,831,868}	IIa	B
• may be considered at the end of the procedure to identify lesions potentially amenable to treatment with additional PCI. ^{350,829,831}	IIb	B

Continued

Choice of revascularization modality		
It is recommended that physicians select the most appropriate revascularization modality based on patient profile, ^c coronary anatomy, ^d procedural factors, ^e LVEF, preferences, and outcome expectations. ^{719,725,728,792–795,801,816,820,822,859,869}	I	C

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, chronic coronary syndrome; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; IVUS, intravascular ultrasound; LAD, left anterior descending; LV, left ventricular; LVEF, left ventricular ejection fraction; MVD, multivessel disease; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; QFR, quantitative flow ratio; STS, Society of Thoracic Surgeons; SYNTAX, SYnergy Between PCI with TAXUS and Cardiac Surgery.

^aClass of recommendation.

^bLevel of evidence.

^cAge, frailty, cognitive status, diabetes, and any other comorbidities.

^dMultivessel disease with/out left main stem involvement, high anatomical complexity, and likelihood of revascularization completeness.

^eLocal expertise and outcomes, surgical and interventional risk.

Recommendation Table 23 — Recommendations for mode of revascularization in patients with chronic coronary syndrome (see also Evidence Table 23)

Anatomically and clinically based recommendations for revascularization in CCS	Class ^a	Level ^b
Left main disease		
In CCS patients at low surgical risk ^c with significant left main coronary stenosis, CABG:		
• is recommended over medical therapy alone to improve survival; ⁷¹⁹	I	A
• is recommended as the overall preferred revascularization mode over PCI, given the lower risk of spontaneous myocardial infarction and repeat revascularization. ^{728,730,782}	I	A
In CCS patients with significant left main coronary stenosis of low complexity (SYNTAX score ≤22), in whom PCI can provide equivalent completeness of revascularization to that of CABG, PCI is recommended as an alternative to CABG, given its lower invasiveness and non-inferior survival. ^{718,728,730,802,813}	I	A
In CCS patients with significant left main coronary stenosis of intermediate complexity (SYNTAX score 23–32), in whom PCI can provide equivalent completeness of revascularization to that of CABG, PCI should be considered, given its lower invasiveness and non-inferior survival. ^{718,728,730,802,805,809,813,820,822}	IIa	A
Left main with multivessel disease^d		
In CCS patients at low surgical risk with suitable anatomy, CABG is recommended over medical therapy alone to improve survival. ^{718,719,870}	I	A
In CCS patients at high surgical risk, PCI may be considered over medical therapy alone. ^{728,813}	IIb	B
Multivessel disease^d and diabetes		
In CCS patients with significant multivessel disease and diabetes, with insufficient response to guideline-directed medical therapy, CABG is recommended over medical therapy alone and over PCI to improve symptoms and outcomes. ^{801,824,871–874}	I	A
In CCS patients at very high surgical risk, PCI should be considered over medical therapy alone to reduce symptoms and adverse outcomes. ^{55,874}	IIa	B
Three-vessel disease, without diabetes		
In CCS patients with significant three-vessel disease, preserved LVEF, no diabetes, and insufficient response to guideline-directed medical therapy, CABG is recommended over medical therapy alone to improve symptoms, survival, and other outcomes. ^{719,722,875}	I	A
In CCS patients with preserved LVEF, no diabetes, insufficient response to guideline-directed medical therapy, and significant three-vessel disease of low-to-intermediate anatomic complexity in whom PCI can provide similar completeness of revascularization to that of CABG, PCI is recommended, given its lower invasiveness, and generally non-inferior survival. ^{326,728,795,798,876}	I	A
Single- or double-vessel disease involving the proximal LAD		
In CCS patients with significant single- or double-vessel disease involving the proximal LAD and insufficient response to guideline-directed medical therapy, CABG or PCI is recommended over medical therapy alone to improve symptoms and outcomes. ^{52,321,719,791,792}	I	A
In CCS patients with complex significant single- or double-vessel disease involving the proximal LAD, less amenable to PCI, and insufficient response to guideline-directed medical therapy, CABG is recommended to improve symptoms and reduce revascularization rates. ^{877–879}	I	B
Single- or double-vessel disease not involving the proximal LAD		
In symptomatic CCS patients with significant single- or double-vessel disease not involving the proximal LAD and with insufficient response to guideline-directed medical therapy, PCI is recommended to improve symptoms. ^{50,321,732}	I	B
In symptomatic CCS patients with significant single- or double-vessel disease not involving the proximal LAD and with insufficient response to guideline-directed medical therapy, not amenable to revascularization by PCI, CABG may be considered to improve symptoms.	IIb	C

CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; LAD, left anterior descending; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SYNTAX, SYnergy Between PCI with TAXUS and Cardiac Surgery.

^aClass of recommendation.

^bLevel of evidence.

^cFor example: absence of previous cardiac surgery, or severe morbidities, or frailty, or immobility precluding CABG.

^dMultivessel disease is defined as the involvement of at least two main coronary arteries.

5. Optimal assessment and treatment of specific groups

5.1. Coronary artery disease and heart failure

About half of acute and chronic HF patients have an ischaemic aetiology.^{880,881} Over the last decades, the proportion of ischaemic HFrEF has decreased while that of HFpEF, defined according to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure,⁵²⁶ has increased.⁸⁸² The evaluation of inducible ischaemia is important in patients with HF, given the high prevalence of CAD.^{883–885} Moreover, patients with HFpEF may present MVA due to CMD.⁸⁸⁶ Indeed, CMD was observed in up to 75% of patients with HFpEF and was associated with worse diastolic relaxation velocities, as well as higher filling pressures, and an increased risk of adverse events.^{883–885,887–890} Clinical assessment alone may under-estimate the proportion of patients with obstructive or non-obstructive CAD, which can be found in up to 81% of HFpEF patients.⁸⁸⁷ Under-estimation of obstructive CAD leads to failure in identifying those patients who may benefit from revascularization. Conversely, in ANOCA patients with preserved LV function, a CFR of <2 was independently associated with diastolic dysfunction and future MACE, especially HFpEF events.⁸⁹¹ This suggests that CMD and myocardial stiffness may contribute to HFpEF pathophysiology.⁸⁹² In HFpEF patients, functional imaging should, therefore, be considered to detect CMD and epicardial CAD.

Exercise or pharmacological stress echocardiography can be used for the assessment of inducible ischaemia and can also help in the differential diagnosis of HFpEF.^{893,894} Stress SPECT or PET can also be used for the detection of inducible ischaemia. Non-invasive stress testing can be difficult in patients with HF because of possible exercise intolerance. CCTA is recommended in patients with HF with a low-to-intermediate pre-test likelihood of obstructive CAD and those with equivocal non-invasive stress tests, provided there is no contraindication to contrast administration.^{894–898} In HFpEF patients, perfusion PET should be considered for the detection of CMD.⁸⁹¹ In patients with HFrEF and moderate-to-severe inducible myocardial ischaemia, surgical revascularization improved long-term survival.^{54,315} The results of the REVIVED-BCIS2 trial seem to contradict these findings, as PCI did not reduce mortality or HF hospitalization in patients with severe LV systolic dysfunction (LVEF ≤ 35%) receiving optimal medical therapy.⁷²⁹ The same trial also revealed that viability testing did not offer any prognostic benefit.⁷⁵⁵

The role of myocardial revascularization and viability testing is further addressed in *Section 4.4.2*.

In HF patients with anginal (or equivalent) symptoms, despite optimized GDMT, CCTA or ICA is recommended to confirm the diagnosis of obstructive CAD and its severity.

Over the past three decades, several landmark clinical trials have provided robust evidence on the prognostic benefit of pharmacological therapies in patients with HFrEF. In these patients, four drug classes [ACE-Is or angiotensin receptor neprilysin inhibitors (ARNIs),⁸⁹¹ beta-blockers, mineralocorticoid receptor antagonists (MRAs), and SGLT2 inhibitors] are recommended for outcome improvement regardless of HF aetiology and comorbidities, including CAD.⁵²⁶

In patients with HFrEF, an ARB is recommended in patients who do not tolerate ACE-Is or ARNIs. Also, ivabradine should be considered in addition to the four pillars. It can be used as an alternative to beta-blockers, when contraindicated or not tolerated, or as additional antianginal therapy in patients with sinus rhythm and heart rate of >70 b.p.m.⁸⁹⁹ Other antianginal drugs (e.g. amlodipine, felodipine, nicorandil, trimetazidine, ranolazine, and nitrates) are effective for improving symptoms in patients with HFrEF.^{546,900–902} Diltiazem and verapamil increase HF-related events in patients with HFrEF and are contraindicated.⁵²⁶ In patients with LVEF ≤35% of ischaemic aetiology, an ICD is strongly recommended for primary prevention; in those with LVEF ≤35% and QRS >130 ms, CRT needs to be considered.⁵²⁶ Further details regarding the management of patients with HFrEF are reported in the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.⁵²⁶

In patients with HFpEF, in addition to diuretics for treating congestion, SGLT2 inhibitors are now recommended for outcome improvement.⁷⁰⁹ Additionally, beta-blockers, long-acting nitrates, CCBs, ivabradine, ranolazine, trimetazidine, nicorandil, and their combinations should be considered in patients with HFpEF and CAD for angina relief, but without foreseen benefits on HF and coronary endpoints. Low-dose rivaroxaban may be considered in patients with CAD and HF, LVEF of >40%, and sinus rhythm when at high risk of stroke and with low haemorrhagic risk.^{526,903,904}

Evidence and recommendations for myocardial revascularization in patients with HF are reported in *Section 4.4.2*. Notably, patients with advanced HF may be candidates for LV assistance devices and/or heart transplantation.⁵²⁶

During of high-risk PCI for complex CAD⁹⁰⁵ in patients with HFrEF, mechanical cardiac support, such as the microaxial flow pump, may minimize the risk of severe complications and provide haemodynamic stability, facilitating the achievement of complete revascularization.^{906,907}

Recommendation Table 24 — Recommendations for management of chronic coronary syndrome patients with chronic heart failure (see also Evidence Table 24)

Recommendations	Class ^a	Level ^b
Managing CCS in heart failure patients		
In HF patients with LVEF ≤35% in whom obstructive CAD is suspected, ICA is recommended with a view towards improving prognosis by CABG, taking into account the risk-to-benefit ratio of the procedures. ^{54,729,749,908}	I	B
In HF patients with LVEF >35% and suspected CCS with low or moderate (>5%–50%) pre-test likelihood of obstructive CAD, CCTA or functional imaging is recommended. ⁸⁸⁷	I	C
In HF patients with LVEF >35% and suspected CCS with very high (>85%) pre-test likelihood of obstructive CAD, ICA (with FFR, iFR, or QFR when needed) is recommended. ⁸⁸⁷	I	C

Continued

In patients with HFpEF with persistent angina or equivalent symptoms and normal or non-obstructive epicardial coronary arteries, PET or CMR perfusion or invasive coronary functional testing should be considered to detect or rule out coronary microvascular dysfunction. ^{883–885,887–889}	IIa	B
In selected patients with HFrEF undergoing high-risk PCI for complex CAD, the use of a microaxial flow pump may be considered in experienced centres. ^{905–907}	IIb	C
Managing heart failure in CCS patients		
It is recommended that CCS patients with HF be enrolled in a multidisciplinary HF management programme to reduce the risk of HF hospitalization and to improve survival. ^{526,909–911}	I	A
An ACE-I, an MRA, an SGLT2 inhibitor (dapagliflozin or empagliflozin), and, in stable conditions, a beta-blocker are recommended for CCS patients with HFrEF to reduce the risk of HF hospitalization and death. ^{526,704,705,912,913}	I	A
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with Heart Failure with mildly reduced Ejection Fraction (HFmrEF) or HFpEF to reduce the risk of HF hospitalization or cardiovascular death. ^{706,707}	I	A
An ARB is recommended in symptomatic patients with CCS and HFrEF unable to tolerate an ACE-I or ARNI to reduce the risk of HF hospitalization and cardiovascular death. ⁹¹⁴	I	B
Sacubitril/valsartan is recommended as a replacement for an ACE-I or ARB in CCS patients with HFrEF to reduce the risk of HF hospitalization and of cardiovascular and all-cause death. ⁶⁹³	I	B
Diuretics are recommended in CCS patients with HF and signs and/or symptoms of congestion to alleviate symptoms, improve exercise capacity, and reduce HF hospitalizations. ⁹¹⁵	I	B
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of ischaemic aetiology (unless they have had an MI in the prior 40 days), and an LVEF $\leq 35\%$ despite ≥ 3 months of optimized medical treatment, provided they are expected to survive substantially longer than 1 year with good functional status. ^{526,916}	I	A
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status, in the absence of reversible causes or unless the ventricular arrhythmia has occurred <48 h after an MI. ^{917–920}	I	A
CRT is recommended for CCS patients with symptomatic HF, sinus rhythm, LVEF $\leq 35\%$ despite GDMT, and a QRS duration ≥ 150 ms with an LBBB QRS morphology to improve symptoms and survival and to reduce morbidity. ^{526,921,922}	I	A
CRT rather than right ventricular pacing is recommended for patients with HFrEF regardless of NYHA class or QRS width who have an indication for ventricular pacing for high-degree AV block in order to reduce morbidity. This includes patients with AF. ^{923–925}	I	A

ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; AV, atrioventricular; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; FFR, fractional flow reserve; GDMT, guideline-directed medical therapy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICA, invasive coronary angiography; ICD, implantable cardioverter defibrillator; iFR, instantaneous wave-free ratio; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PET, positron emission tomography; SGLT2, sodium–glucose cotransporter 2.

^aClass of recommendation.

^bLevel of evidence.

5.2. Angina/ischaemia with non-obstructive coronary arteries

5.2.1. Definition

A large proportion of patients undergoing coronary angiography because of angina do not have obstructive epicardial coronary arteries (ANOCA). In these patients, the prevalence of demonstrable ischaemia (INOCA) varies, depending on the stress test performed, between 10% and 30% (Figure 12).^{926–928} Angina/ischaemia with non-obstructive coronary arteries is more frequent among women (approximately 50% to 70%) than in men (30% to 50%) referred for ICA.^{7,929} The mismatch between blood supply and myocardial oxygen demands leading to angina and ischaemia in ANOCA/INOCA may be caused by CMD and/or epicardial coronary artery spasm.³⁶ However, these conditions are rarely correctly diagnosed, and, therefore, no tailored therapy is prescribed for these patients. As a consequence, these patients continue to experience recurrent angina with poor QoL, leading to repeated hospitalizations, unnecessary repeat coronary angiography, and adverse cardiovascular outcomes in the short and long term.³⁶

5.2.2. Angina/ischaemia with non-obstructive coronary arteries endotypes

Invasive functional coronary testing using Ach and adenosine in individuals suspected of CCS and with non-obstructive coronary arteries enables the differentiation of the following endotypes: (i) endothelial dysfunction; (ii) impaired vasodilation (low coronary flow reserve and/or high microvascular resistance); (iii) epicardial vasospastic angina; (iv) microvascular vasospastic angina; (v) endotype combinations; (vi) equivocal response, i.e. angina without fulfilling any endotype criteria.^{37,38} The prevalence of ANOCA and INOCA in relation to the presence of the endotypes is shown in Figure 12. Angina with non-obstructive coronary arteries occurs in up to 70% of the patients undergoing ICA, of whom 25% have documented ischaemia (INOCA). Among the patients who are tested with Ach, 80% show endothelial dysfunction, 60% have MVA/VSA, and 50% have an impaired CFR and/or high microvascular resistance.^{38,927,930,931} This emphasizes the importance of testing not only patients with INOCA but also all patients with ANOCA to determine the final endotype so that appropriate treatment can be initiated.

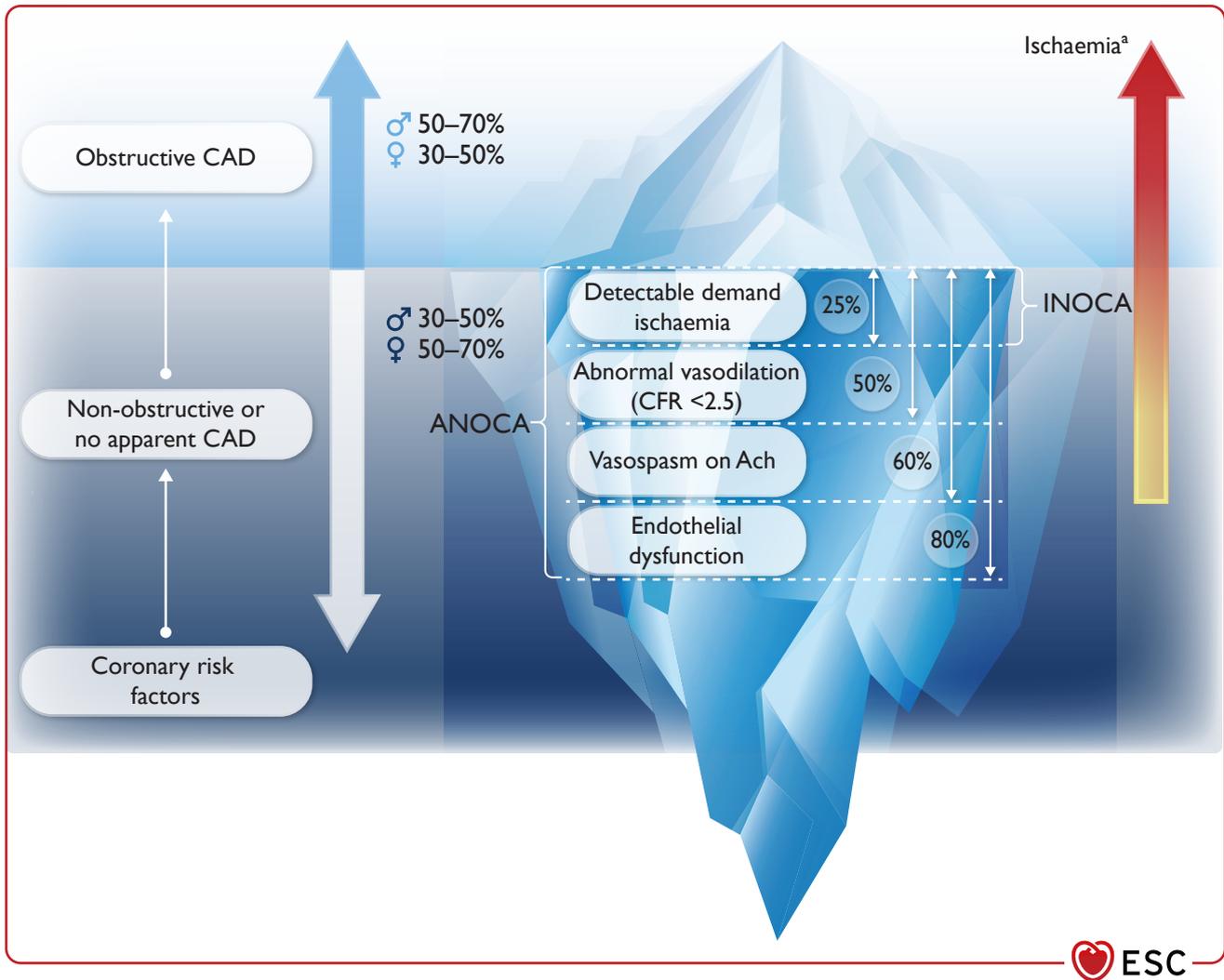


Figure 12 Prevalence of disease characteristics in patients with ANOCA/INOCA referred for invasive coronary functional testing. Ach, acetylcholine; ANOCA, angina with non-obstructive coronary arteries; CFR, coronary flow reserve; i.c., intracoronary; INOCA, ischaemia with non-obstructive coronary arteries. In the ILIAS (Inclusive Invasive Physiological Assessment in Angina Syndromes) registry,⁹²⁷ ANOCA is present in up to 70% of patients referred for invasive coronary angiography and functional testing. Endothelial dysfunction is present in 80% and an acetylcholine test is positive in 60% of these patients. An impaired CFR (≤ 2.5), measured by i.c. Doppler guidewires, is present in 50%, while ischaemia (INOCA) is documented by non-invasive functional testing in only 25% of ANOCA patients. The prevalence of coronary vasospasm can vary in different studies depending on dose of acetylcholine and test protocol. ^aPrevalence of ischaemia by non-invasive functional testing increases from non-obstructive to obstructive CAD.

5.2.2.1. Microvascular angina

Microvascular angina is the clinical manifestation of myocardial ischaemia caused by structural or functional changes in the coronary microvasculature (leading to impaired CFR and/or reduced microcirculatory conductance) and/or abnormal vasoconstriction of coronary arterioles (causing dynamic arteriolar obstruction).^{932,933} Both vascular dysfunction mechanisms may co-exist and contribute to MVA.

The prevalence of MVA was 26% in a study of patients with non-obstructive CAD who had a CFVR below 2 when assessed by transthoracic Doppler echocardiography.⁹³⁴ Studies assessing CMD invasively or by PET with different cut-offs have found that 39% to 54% had CMD.^{935,936} The threshold for CMD varies between studies and depending on the techniques used (PET, CMR, thermodilution, or Doppler); the threshold is a CFR of <2.0–2.5.^{36,39} A thermodilution

CFR of <2.0 has low sensitivity for identifying CMD, but using the same threshold as for Doppler (<2.5) results in reasonable diagnostic accuracy.⁹³⁷

Smoking, age, diabetes, hypertension, and dyslipidaemia are associated with CMD.^{934,935,938} Other studies have shown that diabetes was uncommon among patients with angina and non-obstructive CAD, while hypertension and dyslipidaemia were relatively more prevalent.^{939,940} Inflammatory conditions such as systemic lupus erythematosus (SLE) and rheumatoid arthritis appear to be associated with MVA and are not infrequently encountered in patients with angina.⁹⁴¹ Inflammatory diseases occur more often in women after menopause than in men, which may contribute to the sex differences in MVA.^{942–944} Last, but not least, there is increasing evidence that psychosocial stress is involved in coronary vasomotor disorders.^{945,946}

5.2.2.2. Epicardial vasospastic angina

Vasospastic angina is the clinical manifestation of myocardial ischaemia caused by abnormal vasoconstriction of one or more epicardial coronary arteries leading to a dynamic coronary obstruction. Standardized diagnostic criteria for VSA have been defined.⁷³ Microvascular angina and epicardial VSA can co-exist, which is associated with a worse prognosis.⁹⁴⁷ Concomitant endothelial dysfunction is prevalent in most patients with INOCA with inducible coronary artery spasm and/or impaired adenosine-mediated vasodilation.^{38,948}

The Japanese population has a higher prevalence of coronary vasospasm than Western populations. In addition, the frequencies of multiple coronary spasms (≥ 2 spastic arteries) by provocative testing in Japanese (24.3%) and Taiwanese populations (19.3%) are markedly higher than those in Caucasians (7.5%).^{949–951}

5.2.3. Clinical presentations

Angina/ischaemia with non-obstructive coronary arteries is associated with a wide variation in its clinical presentation, and symptom burden may vary over time. Failure to diagnose epicardial obstructive CAD in a patient with documented ischaemia should stimulate a subsequent search pathway to elucidate ANOCA/INOCA endotypes.

5.2.4. Short- and long-term prognosis

Symptoms of angina/ischaemia with non-obstructive coronary arteries are associated with adverse physical, mental, and social health.⁹⁵² Angina/ischaemia with non-obstructive coronary arteries is associated with poor QoL, higher risk of disability, and a higher incidence of adverse events, including mortality, morbidity, healthcare costs, recurrent hospital readmissions and repeat coronary angiograms.^{300,953–958} The incidence of all-cause death and non-fatal MI in patients with non-obstructive atherosclerosis was higher than in those with angiographically normal epicardial vessels.^{298,959–961} Proven myocardial ischaemia by stress echocardiography or nuclear imaging was associated with a higher incidence of events compared with ischaemia detected by exercise electrocardiographic stress testing.⁹⁵⁸ There is a two- to four-fold higher risk of adverse cardiovascular outcomes in patients with MVA diagnosed by PET or transthoracic echocardiography and a two-fold higher risk in patients with epicardial endothelial-dependent dysfunction.^{300,962} Microvascular angina due to impaired CFR was associated with increased major adverse cardiac events and target-vessel failure rates over a 5-year follow-up period.⁹³¹ Vasospastic angina is associated with major adverse events, including sudden cardiac death, acute MI, and syncope.⁹⁶³ In a group of ANOCA/INOCA patients, abnormal non-invasive testing did not allow the identification of patients with a higher risk of long-term cardiovascular events. However, adding intracoronary physiological assessment to non-invasive information allowed the identification of patient subgroups with up to a four-fold difference in long-term cardiovascular events.³⁵⁷

5.2.5. Diagnosis

The presence of myocardial ischaemia on functional imaging without obstructive CAD on CCTA or ICA should always raise the clinical suspicion of ANOCA/INOCA. The diagnosis of ANOCA/INOCA is exclusively based on invasive functional evaluation of the coronary microcirculation, given that no technique allows direct visualization of the coronary microcirculation *in vivo* in humans. Several non-invasive and invasive tests have been established to assess the coronary microvascular function (Figure 13).^{6,41,964,965}

5.2.5.1. Non-invasive diagnosis

Non-invasive tests (stress echocardiography, PET, perfusion CCTA, and CMR) allow diagnosing ANOCA/INOCA by measuring the CFR.⁴¹ These techniques have an excellent negative predictive value, but the positive predictive value is an issue for most, as obstructive CAD needs to be ruled out before the diagnosis of CMD can be made. Only hybrid techniques such as CCTA with perfusion and PET-CT offer combined imaging of the epicardial coronary arteries and functional testing of the coronary microcirculation in a single test.^{6,964}

5.2.5.2. Invasive coronary functional testing

Invasive coronary functional testing consists of a comprehensive evaluation of the coronary circulation in a single procedure by combining angiography, direct invasive assessment of the coronary haemodynamics by intracoronary pressure and flow measurement either by thermodilution (bolus/continuous) or Doppler techniques, and pharmacological vasomotor testing. Recently, a standardized protocol has been proposed.³⁶

5.2.5.2.1. Basic coronary functional testing. Intracoronary pressure and flow measurements allow assessment of the haemodynamic significance of focal or diffuse coronary lesions by measuring FFR or iFR (see Section 3.3.3.2) and of microcirculatory function by measuring CFR and IMR, HMR, or MRR^{361,961} (see Section 3.3.3.3). Coronary microvascular dysfunction is characterized by decreased CFR and increased microvascular resistance (IMR, HMR, MRR). Decreased CFR can be due to structural or functional microvascular dysfunction.^{926,966} Functional CMD is characterized by increased resting flow linked to enhanced nitric oxide synthase (NOS) activity, whereas patients with structural CMD have endothelial dysfunction, leading to a reduced increase of coronary blood flow during exercise.^{926,966}

A Doppler-derived CFR of < 2.5 in non-obstructive CAD indicates an abnormal microcirculatory response corresponding to a thermodilution-derived CFR of < 2.5 .^{361,926,937,961} Of note, in assessing coronary microvascular function, continuous thermodilution showed significantly less variability than bolus thermodilution on repeated measurements.³⁸² An increased IMR (≥ 25) indicates microvascular dysfunction.^{380,381} For the Doppler-derived HMR, a value of > 2.5 mmHg/cm/s indicates augmented microvascular resistance.⁴² Recently, MRR has been considered abnormal for values < 2.7 .^{364,967} Doppler flow analysis allows assessment of the flow-recovery time after Ach administration as a sign of myocardial ischaemia, which is helpful in the diagnosis of patients with equivocal test results.⁹⁶⁸

5.2.5.2.2. Coronary vasomotor testing. Epicardial and microvascular endothelium-dependent vasodilation and vasospasm are tested by intracoronary bolus administration or graded infusion of Ach, first at a low dose/grade to assess endothelial dysfunction at the microvascular or epicardial level, and after that at a higher dose/grade to eventually induce microvascular or/and epicardial coronary vasospasm. The LAD artery is usually preferred as the pre-specified target vessel reflecting its subtended myocardial mass and coronary dominance. The left circumflex coronary artery is also tested if Ach is administered in the LMCA. Additional studies in the right coronary artery may be appropriate if the initial tests are negative and clinical suspicion is high. As Ach exerts a cholinergic effect on the atrioventricular node, significant bradycardia may ensue if infused especially in the right coronary artery or a dominant left circumflex coronary artery. Bradycardia can be prevented by selective infusion in the LAD, prophylactic ventricular pacing, or reduction of the concentration infused or of the injected dose. If necessary, the

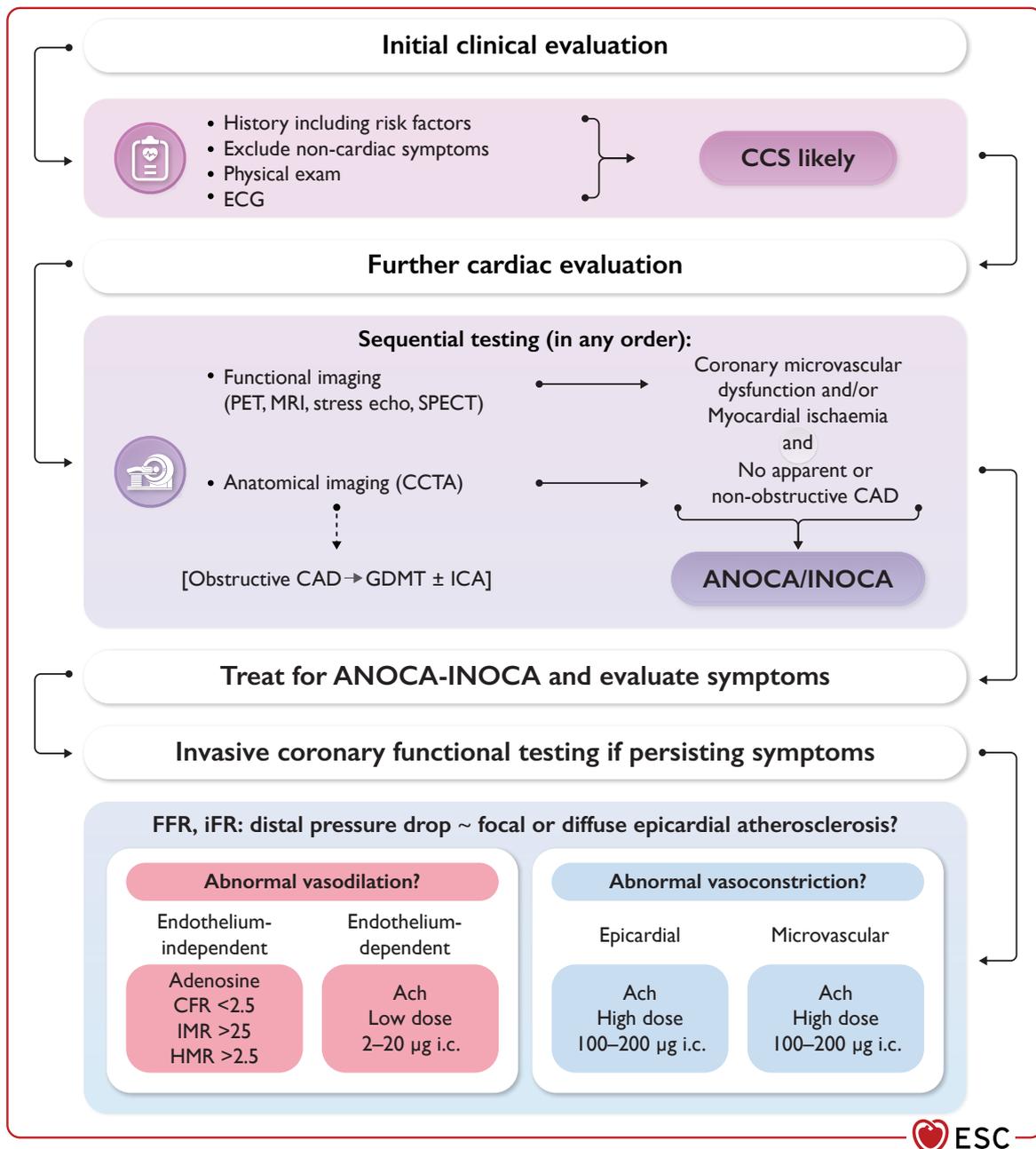


Figure 13 Diagnostic algorithm for patients with angina/ischaemia with non-obstructive coronary arteries. Ach, acetylcholine; ANOCA, angina with non-obstructive coronary arteries; CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CFR, coronary flow reserve; ECG, electrocardiogram; echo, echocardiography; FFR, fractional flow reserve; GDMT, guideline-directed medical therapy; HMR, hyperaemic myocardial velocity resistance; i.c., intracoronary; ICA, invasive coronary angiography; iFR, instantaneous-wave free ratio; IMR, index of microcirculatory resistance; INOCA, ischaemia with non-obstructive coronary arteries; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

bradycardia effect of Ach can be antagonized by atropine. The effect of Ach is short in contrast to the prolonged effect of ergonovine, which was previously used for the provocation of coronary vasospasm.⁹⁶⁹ The diagnosis of MVA and VSA due to microvascular or macrovascular vasospasm is made according to established criteria.^{41,73,932} The test is considered positive for macrovascular spasm if symptoms occur,

accompanied by ischaemic ECG changes and an angiographic $\geq 90\%$ reduction of the coronary lumen. If the lumen reduction is $< 90\%$, the diagnosis of microvascular spasm is made. The vasospastic effect of Ach is rapidly transient and can, if needed, be reversed by intracoronary administration of nitroglycerine, which also allows assessment of endothelium-independent epicardial coronary vasodilation. The safety

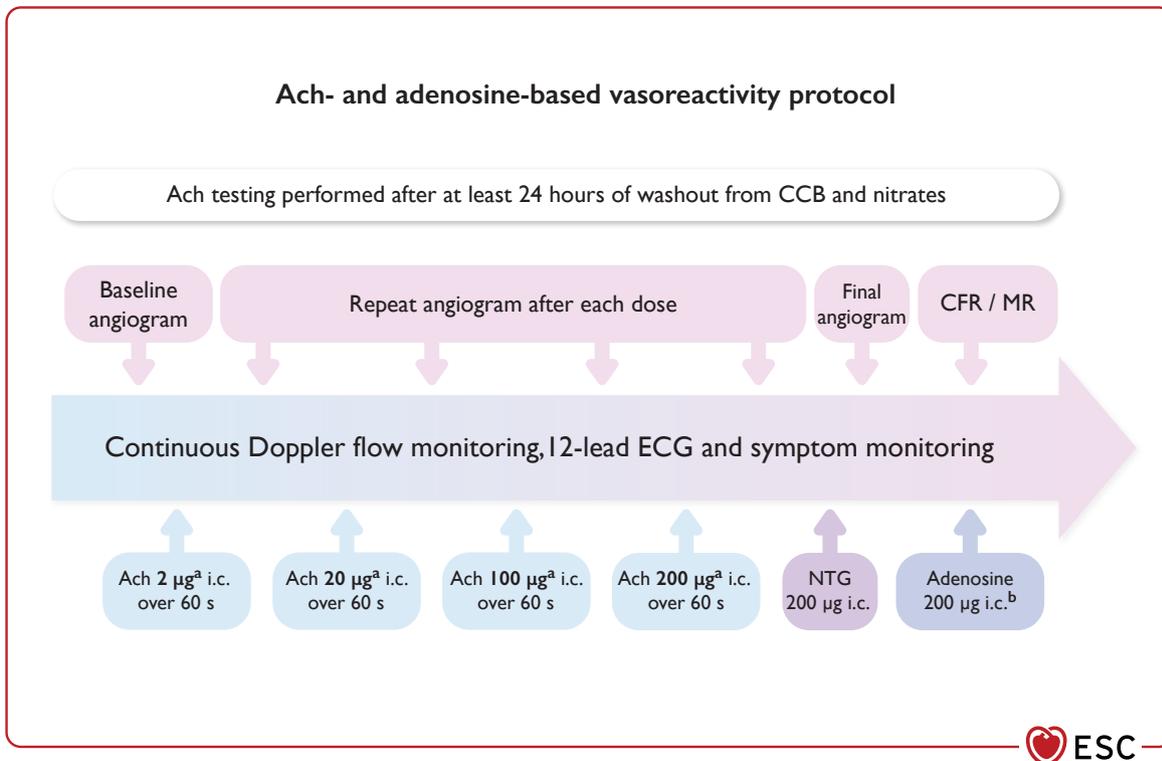


Figure 14 Spasm provocation and functional testing protocol. Ach, acetylcholine; CCB, calcium channel blocker; CFR, coronary flow reserve; ECG, electrocardiogram; i.c., intracoronary; i.v., intravenous; MR, microvascular resistance; NTG, nitroglycerine. i.c. bolus injections of Ach over 60s to assess: (i) endothelial-dependent vasodilation using low-dose Ach (2–20 µg), and (ii) endothelial dysfunction and vasoconstriction using high-dose Ach (100–200 µg). This is followed by i.c. administration of nitroglycerine (200 µg) to revert vasospasm. Endothelial-independent vasodilation is assessed by i.c. adenosine (200 µg) or i.v. infusion to determine CFR and IMR. Coronary flow can be continuously monitored if i.c. Doppler guidewires are used. ^aThe incremental administration of Ach is stopped whenever a coronary vasospasm is induced. ^bi.v. adenosine can also be used.

of coronary vasospasm provocation testing with increasing intracoronary Ach boluses of up to a maximum of 200 µg has been repeatedly reported.^{37,970,971} In a small study, testing coronary vasospasm using this algorithm was also safe in patients with a recent ACS.⁹⁷²

At the end of the procedure, microcirculatory vasomotor response to i.v. administration of the endothelium-independent vasodilator adenosine⁹⁷³ is assessed and CFR, IMR, HMR, or MRR are measured. In patients with contraindications to the use of adenosine, papaverine can be used⁹⁷⁴ but precautionary measures need to be taken given the risk of inducing polymorphic ventricular tachycardia.^{975,976}

Different protocols have been applied in clinical practice. *Figure 14* shows an example of a standardized and stepwise algorithm for ICFT that may be adopted in the cardiac catheterization laboratory for diagnosing vasospasm. Informed consent should be obtained, mentioning unlicensed, parenteral use of Ach, and administration performed by an experienced interventional cardiologist.

5.2.6. Management of angina/ischæmia with non-obstructive coronary arteries

Management should be patient-centred with a patient-oriented multidisciplinary care approach.⁹⁷⁷ *Figure 15* provides an algorithm for the therapeutic management of ANOCA/INOCA. In all patients with established ANOCA/INOCA due to the frequent presence of coronary atherosclerosis and endothelial dysfunction, tailored counselling on lifestyle factors is warranted to address risk factors, reduce symptoms, and

improve QoL and prognosis. Management of traditional CVD risk factors, hypertension, dyslipidaemia, smoking, and diabetes should be as per clinical practice guidelines recommendations.

Treatment of anginal symptoms in patients with ANOCA/INOCA is challenging as the patients represent a heterogeneous group and randomized trials are lacking. A small study showed that a stratified antianginal therapy algorithm based on coronary functional testing resulted in improved angina symptoms and QoL compared with a control group treated with standard therapy.⁹⁷⁸ In patients with MVA and reduced CFR and/or increased IMR (which may reflect arteriolar remodelling), beta-blockers, CCBs, ranolazine, and ACE-Is are used.⁹⁷⁹ In these patients, anti-ischaemic therapy with amlodipine or ranolazine resulted in a significant improvement in exercise time.⁹⁸⁰ In patients with either epicardial or microvascular spasm following Ach testing, calcium antagonists should be considered as first-line therapy. In patients with severe VSA, it may be necessary to administer unusually high dosages of calcium antagonist (2 × 200 mg diltiazem daily or higher up to 960 mg daily) or even a combination of non-dihydropyridine (such as diltiazem) with dihydropyridine calcium blockers (such as amlodipine). Of note, a small study using either oral diltiazem or placebo up to 360 mg/day in CMD for 6 weeks did not substantially improve symptoms or QoL, but diltiazem therapy did reduce the prevalence of epicardial spasm.⁹⁸¹ Nicorandil, a combinatorial vasodilator agent acting via nitrate- and potassium-channel activation, may be an effective alternative, although side effects are frequent.⁹⁸² First-line therapy can also be combined

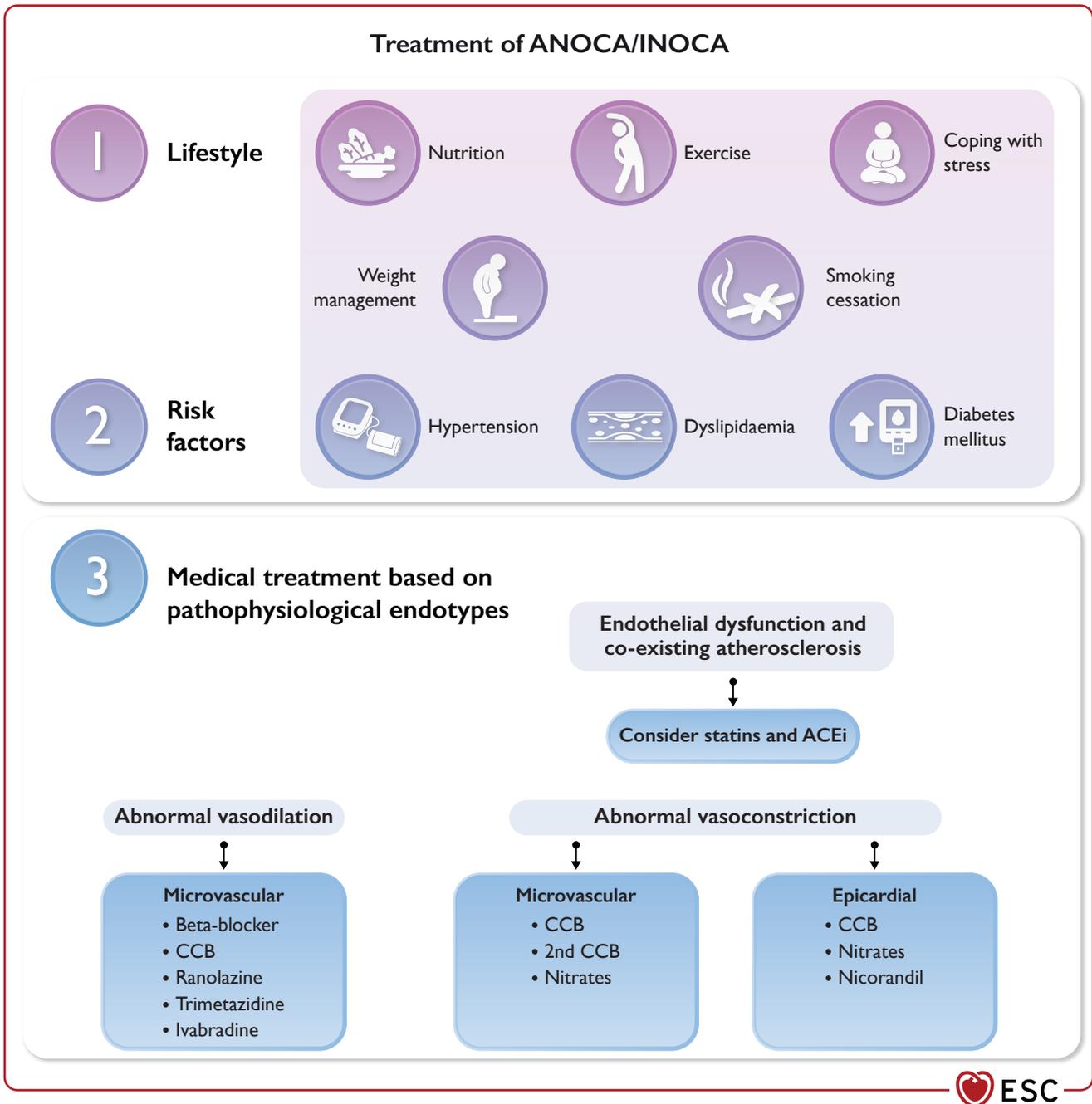


Figure 15 Treatment of angina/ischæmia with non-obstructive coronary arteries. ACE-I, angiotensin-converting enzyme inhibitor; ANOCA, angina with non-obstructive coronary arteries; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; INOCA, ischaemia with non-obstructive coronary arteries. Treatment of ANOCA/INOCA patients includes lifestyle modification, management of cardiovascular risk factors, and antianginal treatment according to underlying endotypes. Note: endotypes frequently overlap, requiring combined medical therapy.

with ranolazine, an antianginal agent that improves myocyte relaxation and ventricular compliance by decreasing sodium and calcium overload.⁹⁸³ Spinal cord stimulation is an option for patients who remain refractory after medical therapy.⁹⁸⁴

There are currently several studies evaluating therapies specific to ANOCA/INOCA. The Women's Ischemia Trial to Reduce Events in Non-Obstructive Coronary Artery Disease (WARRIOR, NCT03417388) is currently enrolling subjects in a multicentre,

prospective, randomized, blinded outcome evaluation to assess intensive statin and ACE-I/ARB therapy (ischaemia-intensive medical therapy) vs. usual care on MACE in symptomatic women with ANOCA. The Precision Medicine with Zibotentan in Microvascular Angina (PRIZE) trial holds future promise (NCT04097314). Zibotentan is an oral, endothelin A receptor antagonist that may provide benefit by opposing the reported vasoconstrictor response of coronary microvessels to endothelin.

Recommendation Table 25 — Recommendations for diagnosis and management of patients with angina/ ischaemia with non-obstructive coronary arteries (see also Evidence Table 25)

Recommendations	Class ^a	Level ^b
Diagnosis of ANOCA/INOCA endotypes		
In persistently symptomatic patients despite medical treatment with suspected ANOCA/INOCA (i.e. anginal symptoms with normal coronary arteries or non-obstructive lesions at non-invasive imaging, or intermediate stenoses with normal FFR/iFR at coronary arteriography) and poor quality of life, invasive coronary functional testing is recommended to identify potentially treatable endotypes and to improve symptoms and quality of life, considering patient choices and preferences. ^{36,37,298,930,939,985}	I	B
In persistently symptomatic patients with documented or suspected ANOCA/INOCA, transthoracic Doppler of the LAD, stress echocardiography, CMR, and PET may be considered for the non-invasive assessment of coronary/myocardial flow reserve. ^{44,231,233–235,300,986,987}	IIb	B
Diagnostic tests for vasospastic angina		
In individuals with suspected vasospastic angina, a resting 12-lead ECG recording during angina is recommended.	I	C
In patients with suspected vasospastic angina and repetitive episodes of rest angina associated with ST-segment changes that resolve with nitrates and/or calcium antagonists, invasive coronary functional testing is recommended to confirm the diagnosis and to determine the severity of underlying atherosclerotic disease.	I	C
In individuals with suspected vasospastic angina and frequent symptoms, ambulatory ST-segment monitoring should be considered to identify ST-segment deviation during angina. ^{192–194}	IIa	B
Management of ANOCA/INOCA		
In symptomatic patients with ANOCA/INOCA, medical therapy based on coronary functional test results should be considered to improve symptoms and quality of life. ^{298,977}	IIa	A
For the management of endothelial dysfunction, ACE-I should be considered for symptom control. ⁹⁸⁸	IIa	B
For the management of microvascular angina associated with reduced coronary/myocardial blood flow reserve, antianginal medications aiming at preventing demand myocardial ischaemia should be considered for symptom control. ^{989,990}	IIa	B

Continued

For the treatment of isolated vasospastic angina		
Calcium channel blockers are recommended to control symptoms and to prevent ischaemia and potentially fatal complications. ^{991–996}	I	A
Nitrates should be considered to prevent recurrent episodes. ^{993,997,998}	IIa	B
For the treatment of overlapping endotypes		
In patients with evidence of overlapping endotypes, combination therapy with nitrates, calcium channel blockers, and other vasodilators may be considered. ^{999,1000}	IIb	B

ACE-I, angiotensin-converting enzyme inhibitor; ANOCA, angina with non-obstructive coronary arteries; CMR, cardiac magnetic resonance; ECG, electrocardiogram; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; INOCA, ischaemia with non-obstructive coronary arteries; LAD, left anterior descending; PET, positron emission tomography.

^aClass of recommendation.

^bLevel of evidence.

5.3. Other specific patient groups

5.3.1. Older adults

Between 2015 and 2050, the proportion of the world's population aged >60 years is set to nearly double to 22%. Ageing predisposes patients to a high incidence and prevalence of CAD, in both men and women. Typically, in the context of CVD, older patients are defined as those ≥75 years of age;¹ it should be noted, however, that such age cut-offs are relatively arbitrary, and biological age influences this threshold in clinical practice. Clinical characteristics of the older adult population are heterogeneous, with frailty, comorbidity, cognitive function, and health-related QoL playing important roles in guiding clinical care and as predictors of adverse outcomes.^{1001–1005} Older patients often present with symptoms other than angina, which may delay the diagnosis of CCS.¹⁰⁰⁴

Ageing is often accompanied by both comorbidities and frailty, and consequently leads to potentially excessive polypharmacy.⁵³¹ In making treatment decisions, clinicians should take into account the limited external validity of RCTs for older adults.³⁶ Older people are often underrepresented in RCTs as a consequence of exclusion criteria and under-recruitment,^{531,1006,1007} though they have been shown to have a higher underlying risk for cardiovascular outcomes.¹⁰⁰⁸ The treatment of CCS in older adults is complicated by a higher vulnerability to complications for both conservative and invasive strategies, such as bleeding, renal failure, and neurological impairments, all of which require special attention. The use of DES, compared with bare-metal stents, in combination with a short duration of DAPT, is associated with significant safety and efficacy benefits in older adults.¹⁰⁰⁹ Frailty is of utmost importance in the clinical decision-making.¹⁰¹⁰

5.3.2. Sex differences in chronic coronary syndromes

Ischaemic heart disease is the leading cause of mortality for women, yet they have been historically underrepresented in RCTs.^{1011–1013} Differences in symptom presentation, in the accuracy of diagnostic tests for obstructive CAD, and other factors that lead to differential triage, evaluation, or early treatment of women with myocardial ischaemia

compared with men could contribute to unfavourable outcomes. There are also risk factors that are unique to women.^{1014,1015} Not only premature menopause,¹⁰¹⁶ but also hypertensive disorders of pregnancy, pre-term delivery, gestational diabetes, small-for-gestational-age delivery, placental abruption, and pregnancy loss are predictors of subsequent CVD.¹⁰¹⁷ Also, the association between low socioeconomic status and increased cardiovascular risk seems stronger in women.¹⁰¹⁸ In addition, higher levels of residential segregation are associated with incident CVD and obesity among black women.¹⁰¹⁹

Women are less likely to be referred for diagnostic testing and are under-treated for essential secondary prevention therapies.¹⁰²⁰ Compared with men, women have a shorter survival after PCI¹⁰²¹ and CABG.¹⁰²² In a large-scale, individual-patient data pooled analysis of contemporary PCI trials with early and new-generation DES, women had a higher risk of MACE and ischaemia-driven target-lesion revascularization compared with men at 5 years following PCI.¹⁰²¹ However, the excess risk after PCI among women can be primarily explained by a greater burden of cardiovascular risk factors and comorbid conditions.¹⁰²³ Nevertheless, in a population undergoing contemporary PCI, women and men had similar risks of death or new Q-wave MI at 2 years, but women faced a higher risk of bleeding and haemorrhagic stroke compared with men.¹⁰²⁴

Women with signs and symptoms suggestive of cardiac ischaemia should be investigated carefully. The same guideline-recommended cardiovascular preventive therapy should be provided to women and men.¹⁰²⁵ Hormone replacement therapy in post-menopausal women does not reduce the risk of ischaemic myocardial disease¹⁰¹⁵ and it may come at the cost of other health risks,¹⁰²⁶ which should be discussed with the patient.

5.3.3. High bleeding-risk patients

An HBR is increasingly present in many CCS patients referred for coronary revascularization. The ARC-HBR consortium provided a consistent definition of HBR for patients undergoing PCI. Patients are considered at HBR if at least one major or two minor criteria are met.⁵⁹⁰ In the context of PCI in HBR patients, short duration of DAPT (1–3 months) and PCI with a DES was beneficial in many recent studies.^{1009,1027–1032}

5.3.4. Inflammatory rheumatic diseases

Patients with inflammatory rheumatic diseases have an increased risk of CVD compared with the general population.^{1033,1034} Accumulating evidence has shown elevated cardiovascular morbidity and mortality in other rheumatic and musculoskeletal diseases, including gout, vasculitis, systemic sclerosis, myositis, mixed connective tissue disease, Sjögren syndrome, SLE, and the antiphospholipid syndrome.^{1035–1044}

Some of these patient categories have two- to three-fold higher prevalences of asymptomatic ASCVD compared with the general population,^{1045–1051} which is linked to ASCVD outcomes.^{1049,1052–1054} Thus, identification of ASCVD such as carotid artery plaque(s) may be considered in ASCVD and CAD risk evaluation.^{1050,1055–1057}

In patients with inflammatory rheumatic diseases and CCS, CVD preventive medications such as lipid-lowering medications and antihypertensive treatment should be used as in the general population.^{1058–1062}

5.3.5. Hypertension

Blood pressure lowering has been associated with favourable cardiovascular outcomes in patients regardless of the presence of CAD.¹⁰⁶³

Due to concerns of a possible J-curve relationship between achieved BP and cardiovascular outcomes in patients with CAD, previous guidelines did not recommend a target BP of <120/70 mmHg. In line with the 2024 ESC Hypertension Guidelines¹⁰⁶⁴, the present guidelines recommend that treated systolic BP values in most CCS patients be targeted to 120–129 mmHg, provided the treatment is well tolerated. In cases where on-treatment systolic BP is at or below target (120–129 mmHg) but diastolic BP is not at target (≥ 80 mmHg), intensifying BP-lowering treatment to achieve an on-treatment diastolic BP of 70–79 mmHg may be considered to reduce CVD risk.¹⁰⁶⁵ More lenient targets (e.g. 140/90 mmHg) can be considered in older patients (≥ 85 years of age) or patients with pre-treatment symptomatic orthostatic hypotension. In hypertensive patients with a history of MI, beta-blockers and RAS blockers are first-line treatments. In patients with symptomatic angina, beta-blockers and/or CCBs can be useful.¹⁰⁶⁵

5.3.6. Atrial fibrillation

Diagnostic assessment of CAD (CCTA and non-invasive tests) may be difficult in AF with a high ventricular rate. In patients with CAD and AF, rhythm or rate control strategies may help improve symptoms of myocardial ischaemia. Amiodarone or dronedarone are drugs of choice for rhythm control, as an alternative to catheter ablation, in patients with CAD and AF. Sotalol may also be considered. Beta-blockers, diltiazem, verapamil, or digoxin can be used for rate control depending on the LVEF.⁶¹³ After PCI, combined anticoagulant and antiplatelet therapies are needed. Recommendations on post-PCI antithrombotic therapy in patients with AF and indication for OAC are detailed in Section 4.3.1.2.2 and Recommendation Table 17.^{613,621,659} Surgical ablation of AF during isolated CABG seems to be safe and effective in improving long-term outcomes.¹⁰⁶⁶ Concomitant surgical closure of the left atrial appendage is recommended as an adjunct to oral anticoagulation in patients with AF undergoing cardiac surgery (e.g. CABG) to prevent ischaemic stroke and thrombo-embolism (see the ESC 2024 Guidelines for the management of Atrial Fibrillation).¹⁰⁶⁷

5.3.7. Valvular heart disease

In patients with valvular heart disease with a risk for associated CAD who require surgery or in whom a decision of a percutaneous or surgical approach is still pending, ICA or CCTA is recommended to determine the need for coronary revascularization.¹⁰⁶⁸ Evidence of CAD in patients with valvular heart disease can drive to a surgical instead of a percutaneous treatment of valvular heart disease. Invasive coronary angiography is recommended in patients with secondary mitral regurgitation as this condition is frequently due to ischaemic LV dysfunction.¹⁰⁶⁸ Routine stress testing to detect CAD associated with severe symptomatic valvular heart disease is not recommended because of low diagnostic value and potential risk. The usefulness of FFR or iFR in patients with valvular heart disease is not well established, and caution is warranted in interpreting these measurements, especially in the presence of aortic stenosis.¹⁰⁶⁸ Beta-blockers need to be used with caution in patients with aortic valve disease. Coronary artery bypass grafting is recommended in patients with a primary indication for aortic/mitral/tricuspid valve surgery and significant coronary stenosis. Percutaneous coronary intervention should be considered in patients with a primary indication of transcatheter aortic valve implantation or transcatheter mitral valve intervention and coronary artery diameter stenosis of >70% in proximal segments.¹⁰⁶⁸

5.3.8. Chronic kidney disease

Chronic kidney disease increases the risk of CAD progression and is associated with high mortality rates due to cardiovascular causes.^{1069,1070} Patients with CKD have a higher burden of atherosclerosis and more advanced plaque features.¹⁰⁷⁰ Despite the higher prevalence of disease, non-invasive diagnostic testing is often less accurate, and guidance related to the use of pharmacological and interventional therapy is limited due to inconsistent definitions of CKD and underrepresentation of CKD patients in clinical trials.^{1070–1072}

Careful assessment of the risk-to-benefit ratio is needed in patients with CKD before considering ICA, CCTA, or non-invasive tests requiring nephrotoxic agents.¹⁰⁷³ Pre-existing CKD is the primary patient-related risk factor for the development of acute kidney injury (AKI), whereas DM increases the susceptibility to develop AKI. The most important measures to prevent AKI are using the lowest necessary total dose of low-osmolality or iso-osmolality contrast medium and sufficient pre- and post-hydration.¹⁰⁷³

CKD raises the risks associated with both CABG and PCI.³¹⁶ The ISCHEMIA-CKD trial included patients with advanced CKD [estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m² or dialysis] and CCS with moderate or severe myocardial ischaemia detected by stress test. An invasive strategy of ICA and PCI was not superior to conservative management in reducing the primary endpoint of death or non-fatal MI.¹⁰⁷⁴

In a propensity score-matched analysis involving 5920 CKD patients (2960 pairs), PCI utilizing second-generation DES displayed a reduced risk of death, stroke, and repeat revascularization at 30 days when compared with CABG.¹⁰⁷⁵ However, PCI was associated with a higher risk of repeat revascularization over the long term. Conversely, among patients on dialysis, the findings favoured CABG over PCI. Additionally, a meta-analysis of 11 registries revealed lower rates of death, MI, and repeat revascularization with CABG in contrast to PCI among patients with eGFR of <60 mL/min/1.73 m².¹⁰⁷⁶ Nevertheless, there is a notable absence of large RCTs comparing revascularization modalities among CKD patients.

5.3.9. Cancer

Several cancer treatments are associated with an increased risk of CCS. Spontaneous bleeding in ACS and CCS patients has been associated with subsequent cancer diagnosis.¹⁰⁷⁷ A prompt evaluation of bleeding may be useful to enable an early detection of cancer. The management of CCS is similar in patients with and without cancer. However, decisions regarding coronary revascularization should be undertaken by a multidisciplinary team. The approach should be individualized and based on life expectancy, additional comorbidities such as thrombocytopenia, increased thrombosis, or bleeding risk, and potential interactions between drugs used in CCS management and anticancer therapy.^{1078,1079}

5.3.10. Optimal treatment of patients with human immunodeficiency virus

Patients with human immunodeficiency virus (HIV) have longer life expectancy than before due to effective antiretroviral therapy (ART), but are twice as likely to develop CVD compared with the general population.¹⁰⁸⁰ The long-term CVD outcomes in patients with HIV may change, given the

relatively recent epidemiological transition of HIV to a chronic disease. Dyslipidaemia is a common condition in patients with HIV, whether treated or untreated with ART.¹⁰⁸¹ The treatment of dyslipidaemia in patients with HIV includes both non-pharmacological and pharmacological options. Special attention to the impact of polypharmacy, drug interactions between ART and lipid-lowering medications, and close monitoring for adverse events is critical to successfully managing dyslipidaemia and risk of CVD in patients with HIV. Hepatic cytochrome P450 3A4 (CYP3A4) metabolizes many statins; many ARTs are also metabolized by CYP3A4 and, thus, may have interactions with statins. Simvastatin and lovastatin are contraindicated with protease inhibitors; atorvastatin has less of a CYP3A4 interaction; pravastatin, fluvastatin, pitavastatin and rosuvastatin are not or minimally metabolized through CYP3A4.^{1082,1083} Ezetimibe has no interactions with CYP3A4 or ART.¹⁰⁸¹

A clinical trial investigating the impact of PCSK9 inhibitor therapy on lipids, inflammatory markers, and subclinical ASCVD (including non-calcified plaque and arterial inflammation) in HIV is currently being conducted [EPIC-HIV study (Effect of PCSK9 Inhibition on Cardiovascular Risk in Treated HIV Infection), NCT03207945]. Future studies are needed to evaluate the impact of PCSK9 inhibition on clinical events in HIV.

5.3.11. Socially and geographically diverse groups

A lower socioeconomic status has implications of increased CVD mortality¹⁰⁸⁴ and poorer CVD risk factor profiles.¹⁰⁸⁵ A multicohort study of 1.7 million adults followed up for any cause of death for an average of 13 years found that low socioeconomic status was associated with a 2.1-year reduction in life expectancy between the ages 40 and 85 years.¹⁰⁸⁶ Education level, occupation, household income, health, disability, and living conditions also contribute to socioeconomic status. There were different rates of decline in mortality from CVD in Europe between the most and the least deprived.¹⁰⁸⁷ It has been proposed that on this basis, CVD could become a disease prevalent of the lower socioeconomic groups by the mid-2020s.¹⁰⁸⁸

Black patients with diabetes have a higher hospitalization burden with a concomitant disparity in comorbid presentation and outcome compared with other patients with diabetes.¹⁰⁸⁹ South Asian ethnicity, even after adjustment for traditional risk factors, is associated with an increased risk of coronary heart disease outcomes. This risk was greater than other studied racial/ethnic groups and second only to diabetes in coronary heart disease risk prediction.¹⁰⁹⁰

Within a large prospective study, South Asian individuals had a substantially higher risk of ASCVD than individuals of European ancestry.¹⁰⁹¹ South Asians have a more diffuse pattern with multivessel involvement. However, less is known about other morphological characteristics, such as atherosclerotic plaque composition and coronary diameter in South Asian populations. Despite a similar coronary calcification burden, higher non-calcified plaque contribution, elevated thrombosis, and inflammatory markers likely contribute to the disease pattern. Although the current evidence on the role of coronary vessel size remains inconsistent, smaller diameters in South Asians could play a potential role in the higher disease prevalence.¹⁰⁹² Individuals of South Asian descent have a high prevalence of CYP2C19 loss-of-function alleles (poor metabolizers: 13% vs. 2.4% in European populations),¹⁰⁹³ which are associated with reduced efficacy of clopidogrel.

Recommendation Table 26 — Recommendations for older, female, high bleeding risk, comorbid, and socially/geographically diverse patients (see also Evidence Table 26)

Recommendations	Class ^a	Level ^b
Older adults		
In older adults (≥75 years), particular attention to drug side effects, intolerance, drug–drug interactions, overdosing, and procedural complications is recommended.	I	C
In older, as in younger, individuals, diagnostic and revascularization decisions based on symptoms, extent of ischaemia, frailty, life expectancy, comorbidities, and patient preferences are recommended.	I	C
Sex		
Similar guideline-directed cardiovascular preventive therapy is recommended in women and men.	I	C
Systemic post-menopausal hormone therapy is not recommended in women with CCS, given the lack of cardiovascular benefit and an increased risk of thrombo-embolic complications. ^{1026,1094,1095}	III	A
High bleeding risk		
Bleeding risk assessment is recommended using the PRECISE-DAPT score, the qualitative ARC-HBR tool or other, validated methods. ^{589,590}	I	B
HIV		
Attention to interaction between antiretroviral treatment and statins is recommended in patients with HIV. ¹⁰⁹⁶	I	B
Socioeconomic, geographical, and under-investigated groups		
Continued targeted efforts are recommended: <ul style="list-style-type: none"> to increase delivery of safe and effective cardiac care to all CCS patients, especially those of lower socioeconomic classes; and to enhance inclusion in future clinical trials of geographical, social, or other groups that are currently underrepresented. 	I	C

© ESC 2024

ARC-HBR, Academic Research Consortium for High Bleeding Risk; CCS, chronic coronary syndrome; HIV, human immunodeficiency virus; PRECISE-DAPT, PREdicting bleeding Complications In patients undergoing Stent implantation and subSequent Dual AntiPlatelet Therapy.

^aClass of recommendation.

^bLevel of evidence.

5.4. Screening for coronary artery disease in asymptomatic individuals

Presence of asymptomatic atherosclerotic CAD is common in the general population.^{1097–1100} In the Swedish Cardiopulmonary Bioimage Study, CCTA was performed in randomly selected individuals from the general population.¹⁰⁹⁷ In the 25 182 individuals without known CAD, atherosclerotic plaque was present in 42% of participants. Plaque was more common in older individuals and in males (males 50–54 vs. 60–64 years old: 41% vs. 69%, and females 50–54 vs. 60–64 years old: 19% vs. 40%). Obstructive coronary stenosis was present in 5% of participants. In the PESA study (Progression of Early

Subclinical Atherosclerosis), 63% of asymptomatic middle-aged participants had subclinical atherosclerosis,¹⁵⁷ although most of them were categorized as low-risk individuals by several risk scores.¹⁴²

The risk of adverse events in asymptomatic subjects can be estimated using the European risk-estimation system [Systematic Coronary Risk Estimation 2 (SCORE2)], described in the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice.^{16,1101} Systematic screening of risk factors cannot be strongly recommended in the general population as it did not affect CVD outcomes.¹¹⁰² However, when patients are seen for other reasons, opportunistic screening is effective at increasing detection rates of CVD risk factors, such as high BP or lipids. Hence, opportunistic screening is recommended, although its beneficial effect on clinical outcomes remains uncertain.¹¹⁰³

Information on CAC can be used to guide risk-factor management, and initiate lipid-lowering and antithrombotic treatment in patients with estimated future risk around treatment decision thresholds.¹¹⁰⁴ To date, two randomized screening studies have indicated that statin therapy impacts outcomes when guided by CACS in younger patients with high CACS.^{1105,1106} Coronary artery calcium score could potentially guide not only risk-factor management but also primary prophylaxis with aspirin, but randomized studies are lacking.¹¹⁰⁷ Importantly, opportunistic screening of the burden of calcified atherosclerotic CAD can be accurately accessed with non-ECG-gated chest CT performed for other reasons.^{17,1108} Reporting the visual interpretation of the coronary plaque burden according to a simple score with four categories (none, mild, moderate, severe) is recommended.^{1108–1110} However, there is no current evidence to support further diagnostic imaging in asymptomatic individuals on the basis of presence of calcified plaque alone.

Carotid ultrasound,¹¹¹¹ aortic pulse wave velocity, arterial augmentation index, and ankle–brachial index are other modalities to improve the prediction of future CVD events. However, evidence is less extensive for these modalities compared with CACS.

Recommendation Table 27 — Recommendations for screening for coronary artery disease in asymptomatic individuals (see also Evidence Table 27)

Recommendations	Class ^a	Level ^b
Opportunistic screening of healthy individuals for cardiovascular risk factors and to estimate the risk of future cardiovascular events using scoring systems, e.g. SCORE2 and SCORE-OP, is recommended to detect individuals at high risk and guide treatment decisions. ^{16,1101,1112}	I	C
When coronary artery calcification findings are available from previous chest CT scans, using these findings to enhance risk stratification and guide treatment of modifiable risk factors should be considered. ^{17,1108–1110}	IIa	C
CACS may be considered to improve risk classification around treatment decision thresholds. ^{1104–1106}	IIb	C
An ultrasound of the carotid arteries may be considered as an alternative when CACS is unavailable or not feasible to detect atherosclerotic disease and to improve risk classification around treatment decision thresholds. ¹¹¹¹	IIb	B

CACS, coronary artery calcium scoring; CT, computed tomography; SCORE2, Systematic Coronary Risk Estimation 2; SCORE-OP, Systematic Coronary Risk Estimation 2–Older Persons.

^aClass of recommendation.

^bLevel of evidence.

6. Long-term follow-up and care

6.1. Voice of the patient

A diagnosis of CCS can have an impact on self-identity, lifestyle, employment, and cause anxiety, depression, and burdensome treatment. Patients are experts in their own conditions, and their voices and preferences are integral to decisions about treatment. Health outcomes improve with better patient involvement, and *shared decision-making* is central to future patient care.¹¹¹³

6.1.1. Communication

Communication is essential to support patients' understanding, adherence, and engagement in decision-making.¹¹¹⁴ Good communication requires providing information at an appropriate level, active listening, assessing patient understanding, and determining patient perspectives and priorities. A meta-analysis summarizing a total of 127 studies of communication training concluded that patients were 19% more likely to be non-adherent when physicians had poor communication, and 12% more likely to be non-adherent when their physicians had not received communication training.¹¹¹⁵ Communication and shared decision-making can be particularly challenging when patients have comorbidities, low health literacy, language differences, cognitive impairment, depression, or anxiety, and when evidence for treatment is less robust.

Patient reported outcome measures can be useful to improve assessment and communication of symptoms, function, and QoL, and can highlight problems that may not have been previously discussed. Under- and overestimation of symptoms can lead to a lack of or inappropriate treatment.^{1116,1117} The routine use of PROMs in clinical practice is hampered by the challenge of interpretation of scores and their integration into routine clinical processes.¹¹¹⁶

Although quality of communication can be improved through training, meta-analyses have not found evidence of significant impact on outcomes such as physical or mental health, satisfaction, QoL, or specific risk factors in patients with cancer, diabetes, and hypertension.^{1115,1118,1119} Structured tools and a flexible range of resources (including videos, workbooks, and health-literacy materials) that provide individualized information and decision aids can be adjuncts to better communication and shared decision-making.⁴⁴³ A systematic review of 17 RCTs of tools to support decision-making in severe illness concluded that they improved patient knowledge and readiness to make decisions.¹¹²⁰

Communicating the risk of future CVD events and how risk can be lowered through lifestyle and medications is best presented using visual or imaging approaches, natural frequencies rather than percentages, and positive framing (focusing on risk-reduction benefits).^{1121–1125} Relative risk reduction is more persuasive than either absolute risk reduction or the number needed to treat.¹¹²² The use of risk prediction estimates may have an impact on individuals' health when their information (i.e. predicted risk stratification) changes individuals' behaviour, self-management decisions, and even treatment decisions.⁴⁴⁶ This enables patients to gain insights into their cardiovascular prognosis and to empower them to take part in the decision-making process.¹¹²⁶ This approach may increase self-motivation for therapy adherence and lifestyle changes, including changes in nutrition, physical activity, relaxation training, weight management, and participation in smoking cessation programmes for resistant smokers.⁴⁴⁶ Previous unsuccessful attempts to change to a healthy lifestyle or take guideline-recommended treatment can be addressed to set realistic goals.⁴⁴⁶

Communication should be clear regarding symptoms, even if not cardiac. Patients with CCS experiencing non-cardiac chest pain experience uncertainty about the cause and actions to take. A multidisciplinary approach and evaluation of non-cardiac aetiology with an appropriate referral are advocated to ensure that appropriate treatment is initiated.^{1127,1128}

6.1.2. Depression and anxiety

Depression is common (15%–20% prevalence) in CVD, and associated with poor adherence and worse outcomes, including MACE and premature death.¹¹²⁹ Coronary microvascular dysfunction (prevalent in INOCA) is linked with psychological stress and depression.⁹⁴⁶ Unfortunately, depression and psychological stress are often unrecognized due to a lack of systematic screening using validated tools.¹¹²⁹ For anxiety, a recent meta-analysis involving 16 studies reported a prevalence in post-MI between 5.5% and 58%, and a 27% greater risk of poor clinical outcomes in anxious patients compared with those without anxiety.¹¹³⁰ In contrast, in a 15-year follow-up of 1109 patients with CCS moderate anxiety did not increase the risk of cardiovascular events compared with low anxiety levels. Patients on a high but decreasing anxiety trajectory had an HR of 1.72 (95% CI, 1.11–2.68) for cardiovascular events.¹¹³¹ Treatment of psychosocial factors, depression, and anxiety with pharmacotherapy, psychotherapy, and/or exercise can improve symptoms and QoL in some patients, and there is some evidence for improvement in cardiac outcomes.^{472,1132–1134} Stepped care (initial therapy based on patient preferences) and a combination of therapies may be more efficacious.^{1129,1135} First-line treatment with selective serotonin reuptake inhibitors (recommended in CCS) or non-pharmacological interventions and a multidisciplinary collaborative approach are recommended.¹¹²⁹

6.2. Adherence and persistence

Earlier analyses reported that adherence to long-term therapies in chronic conditions in Western countries averaged 50% and was lower in developing countries.¹¹³⁶ Pooled prevalence of non-adherence from a recent meta-analysis of eight studies ($n = 3904$ patients with multimorbidity) was 42.63% (95% CI, 34%–51%).¹¹³⁷ Data from the ESC-EORP EUROASPIRE V registry indicate that many CCS patients still have unhealthy lifestyles in terms of smoking, diet, and sedentary behaviour.¹¹³⁸ Poor adherence and persistence (duration of time in which medications and healthy behaviours are continued) have a profound effect on effective management, patient safety, and outcomes. The World Health Organization (WHO) advocates training in adherence for healthcare professionals, a multidisciplinary approach, support rather than blame, tailored interventions based on illness-related demands for each patient, and viewing adherence as a dynamic process.¹¹³⁶

The five dimensions of adherence are patient, disease, provider, therapy, and healthcare system (Figure 16).¹¹³⁹ Therefore, identifying patients at risk of non-adherence, addressing all five dimensions, developing a multidisciplinary pathway to support *sustained* adherence, and a follow-up strategy are essential steps.¹¹³⁹

6.2.1. Adherence to healthy lifestyle behaviours

Different strategies may help improve long-term adherence to a healthy lifestyle (Figure 17).

6.2.1.1. Why behavioural changes are difficult

Making changes to unhealthy lifestyles and controlling risk factors can be a daunting task as these are usually longstanding habits and patterns

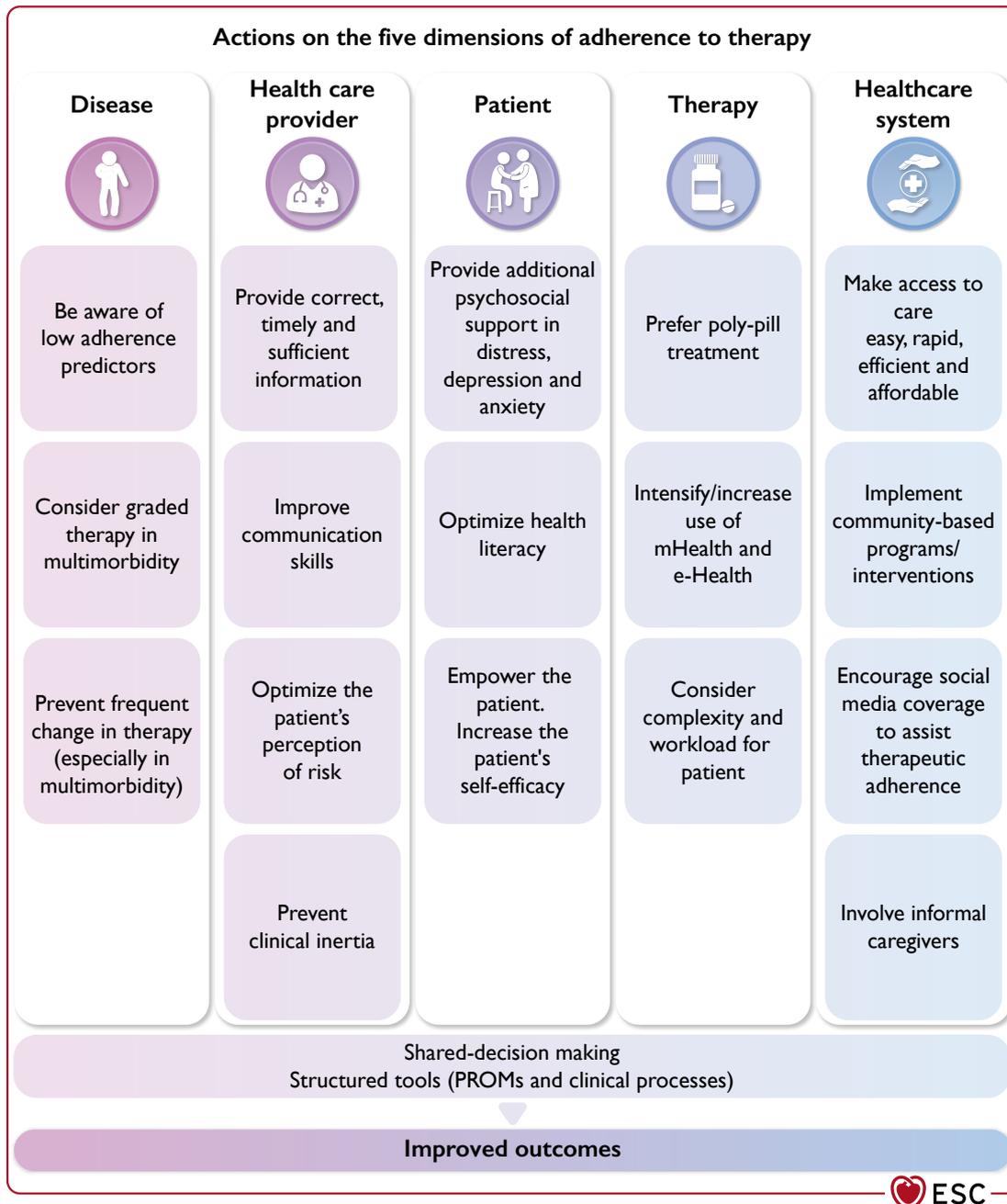


Figure 16 Actions on the five dimensions of adherence to therapy. e-Health, healthcare services provided electronically; mHealth, mobile device-based healthcare; PROMs, patient-reported outcome measures. Adapted from Pedretti et al.¹¹³⁹.

of behaviour. Habits and environmental cues primarily govern behaviours, so education and information alone are seldom enough.¹¹⁴⁰ Factors such as psychological state and low health literacy (associated with depression and worse behavioural risk factors) also impact the ability to make changes.^{1141,1142}

6.2.1.2. How to change behaviour and support healthy lifestyles

A multidisciplinary approach and behavioural counselling can improve adherence. A systematic review and meta-analysis of 12 RCTs of

nurse-led patient-centred interventions for secondary prevention found greater adherence to smoking cessation and physical activity, and better control of total cholesterol (with medication titration), but no improvements in dietary habits, BP, blood glucose, or survival.¹¹⁴³ A systematic review of behavioural counselling found that medium- to high-contact counselling resulted in 20% lower risk of CVD events, lower BP, and decreased LDL-C and adiposity in adults with CVD risk factors.¹¹⁴⁴ Incorporating cardiovascular visual images into risk-factor discussions is effective in reducing subsequent 10-year risk assessment and individual risk factors.⁴⁴⁵

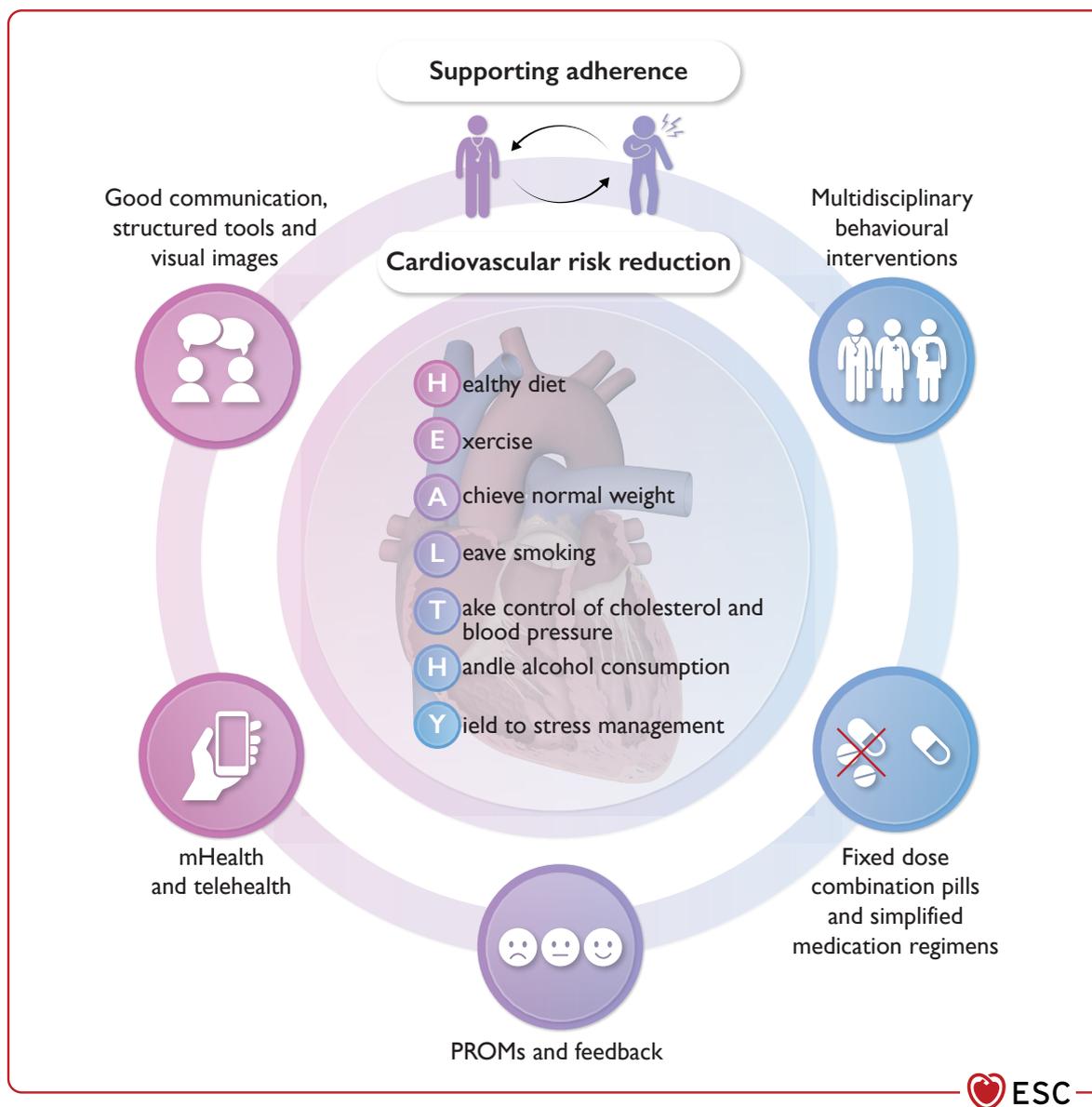


Figure 17 Strategies for long-term adherence to a healthy lifestyle. mHealth, mobile device-based healthcare; PROMs, patient-reported outcome measures.

Lifestyle changes also impact relatives, partners, and friends, so they should be involved in patient support.¹¹³⁹ Physical activity can be incorporated flexibly, either daily, or limited to specific days. Activity patterns limited to 1–2 sessions per week but meeting recommended levels of physical activity have been shown to reduce or postpone all-cause, CVD, and cancer mortality risk.⁴⁷⁷ Importantly, maintaining changed behaviour over time is a challenge. Some trials have shown an impact of lifestyle intervention on cardiovascular health and behavioural metrics, which became attenuated in the long term as the intensity of the intervention declined.¹¹⁴⁵

6.2.1.3. Digital and mHealth

Behavioural change and habit formation can be facilitated through technology such as wearable devices, the internet, and smartphones. In 27

studies including 5165 patients with CAD or cerebrovascular disease, text messaging and smartphone apps resulted in a greater ability to reach BP targets and exercise goals, less anxiety, and increased awareness of diet and exercise compared with control.¹¹⁴⁶ Nevertheless, there was no significant difference in smoking cessation, LDL-C, and hospital readmissions.¹¹⁴⁶ Digital interventions mainly stimulate healthy behavioural factors but are less effective in reducing unhealthy behavioural factors (smoking, alcohol intake, sedentary behaviour, and unhealthy diet) and clinical outcomes.^{1146,1147}

The use of wearable devices has significantly increased physical activity and decreased waist circumference, systolic BP, and LDL-C among individuals with chronic conditions including CVD.⁴⁹¹ Younger age has been associated with a higher increase in physical activity, and CVD has been associated with a lower increase. Wearable activity trackers have shown effectiveness, but the effect was greater when

combined with other behaviour-change strategies.⁴⁹¹ A systematic review of CCS patients that used activity trackers combined with feedback by healthcare professionals (most also giving lifestyle education) showed a significant increase in peak VO₂ in studies using an accelerometer (but not a pedometer) compared with non-users. The overall effect across studies reduced MACE and improved QoL.¹¹⁴⁸ Similarly, smartphone and tablet computer apps have been shown to increase physical activity (minutes per week or steps per day) among people with CVD (1543 participants, most of them with CCS). This effect was largest in small studies focused on physical activity only, participants ≥60 years old, and duration of up to 3 months.¹¹⁴⁹ Adherence to the apps was 20% to 85% and tended to wane over time. Of note, the implementation of digital and mHealth should not be at odds with a less digital-oriented care for those unfamiliar with new technologies (e.g. elderly people).

6.2.1.4. How to assess adherence

Addressing lifestyle behaviour and medication adherence in a non-judgemental way at clinical encounters is important to identify barriers and offer tailored solutions to promote healthier actions. The encounter can be useful to review patient self-monitoring records (digital or written), accelerometer data, and diaries, or validated questionnaires on physical activity.

6.2.2. Adherence to medical therapy

Guideline-directed medications are key to the effective management of CCS and prevention of subsequent cardiovascular events, but dependent on patient adherence and persistence with treatment. Despite robust evidence of benefits in terms of mortality and morbidity,¹¹⁵⁰ adherence remains suboptimal.¹¹⁵¹ Although adherence is usually higher in RCTs, approximately 28% of CCS patients in the ISCHEMIA trial were non-adherent to prescribed medications at baseline.¹¹⁵² Non-adherence was associated with significantly worse health status regardless of randomization to the conservative or invasive strategy.¹¹⁵² Medication adherence can be intentional or unintentional, and can be adversely affected by polypharmacy, complex drug regimens, high cost, and side effects.

6.2.2.1. Strategies to improve medication adherence

Improving adherence to medications has proved challenging.¹¹⁵³ One systematic review and meta-analysis (771 studies to 2015) found that interventions that were behaviourally focused, e.g. linking medication-taking to existing habits, were more effective than those that were cognitively focused.¹¹⁵⁴ A systematic review of 17 trials of adherence for secondary CVD prevention found that a short message service, a fixed-dose combination pill, and a community health worker-based intervention (one trial each) increased adherence compared with usual care.¹¹⁵⁵ Behavioural and mixed behavioural/educational interventions improved adherence in older adults with multiple medications (low-quality evidence), with little evidence for educational-only interventions.¹¹⁵⁶ Drug reminder packaging—i.e. incorporating the date and time for the medication to be taken in a package (pre-filled containers)—can act as a prompt, with some evidence that it increases pills taken and improves diastolic BP and HbA1c levels.¹¹⁵⁷ Treating depression is important, as depression was associated with reduced adequate and optimal adherence to recommended medications 12 months post-PCI in an analysis of 124 443 patients.¹¹⁵⁸

Simplifying medication regimens using fixed-dose polypills has been shown to increase adherence.^{1159–1162} The SECURE trial demonstrated that patients 6 months post-MI randomized to a polypill containing aspirin, ramipril, and atorvastatin had significantly lower MACE and were more likely to have high adherence at 6 and 24 months compared with the usual care group.¹¹⁶³

6.2.2.2. mHealth strategies for medication adherence

A review of mobile phone text messaging found promising, if limited, evidence that such messaging could improve medication adherence up to 12 months after acute coronary events.¹¹⁶⁴ Similarly, another review of 24 studies of text messages and/or apps found robust evidence for adherence to pharmacological therapy.¹¹⁶⁶ A pilot trial of 135 non-adherent patients with hypertension and/or diabetes randomized patients to a highly tailored digital intervention (text messages and interactive voice response) or usual care for 12 weeks. Medication adherence was significantly improved in the intervention group, along with improvements in systolic BP and HbA1c, compared with the control group.¹¹⁶⁵

Recommendation Table 28 — Recommendations for adherence to medical therapy and lifestyle changes (see also Evidence Table 28)

Recommendations	Class ^a	Level ^b
Mobile health interventions (e.g. using text messages, apps, wearable devices) are recommended to improve patient adherence to healthy lifestyles and medical therapy. ^{491,1148,1149,1154,1156,1164}	I	A
Behavioural interventions are recommended to improve adherence. ^{491,1140,1144}	I	B
Simplifying medication regimens (e.g. using fixed-dose drug combinations) is recommended to increase patient adherence to medications. ^{1139,1163,1166}	I	B
Multiprofessional and family involvement is recommended to promote adherence, in addition to patient education and involvement. ¹¹³⁹	I	C

^aClass of recommendation.

^bLevel of evidence.

6.3. Diagnosis of disease progression

Long-term follow-up of patients with CCS who have either established CAD (prior acute MI, revascularization, known CAD) or non-obstructive CAD includes surveillance for disease progression. However, current literature is sparse regarding mode, frequency, and duration. Follow-up of patients is based on their clinical condition, which includes cardiovascular risk factors, residual symptoms, cardiac complications [such as post-infarction LV remodelling and dysfunction, associated mitral regurgitation (mostly functional), known HF, significant arrhythmias], and non-cardiac comorbidities like PAD, stroke, and renal dysfunction.

The main goal of follow-up is to determine the patient's risk of developing new cardiac events through risk stratification and to identify symptoms suggestive of CAD progression. A second goal is

to promptly diagnose and manage extracoronary complications, such as the onset of HF, arrhythmias, and valvular dysfunction. Additionally, during long-term follow-up, antianginal and disease-modifying medication should be optimized and adjusted based on the development of comorbidities. The potential benefits vs. bleeding risks of antithrombotic drugs should be considered and evaluated over time.

Although assessing the anginal status is traditionally considered the cornerstone of clinical follow-up, it is worth noting that angina resolves in 40% of CCS patients at 1 year with further annual decreases, most often without revascularization or adaptation of antianginal therapy.⁴⁰⁴ In contrast to patients with resolving symptoms, those with persistent or recurrent angina are at higher risk of cardiovascular death or MI.⁴⁰⁴ The worse prognosis of persisting angina, however, was only observed in patients with a previous MI.⁴⁰⁸

6.3.1. Risk factors for recurrent coronary artery disease events

Patients with established ASCVD are at high risk of recurrent events and different risk factors have been identified. The REACH registry demonstrated that, in addition to the traditional risk factors, the burden of disease, lack of treatment, and geographical location are all related to an increased risk of cardiovascular morbidity and mortality in CCS patients and validated a risk score that allows estimation of the risk for MACE.¹¹⁶⁷ Using data from stabilized CCS patients from 27 European countries included in the EUROASPIRE IV and V surveys, a new risk model with an online risk calculator to predict recurrent CVD events in patients under the age of 75 years was developed and externally validated in the SWEDEHEART registry.^{1168,1169} This model indicated that the risk of recurrent MACE is mainly driven by comorbidities including diabetes, renal insufficiency, and dyslipidaemia, but also symptoms of depression and anxiety. A study of patients with established CAD from the UK Biobank confirmed the value of classical risk factors, lifestyle, and sociodemographic factors in predicting recurrent MACE.¹¹⁷⁰ In addition, it was found that high genetic predisposition to CAD, low HDL-C, and younger age at first ACS event most strongly predicted the recurrence risk. A polygenic risk score, when added to the Framingham score, improved predictions of events in a large population in the USA.¹¹⁷¹ Although the prediction of recurrent MACE has been refined, it must be emphasized that the predictive power of the different risk factors is weak and that a significant part of recurrent MACE in CCS patients remains unexplained. Furthermore, the models do not incorporate information on LV function, HF, concomitant valvular disease, atherosclerotic disease burden in other vascular beds, or the severity of existing CAD.¹¹⁷² While risk factors for recurrent cardiac events have been established, no clinical studies have tested predefined clinical pathways for long-term follow-up of various types of CCS patients. As a result, the long-term clinical follow-up of CCS patients is primarily empirical, based on good clinical judgement, and on the same criteria used in the initial diagnostic process to define high risk of adverse events (Section 3.3.5 and Figure 18).

6.3.2. Organization of long-term follow-up

When scheduling long-term follow-up for CCS patients with recurring or worsening angina, it is important to consider factors such as patient type, the presence of risk factors, availability of diagnostic techniques, and cost-effectiveness following regional or national healthcare policies. Different CCS phenotypes may develop or recur during long-term follow-up, altering the follow-up needed over time. The intervals and

examination methods during long-term follow-up may vary based on the CCS phenotype, coronary atherosclerotic burden, presence of CMD, and severity of ischaemic LV dysfunction.

A stepwise approach based on risk assessment can be followed, like that applied for diagnosing and treating individuals with suspected CCS.

Step 1: This involves an annual clinical evaluation, by a general practitioner or a cardiologist, encompassing symptom evaluation, medication review, physical examination, a resting 12-lead ECG, and blood tests for lipid profile, renal function, glycaemic status, and full blood count. The ECG should be scrutinized for heart rate, rhythm, evidence of silent ischaemia/infarction, and evaluation of PR, QRS, and QT intervals. Any new symptoms suggestive of ACS, especially with ECG changes, warrant adherence to the 2023 ESC Guidelines for the management of patients with acute coronary syndromes.⁶⁵ Current medical therapy and lifestyle measures for risk-factor control can be maintained or optimized for asymptomatic patients.

Step 2: If CCS patients develop new or worsening angina or HF symptoms, arrhythmias or ECG changes, further cardiac evaluation is crucial, especially if symptoms persist despite optimized GDMT. Recurrent CAD event risk should be assessed based on symptoms, progression of risk factors, and resting ECG changes. Echocardiography may be performed to assess LV function, cardiac dimensions, and valvular abnormalities. Exercise ECG testing may be considered to confirm symptoms and evaluate functional capacity if it alters patient management. However, routine functional testing is not recommended for asymptomatic post-PCI patients, as it has not been shown to improve outcomes compared with standard care after 2 years.¹¹⁷³

Step 3: CCS patients with persistent symptoms at low exercise levels despite optimized GDMT or unexpectedly reduced LV function, especially with regional contraction abnormalities, need further cardiac testing to detect the progression of CAD and assess the event risk.

For patients with known non-obstructive CAD, CCTA can help detect new obstructive stenoses, evaluate atherosclerotic disease progression, and identify high-risk plaque features, while functional imaging is reasonable for detecting myocardial ischaemia and guiding further management. In patients with ANOCA/INOCA and stratified medical therapy, CCTA can be useful to detect new or progressing CAD.

For patients with obstructive CAD or previous cardiac events, non-invasive functional imaging is the preferred method to detect and quantify myocardial ischaemia and/or scar. However, in patients with severely limiting angina and known severe ischaemia on functional testing or high-risk CAD on CCTA, direct referral to ICA for revascularization is preferred due to the very high risk of recurrent CAD events. Although CCTA can detect CABG graft patency and exclude in-stent restenosis (ISR) in broad lumen arteries, functional imaging is preferred for assessing patients with prior revascularization because of the high frequency of extensive CAD in these patients.^{1174–1176}

Step 4: In all patients with recurrent or worsening anginal symptoms, lifestyle modifications, risk-factor management, and GDMT should be intensified before considering further interventions. For patients with significant inducible myocardial ischaemia or high-risk CAD, and persistent anginal symptoms despite lifestyle modifications and intensified GDMT, repeat coronary revascularization may be necessary to alleviate symptoms and improve prognosis. For patients with prior CABG experiencing stable symptoms, it's important to optimize GDMT whenever possible. If frequent angina persists despite GDMT optimization, ICA or CCTA can assist in guiding treatment decisions.^{1177–1179} When symptoms are uncertain, functional testing may help clarify the presence and extent of myocardial ischaemia.

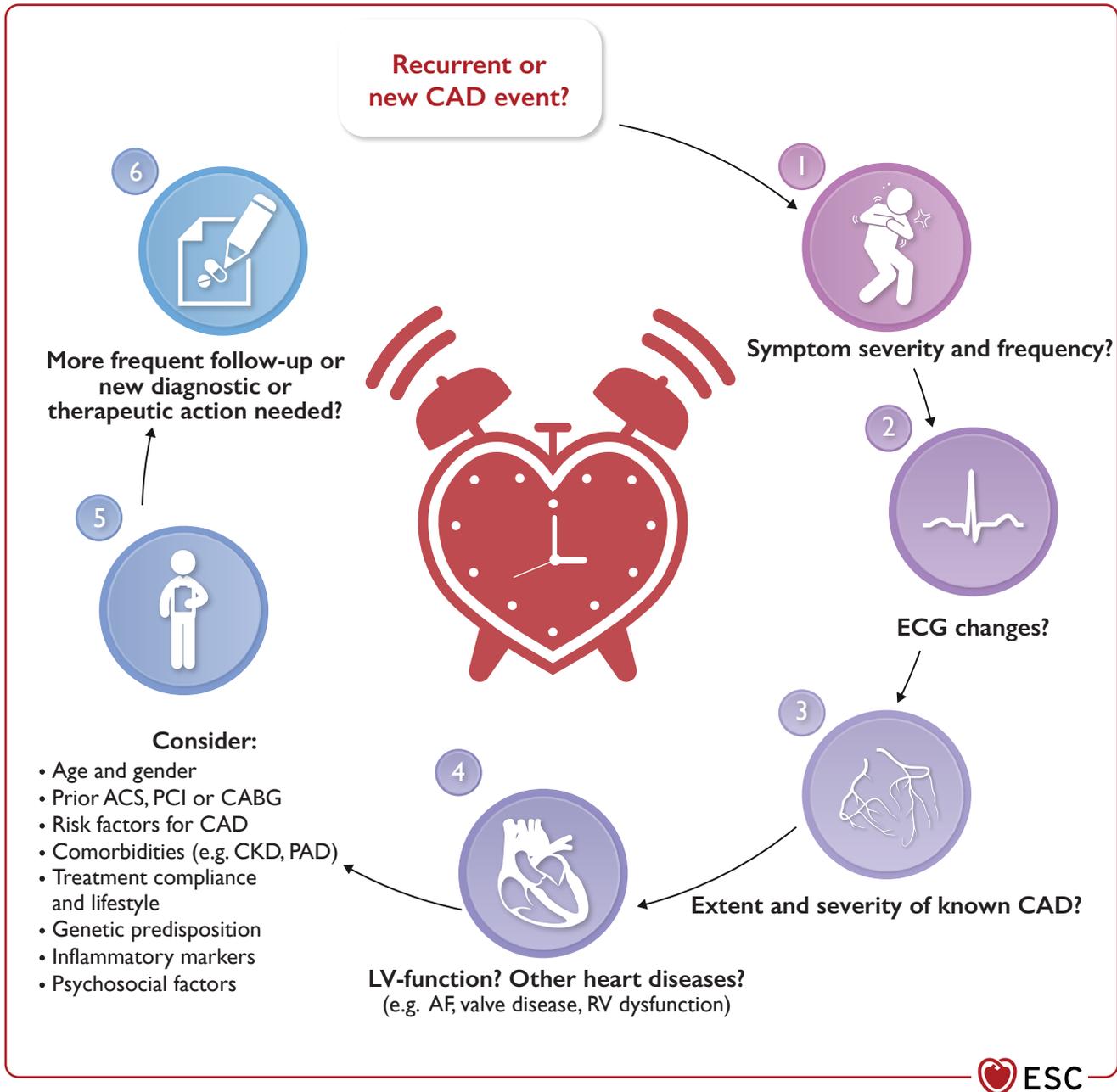


Figure 18 Approach for the follow-up of patients with established chronic coronary syndrome. ACS, acute coronary syndrome; AF, atrial fibrillation; CABG, coronary aortic bypass grafting; CAD, coronary artery disease; CCS, chronic coronary syndrome; CKD, chronic kidney disease; ECG, electrocardiogram; LV, left ventricle; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RV, right ventricle.

6.3.3. Non-invasive diagnostic testing

All non-invasive diagnostic testing, including CCTA, stress SPECT, or PET myocardial perfusion imaging, stress echocardiography, and stress CMR have been shown to provide prognostic information in patients with established CAD.^{296,1180,1181} Anatomical imaging with CCTA has the advantage of providing information on left main disease and graft patency. Stress imaging provides information on the degree of ischaemia, which helps guide an appropriate

management plan. For example, symptomatic patients with moderate-to-severe myocardial ischaemia despite GDMT will usually undergo additional revascularization. In patients with known ANOCA/INOCA, non-invasive imaging with stress SPECT or PET myocardial perfusion imaging, stress CMR, or stress echocardiography remain first-line investigations, although the diagnostic yield may be low;⁹²⁷ however, the current standard remains invasive coronary functional testing.

Recommendation Table 29 — Recommendations for diagnosis of disease progression in patients with established chronic coronary syndrome (see also Evidence Table 29)

Recommendations	Class ^a	Level ^b
Asymptomatic patients with established chronic coronary syndromes		
Regardless of symptoms, periodic visits (e.g. annual) to a general practitioner or cardiovascular healthcare professional are recommended to evaluate cardiovascular risk factor control and to assess changes in risk status, disease status, and comorbidities that may require lifestyle, medical, or procedural interventions.	I	C
Symptomatic patients with established chronic coronary syndromes		
Reassessment of CAD status is recommended in patients with deteriorating LV systolic function that cannot be attributed to a reversible cause (e.g. longstanding tachycardia or myocarditis).	I	C
Risk stratification is recommended in patients with new or worsening symptoms, preferably using stress imaging.	I	C
In patients with symptoms refractory to medical treatment or at high risk of adverse events, invasive coronary angiography (with FFR/iFR when necessary) is recommended for risk stratification and for possible revascularization aimed at improving symptoms and prognosis.	I	C
In CCS patients with symptoms refractory to medical treatment, and who have had previous coronary revascularization, CCTA should be considered to evaluate bypass graft or stent patency (for stents ≥3 mm). ^{1174–1176}	IIa	B

© ESC 2024

CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; LV, left ventricular; QFR, quantitative flow ratio.

^aClass of recommendation.

^bLevel of evidence.

6.4. Treatment of myocardial revascularization failure

One in five revascularized patients needs a repeat revascularization within the first 5 years after myocardial revascularization, with higher risk after PCI compared with CABG.¹¹⁸² Revascularization failure can manifest either shortly after the initial procedure (within 30 days) or later on, and recurring symptoms may result from either restenosis of the treated coronary segment or the failure of bypass grafts,⁷⁷² alongside the progression of underlying native CAD.^{1183,1184} Published evidence regarding diagnosis and management of myocardial revascularization failure has been summarized in the 2020 EAPCI (European Association of Percutaneous Cardiovascular Interventions) Expert Consensus Paper.¹¹⁸²

6.4.1. Percutaneous coronary intervention failure

Stent thrombosis and ISR are the most frequent reasons for PCI failure. Stent thrombosis occurs infrequently and is multifactorial. Anatomical and mechanical factors, as well as lack of adherence or hyporesponsiveness to antiplatelet treatment, are frequently the reasons behind this.^{1182,1185} The majority of patients with stent thrombosis present with ACS and should be treated according to the 2023 ESC Guidelines for the management of patients with acute coronary syndromes.⁶⁵ Urgent ICA to confirm diagnosis and treatment is indicated. After restoration of coronary flow, intracoronary imaging to identify mechanical failure should be performed. Repeated DES implantation is indicated in case of stent fracture or collapse and residual edge dissections, while high-pressure non-compliant balloon dilation is indicated in case of stent under-expansion or malapposition.

In-stent restenosis results as a response to vessel wall injury (neointimal hyperplasia) or neoatherosclerosis in the stented segment of the coronary artery. Although significantly less frequent than after bare-metal stent implantation, the incidence of clinical in-DES restenosis is up to 10% within the first 10 years after DES implantation¹¹⁸² and remains the most frequent cause of PCI failure. The clinical presentation of ISR is mostly CCS, with 20% ACS, and the remaining asymptomatic. The indication to treat ISR is like that for native CAD. Radiological stent enhancement and intracoronary imaging are encouraged to determine the ISR mechanism. PCI treatment of ISR should be focused on the stenotic segment. Lesion preparation (ultra-high pressure balloon dilation, intravascular lithotripsy, rotation atherectomy) and correction of mechanical issues are required.¹¹⁸² Thereafter, drug-coated balloon angioplasty or DES implantation is necessary.^{1186,1187} Drug-eluting balloon angioplasty and repeat stenting with DES were equally effective and safe in treating bare-metal ISR, but drug-coated balloon angioplasty was less effective than repeat paclitaxel DES implantation in treating DES ISR.¹¹⁸⁶ However, at 10-year follow-up there was no difference in clinical endpoints between drug-coated balloon angioplasty and DES implantation, whereas both were more effective than balloon angioplasty in preventing target-lesion revascularization.¹¹⁸⁷ Everolimus DES was associated with better long-term outcomes than drug-coated balloons.¹¹⁸⁸

6.4.2. Managing graft failure after coronary artery bypass grafting

A variety of reasons have the potential to adversely affect bypass graft patency.¹¹⁸⁹ These include technical (quality of graft material, surgical precision) and pathophysiological aspects (competitive flow, activity of the coagulation system, disease progression, etc.). Technical aspects and competitive flow are thought to influence early graft failure, while disease progression and graft degeneration affect long-term patency.^{1182,1189}

The majority of graft occlusions are clinically silent.¹¹⁸⁹ If symptoms occur, prompt diagnostic workup (including ECG, assessment of biomarkers, and possibly repeat coronary angiography) is warranted to limit or prevent potential damage from graft occlusion.³¹⁶ Acute CABG graft failure (<1 month after surgery) is observed in approximately 12% of grafts mostly due to technical problems.¹¹⁹⁰ Late failure of saphenous vein grafts occurs in up to 50% at 10 years, with vein graft occlusion rates in up to 27% within 1 year after surgery.^{771,1191}

The decision for optimal treatment (conservative, CABG revision/redo CABG or PCI of the native vessel or of the failed graft) should be made individually considering haemodynamic stability, technical

reasons for graft failure, and ability to treat native CAD. PCI is the first choice over redo CABG for late graft failure, with PCI of the native vessel rather than PCI of the graft.^{772,1182,1192,1193}

If re-operation is required, the surgical risk is generally increased.^{1182,1192} If acute re-operation is required, acute ischaemia is generally present, and adhesions and the presence of patent grafts increase the complexity of the procedure. It is, therefore, important to weigh this risk against the expected benefit. Since a patent left internal thoracic artery (LITA) to the LAD confers the largest part of CABG prognostic potential,^{1189,1194} redo CABG is primarily recommended in patients with indications for CABG and occluded LITA or if the LITA was not used during the first operation.⁷⁷²

Recommendation Table 30 — Recommendations for treatment of revascularization failure (see also Evidence Table 30)

Recommendations	Class ^a	Level ^b
DES is recommended over drug-coated balloons for treatment of in-DES restenosis. ^{1186–1188}	I	A
LIMA is indicated as the conduit of choice for redo CABG in patients in whom the LIMA was not used previously. ¹¹⁹⁵	I	B
Redo CABG should be considered for patients without a patent LIMA graft to the LAD. ^{842,1192,1196}	IIa	B
PCI of the bypassed native artery should be considered over PCI of the bypass graft. ¹¹⁹⁷	IIa	B

© ESC 2024

CABG, coronary artery bypass grafting; DES, drug-eluting stent; LAD, left anterior descending; LIMA, left internal mammary artery; PCI, percutaneous coronary intervention.

^aClass of recommendation.

^bLevel of evidence.

6.5. Recurrent or refractory angina/ischaemia

An ageing population and an increased survival rate in patients with CAD due to improvements in anti-ischaemic medical therapy and coronary revascularization have led to a growing number of patients with severe and diffuse CAD not amenable to further revascularization procedures. Despite the use of antianginal drugs and/or PCI or CABG, the proportion of patients with CAD who have daily or weekly angina ranges from 2% to 24%.⁵⁵⁵

Refractory angina is defined as long-lasting symptoms (for >3 months) due to established reversible ischaemia: (i) in the presence of obstructive CAD, which cannot be controlled by escalating medical therapy with additional antianginal drugs, bypass grafting, or PCI including recanalization of chronic total coronary occlusion; or (ii) due to ANOCA/INOCA. In the case of ANOCA/INOCA, further investigations are required to define the different endotypes (Section 4.4.2) and appropriate treatment (Section 6.3) before diagnosing refractory angina.³⁶

The QoL of patients with refractory angina is poor, with frequent hospitalization and a high level of resource utilization.⁵⁵⁵ Once conventional anti-ischaemic targets have been exhausted, novel therapies can be ranked by mechanism of action, promotion of collateral growth, transmural redistribution of blood flow, and neuromodulation of the cardiac pain syndrome.

Considering the chronic nature of the disease and according to risk–benefit assessments, among the currently available options, the most

promising and easily implementable in everyday clinical practice are enhanced external counterpulsation and the coronary sinus reducer device,⁵⁵⁵ after all medical therapy and mechanical revascularization options have been exhausted (see Sections 4.2 and 4.4). Enhanced external counterpulsation has been shown to ameliorate refractory angina in several trials.¹¹⁹⁸

The coronary sinus reducer consists of controlled coronary sinus narrowing with the implantation of a large stainless-steel device to increase coronary sinus pressure and improve perfusion in the LAD territory.¹¹⁹⁹ In a recent meta-analysis including eight registries and one RCT, in a total of 846 patients with refractory angina, use of a coronary sinus reducer led to improvement of ≥ 1 CCS class in 76% (95% CI, 73%–80%) of patients and an improvement of ≥ 2 CCS class in 40% (95% CI, 35%–46%) of patients.¹²⁰⁰ The Coronary Sinus Reducer Objective Impact on Symptoms, MRI Ischaemia and Microvascular Resistance (ORBITA-COSMIC) trial, a small proof-of-concept RCT, found no evidence that implantation of a coronary sinus reducer improved transmural myocardial perfusion, but it was associated with improved angina symptoms compared with placebo.¹²⁰¹

There are several ongoing RCTs evaluating the use of coronary sinus reducer in ANOCA/INOCA, such as COronary Sinus Reducer for the Treatment of Refractory Microvascular Angina (COSIMA; NCT04606459), and the Efficacy of the COronary Sinus Reducer in Patients with Refractory Angina II (COSIRA-II; NCT05102019).

A variety of new pharmacological approaches is becoming available and includes angiogenetic therapies with vascular endothelial growth factors and fibroblast growth factors, as well as stem cell therapy with intramyocardial delivery of CD34⁺ cells.^{1202,1203} However, further RCTs are needed to validate the feasibility of such therapeutic strategies.

To date, the main limitations of reported experiences with all novel therapeutic options regard the small number of treated patients and the duration of follow-up. Larger sham-controlled RCTs are required to define the role of each treatment modality for specific subgroups, and ultimately to aim at the best possible personalized treatment algorithm, based on aetiology stratification, and escalation of available therapeutic modalities.

Recommendation Table 31 — Recommendations for recurrent or refractory angina/ischaemia (see also Evidence Table 31)

Recommendations	Class ^a	Level ^b
In patients with refractory angina leading to poor quality of life and with documented or suspected ANOCA/INOCA, invasive coronary functional testing is recommended to define ANOCA/INOCA endotypes and appropriate treatment, considering patient choices and preferences. ^{36,37,298,930,939,985}	I	B
In patients with debilitating angina and obstructive CAD refractory to optimal medical and revascularization strategies, a reducer device for coronary sinus constriction may be considered to improve symptoms, in experienced centres. ^{1199–1201,1204}	IIb	B

© ESC 2024

ANOCA, angina with non-obstructive coronary arteries; CAD, coronary artery disease; INOCA, ischaemia with non-obstructive coronary arteries.

^aClass of recommendation.

^bLevel of evidence.

6.6. Treatment of disease complications

Patients with CCS who develop LV dysfunction may experience advanced HF, malignant arrhythmias and secondary valvular heart disease (i.e. mitral and tricuspid regurgitation).

Prior MI and ischaemic aetiology are negative prognostic markers in patients with advanced HF,¹²⁰⁵ as well as in those with secondary mitral regurgitation.¹²⁰⁶ Specific treatments need to be considered in these patients regardless of HF aetiology (i.e. ischaemic).⁵²⁶ Advanced HF treatments include: high diuretic doses; a combination of diuretics and renal replacement therapy to treat congestion; inotropic and vasopressor agents to reduce hypoperfusion; and mechanical circulatory support in selected patients with severe symptoms or exercise intolerance, despite optimal medical therapies, and without right ventricular dysfunction. Heart transplantation is recommended for patients with advanced HF, refractory to medical/device therapy, and who do not have absolute contraindications. Early evaluation for mechanical circulatory supports or heart transplantation is currently suggested also in patients with mild symptoms [i.e. New York Heart Association (NYHA) class II] and high-risk profile (i.e. LVEF of <20%, recurrent HF events, hypotension, intolerance to medical therapy, worsening organ failure, ventricular arrhythmias/ICD shock).⁵²⁶

An ICD is recommended in patients with ischaemic cardiomyopathy and LVEF of <35% or who have recovered from ventricular arrhythmias.⁵²⁶ Frequent, symptomatic ventricular arrhythmias in ICD recipients should be treated medically with either beta-blockers or amiodarone. In patients with CCS who develop ventricular fibrillation or polymorphic ventricular tachycardia, assessment for myocardial ischaemia should be performed without delay. In patients with CAD in whom sustained monomorphic ventricular tachycardia recurs while on amiodarone treatment, catheter ablation is recommended over the escalation of antiarrhythmic drugs.¹²⁰⁷ Percutaneous treatment of secondary mitral regurgitation in patients with advanced HF may be considered to improve symptoms.⁵²⁶ Treatment of secondary tricuspid regurgitation in advanced stages of disease was, until recently, supported by limited evidence.¹²⁰⁸ Percutaneous tricuspid transcatheter edge-to-edge repair was found to reduce significantly severe tricuspid regurgitation and was associated with improvements in QoL at 1 year.¹²⁰⁹

7. Key messages

- Symptoms of myocardial ischaemia due to obstructive atherosclerotic CAD overlap with those of CMD or vasospasm.
- Similar guideline-directed cardiovascular preventive therapy is recommended in women and men in spite of the sex differences in the clinical presentation.
- Inclusion of risk factors to classic pre-test likelihood models of obstructive atherosclerotic CAD improves the identification of patients with very low ($\leq 5\%$) pre-test likelihood of obstructive CAD in whom deferral of diagnostic testing should be considered.
- CACS is a reliable 'simple' test to modify the pre-test likelihood of atherosclerotic obstructive CAD.
- First-line diagnostic testing of suspected CCS should be done by non-invasive anatomic or functional imaging.
- Selection of the initial non-invasive diagnostic test should be based on the pre-test likelihood of obstructive CAD, other patient characteristics that influence the performance of non-invasive tests, and local expertise and availability.

- CCTA is preferred to rule out obstructive CAD and detect non-obstructive CAD.
- Functional imaging is preferred to correlate symptoms to myocardial ischaemia, estimate myocardial viability, and guide decisions on coronary revascularization.
- PET is preferred for absolute MBF measurements, but CMR perfusion studies may offer an alternative.
- Selective second-line cardiac imaging with functional testing in patients with abnormal CCTA and CCTA after abnormal functional testing may improve patient selection for ICA.
- ICA is recommended to diagnose obstructive CAD in individuals with a very high pre- or post-test likelihood of disease, severe symptoms refractory to GDMT, angina at a low level of exercise, and/or high event risk.
- When ICA is indicated, it is recommended to evaluate the functional severity of 'intermediate' stenoses by invasive functional testing (FFR, iFR) before revascularization.
- Computed FFR based on the 3D reconstruction of ICA is emerging as a valuable alternative to wire-based coronary pressure to evaluate the functional severity of 'intermediate' stenoses.
- The use of imaging guidance is now recommended when performing complex PCI.
- A single antiplatelet agent, aspirin or clopidogrel, is generally recommended long term in CCS patients with obstructive atherosclerotic CAD.
- For high thrombotic-risk CCS patients, long-term therapy with two antithrombotic agents is reasonable, as long as bleeding risk is not high.
- For CCS patients with sinus rhythm, DAPT is recommended at the time of PCI and for 1 to 6 month(s), according to high or low bleeding risk, respectively.
- For CCS patients requiring OAC and undergoing PCI, OAC and DAPT (aspirin and clopidogrel) for 1 to 4 weeks, followed by OAC and clopidogrel for up to 6 months in patients not at high ischaemic risk and up to 12 months in patients at high ischaemic risk, followed by OAC alone should be considered.
- In CCS patients with functionally significant multivessel CAD, current evidence indicates benefit of myocardial revascularization over GDMT alone for symptom improvement, prevention of spontaneous MI, and reduction of cardiovascular mortality at long follow-up.
- Among CCS patients with normal LV function and no significant left main or proximal LAD lesions, current evidence indicates that myocardial revascularization over GDMT alone does not prolong overall survival.
- Among CCS patients with reduced LV function and ischaemic cardiomyopathy, current evidence indicates that surgical revascularization compared with GDMT alone prolongs overall survival at very long follow-up.
- Among patients with complex multivessel CAD without LMCAD, particularly in the presence of diabetes, who are clinically and anatomically suitable for both revascularization modalities, current evidence indicates longer overall survival after CABG than PCI.
- Among patients who are clinically and anatomically suitable for both revascularization modalities, a greater need for repeat revascularization after PCI than surgery, independently of multivessel CAD anatomical severity, has been consistently reported with current surgical and stent technology.
- Lifestyle and risk-factor modification combined with disease-modifying and antianginal medications are cornerstones in the management of CCS.

- Shared decision-making between patients and healthcare professionals, based on patient-centred care, is paramount in defining the appropriate therapeutic pathway for CCS patients. Patient education is key to improve risk-factor control in the long term.
- The relatively high prevalence of ANOCA/INOCA and its associated MACE rate warrants improvement in the diagnosis and treatment of affected patients.
- Persistently symptomatic patients with suspected ANOCA/INOCA who do not respond to GDMT should undergo invasive coronary functional testing to determine underlying endotypes.
- Characterization of endotypes is important to guide appropriate medical therapy for ANOCA/INOCA patients.
- Research on effective methods to support specific healthy lifestyle behaviours, and sustain medication and healthy lifestyle adherence over time, is needed.
- More research is needed on improving the implementation of health-promoting policies and practices in the workplace setting.
- A *post hoc* analysis of ISCHEMIA detected a graded association between the severity of obstructive CAD assessed by CCTA and all-cause mortality and acute MI during follow-up.³¹⁷ There is a need for randomized data comparing contemporary medical treatment against early revascularization plus medical therapy in subsets of patients with an increased risk for death or MI as determined by the *post hoc* analysis. Moreover, because the benefit of an invasive strategy with respect to cardiac mortality was shown in a meta-analysis of chronologically heterogeneous trials, including several conducted more than two decades ago, the impact of early revascularization plus GDMT vs. contemporary GDMT on all-cause and cardiac mortality in patients with CCS should ideally be tested in a well-designed, adequately powered randomized trial.
- Some meta-analyses have reported a reduction in cardiac mortality without a reduction in all-cause mortality. There is a need to clarify the impact of revascularization in CCS patients on cardiovascular and non-cardiovascular mortality.
- Complete revascularization of multivessel CAD by PCI can be achieved as a single procedure (index PCI) or as staged PCI. In the setting of CCS, the value of staged PCI and the optimal interval between interventions needs to be evaluated.
- Whether CABG surgery and PCI are comparable among patients with ischaemic cardiomyopathy and HFrEF in the modern era of HF treatment needs to be evaluated.
- Various imaging techniques, such as low-dose DSE, CMR, and PET/CT, can identify hibernating myocardium with the potential for functional recovery after revascularization.¹²¹¹ Further randomized trials with contemporary, well-defined modalities and strict adherence to protocol are needed to clarify the clinical benefits (if any) of viability testing.
- Residual ischaemia post-PCI, as determined by FFR/iFR, reflects remaining atherosclerotic lesions and/or suboptimal PCI results, but also persistent or worsening microvascular dysfunction. Whether post-PCI FFR/iFR is a 'modifiable' risk factor remains to be proved.
- Among patients suitable for off-pump CABG with complex multivessel CAD but no LMCAD, the impact of hybrid revascularization on outcomes, including peri-operative complications other than MACE, needs more extensive investigation. Data on the optimal time interval between MIDCAB-LIMA and PCI are lacking.
- Whether the decision process based on a multidisciplinary Heart Team leads to better outcomes than standard institutional practice remains to be investigated.
- The medical therapy of ANOCA/INOCA is largely empirical. Therefore, prospective randomized clinical trials are needed to determine the efficacy of antianginal treatments in improving symptoms and outcomes for the different endotypes.
- Research on effective methods to support healthy lifestyle behaviours, and sustain medication and healthy lifestyle adherence over time, is needed. In addition, more research is needed on improving the implementation of health-promoting policies and practices in the workplace setting.
- There is a need for further evidence on the effectiveness of neuromodulation, spinal cord stimulation, therapeutic angiogenesis, and coronary sinus occlusion in patients who suffer from refractory angina, despite guideline-directed medical treatment and revascularization.

8. Gaps in evidence

- It remains unclear if screening for subclinical obstructive CAD in the general population is useful.^{1106,1210} Further large-scale studies are needed to investigate the prognostic benefit of screening and treating asymptomatic CCS in the general population, preferably involving different geographical regions. Optimal screening options remain to be determined for specific groups at high risk (e.g. asymptomatic individuals with diagnosed diabetes for longer than 10 years).
- Most studies assessing diagnostic strategies in individuals with symptoms suspected of CCS were performed in populations with a moderate (>15%–50%) pre-test clinical likelihood of obstructive CAD. Further studies are needed to determine the optimal and most cost-effective diagnostic strategy in individuals with a low (>5%–15%) pre-test clinical likelihood of obstructive CAD.
- The current diagnosis of ANOCA/INOCA and its different endotypes is mainly determined by invasive coronary functional testing.³⁶ Further research is needed to refine and assess non-invasive diagnostic imaging modalities for CMD. Currently available and new non-invasive imaging modalities should be calibrated against invasive testing, allowing the use of their measurements interchangeably.
- The role of antithrombotic therapy in CCS patients with ANOCA/INOCA remains to be established.
- Because of how evidence has accrued over time, there is no clear evidence about the existence of first- and second-line antianginal therapy. It is unclear whether long-acting nitrates, ranolazine, nicorandil, ivabradine, trimetazidine, or any of their combinations improve antianginal symptoms more than beta-blockers or CCBs.
- The optimal type and duration of DAPT is still uncertain in some subsets of patients (e.g. patients with prior revascularization who might benefit from shorter or longer DAPT strategies).
- The long-term benefit of beta-blocker therapy in post-MI patients without reduced EF remains to be elucidated.
- In view of the reported positive impact of low-dose colchicine in patients with CCS in reducing MI, stroke, and revascularization, future studies should identify whether certain patient subgroups (e.g. those with elevated biomarker levels) might derive even greater clinical benefit from this treatment.

9. 'What to do' and 'What not to do' messages from the guidelines

Table 10 lists all Class I and Class III recommendations from the text alongside their level of evidence.

Table 10 'What to do' and 'What not to do'

Recommendations	Class ^a	Level ^b
Recommendations for history taking, risk factor assessment, and resting electrocardiogram in individuals with suspected chronic coronary syndrome		
In individuals reporting symptoms of suspected myocardial ischaemic origin, a detailed assessment of cardiovascular risk factors, medical history, and symptom characteristics (including onset, duration, type, location, triggers, relieving factors, time of day) is recommended.	I	C
If clinical or ECG assessment suggests ACS rather than CCS, immediate referral to the emergency department and/or repeated measurement of blood troponin, preferably using high-sensitivity or ultrasensitive assays, to rule out acute myocardial injury is recommended.	I	B
A resting 12-lead ECG is recommended in all individuals reporting chest pain (unless an obvious non-cardiac cause is identified), particularly during, or immediately after, an episode suggestive of myocardial ischaemia.	I	C
Using ST-segment deviations during supraventricular tachyarrhythmias, particularly during re-entrant atrioventricular tachycardias, per se, as reliable evidence of obstructive CAD, is not recommended.	III	B
Recommendations for basic biochemistry in the initial diagnostic management of individuals with suspected chronic coronary syndrome		
The following blood tests are recommended in all individuals to refine risk stratification, diagnose comorbidities, and guide treatment:		
• lipid profile including LDL-C;	I	A
• full blood count (including haemoglobin);	I	B
• creatinine with estimation of renal function;	I	B
• glycaemic status with HbA1c and/or fasting plasma glucose.	I	B
In patients with suspected CCS, it is recommended to assess thyroid function at least once.	I	B
Recommendations for estimating, adjusting and reclassifying the likelihood of obstructive atherosclerotic coronary artery disease in the initial diagnostic management of individuals with suspected chronic coronary syndrome		
It is recommended to estimate the pre-test likelihood of obstructive epicardial CAD using the Risk Factor-weighted Clinical Likelihood model.	I	B
It is recommended to use additional clinical data (e.g. examination of peripheral arteries, resting ECG, resting echocardiography, presence of vascular calcifications on previously performed imaging tests) to adjust the estimate yielded by the Risk Factor-weighted Clinical Likelihood model.	I	C
Recommendations for resting transthoracic ultrasound and cardiac magnetic resonance imaging in the initial diagnostic management of individuals with suspected chronic coronary syndrome		
A resting transthoracic echocardiogram is recommended: <ul style="list-style-type: none"> • to measure LVEF, volumes and diastolic function; • identify regional wall motion abnormalities; • identify non-coronary cardiac disease (e.g. hypertrophy, cardiomyopathy, valve disease, pericardial effusion); • assess right ventricular function and estimate systolic pulmonary artery pressure; to refine risk stratification and guide treatment.	I	B
Recommendations for the use of exercise ECG in the initial diagnostic management of individuals with suspected chronic coronary syndrome		
Exercise ECG is recommended in selected patients for the assessment of exercise tolerance, symptoms, arrhythmias, BP response, and event risk.	I	C
Exercise ECG is not recommended for diagnostic purposes in patients with ≥ 0.1 mV ST-segment depression on resting ECG, left bundle branch block or who are being treated with digitalis.	III	C
In individuals with a low or moderate (>5–50%) pre-test likelihood of obstructive CAD, an exercise ECG is not recommended to rule out CAD if CCTA or functional imaging tests are available.	III	C
Recommendations for ambulatory ECG monitoring in the initial diagnostic management of individuals with suspected chronic coronary syndrome		
Ambulatory ECG monitoring is recommended in subjects with chest pain and suspected arrhythmias.	I	C

Continued

Recommendations for non-invasive anatomical imaging tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—coronary computed tomography angiography, if available, and supported by local expertise		
In individuals with suspected CCS and low or moderate (>5%–50%) pre-test likelihood of obstructive CAD, CCTA is recommended to diagnose obstructive CAD and to estimate the risk of MACE.	I	A
CCTA is recommended in individuals with low or moderate (>5%–50%) pre-test likelihood to refine diagnosis if another non-invasive test is non-diagnostic.	I	B
CCTA is not recommended in patients with severe renal failure (eGFR <30 mL/min/1.73 m ²), decompensated heart failure, extensive coronary calcification, fast irregular heart rate, severe obesity, inability to cooperate with breath-hold commands, or any other conditions that can make obtaining good imaging quality unlikely.	III	C
Recommendations for non-invasive tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—stress echocardiography, if available, and supported by local expertise		
In individuals with suspected CCS and moderate or high (>15%–85%) pre-test likelihood of obstructive CAD, stress echocardiography is recommended to diagnose myocardial ischaemia and to estimate the risk of MACE.	I	B
During stress echocardiography, when two or more contiguous myocardial segments are not visualized, it is recommended to use commercially available intravenous ultrasound contrast agents (microbubbles) to improve diagnostic accuracy.	I	B
During stress echocardiography, myocardial perfusion using commercially available intravenous ultrasound contrast agents (microbubbles) is recommended to improve diagnostic accuracy and to refine risk stratification beyond wall motion.	I	B
Recommendations for non-invasive functional myocardial imaging tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—resting and stress single-photon emission computed tomography/positron emission tomography—cardiac magnetic resonance imaging, if available, and supported by local expertise		
In individuals with suspected CCS and moderate or high (>15%–85%) pre-test likelihood of obstructive CAD, stress SPECT or, preferably, PET myocardial perfusion imaging is recommended to: <ul style="list-style-type: none"> • diagnose and quantify myocardial ischaemia and/or scar; • estimate the risk of MACE; • quantify myocardial blood flow (PET). 	I	B
In patients selected for PET or SPECT myocardial perfusion imaging, it is recommended to measure CACS from unenhanced chest CT imaging (used for attenuation correction) to improve detection of both non-obstructive and obstructive CAD.	I	B
In individuals with suspected CCS and moderate or high (>15%–85%) pre-test likelihood of obstructive CAD, CMR perfusion imaging is recommended to diagnose and quantify myocardial ischaemia and/or scar and estimate the risk of MACE.	I	B
Recommendations for invasive coronary angiography in individuals with suspected obstructive coronary artery disease		
When ICA is indicated, radial artery access is recommended as the preferred access site.	I	A
When ICA is indicated, it is recommended to have coronary pressure assessment available and to use it to evaluate the functional severity of intermediate non-left main stem stenoses prior to revascularization.	I	A
Invasive coronary angiography is recommended to diagnose CAD in individuals with a very high (>85%) clinical likelihood of disease, severe symptoms refractory to guideline-directed medical therapy, angina at a low level of exercise, and/or high event risk.	I	C
In individuals with de novo symptoms highly suggestive of obstructive CAD that occur at a low level of exercise, ICA with a view towards revascularization is recommended as first diagnostic test after clinical assessment by a cardiologist.	I	C
Recommendations for functional assessment of epicardial artery stenosis severity during invasive coronary angiography to guide revascularization		
During ICA, selective assessment of functional severity of intermediate diameter stenoses is recommended to guide the decision to revascularize, using the following tools: <ul style="list-style-type: none"> • FFR/iFR (significant ≤0.8 or ≤0.89, respectively); • QFR (significant ≤0.8). 	I	A
	I	B
Systematic and routine wire-based coronary pressure assessment of all coronary vessels is not recommended.	III	A
Recommendations for selection of initial diagnostic tests in individuals with suspected chronic coronary syndrome		
It is recommended to select the initial non-invasive diagnostic test based on pre-test likelihood of obstructive CAD, other patient characteristics that influence the performance of non-invasive tests, and local expertise and availability.	I	C
In symptomatic patients in whom the pre-test likelihood of obstructive CAD by clinical assessment is >5%, CCTA or non-invasive functional imaging for myocardial ischaemia is recommended as the initial diagnostic test.	I	B
To rule out obstructive CAD in individuals with low or moderate (>5%–50%) pre-test likelihood, CCTA is recommended as the preferred diagnostic modality.	I	B
CCTA is recommended in individuals with low or moderate (>5%–50%) pre-test likelihood if functional imaging for myocardial ischaemia is not diagnostic.	I	B

Continued

Functional imaging for myocardial ischaemia is recommended if CCTA has shown CAD of uncertain functional significance or is not diagnostic.	I	B
Invasive coronary angiography with the availability of invasive functional assessments is recommended to confirm or exclude the diagnosis of obstructive CAD or ANOCA/INOCA in individuals with an uncertain diagnosis on non-invasive testing.	I	B
Recommendations for definition of high risk of adverse events		
An initial stratification of risk of adverse events is recommended based on basic clinical assessment (e.g. age, ECG, anginal threshold, diabetes, CKD, LVEF).	I	B
The use of one or more of the following test results is recommended to identify individuals at high risk of adverse events: <ul style="list-style-type: none"> • Exercise ECG: <ul style="list-style-type: none"> ◦ Duke Treadmill Score < -10; • stress SPECT or PET perfusion imaging: <ul style="list-style-type: none"> ◦ Area of ischaemia ≥10% of the LV myocardium; • Stress echocardiography: <ul style="list-style-type: none"> ◦ ≥3 of 16 segments with stress-induced hypokinesia or akinesia; • stress CMR: <ul style="list-style-type: none"> ◦ ≥2 of 16 segments with stress perfusion defects or ≥3 dobutamine-induced dysfunctional segments; • CCTA: <ul style="list-style-type: none"> ◦ left main disease with ≥50% stenosis, three-vessel disease with ≥70% stenosis, or two-vessel disease with ≥70% stenosis, including the proximal LAD or one-vessel disease of the proximal LAD with ≥70% stenosis and FFR-CT ≤0.8. 	I	B
In individuals at high risk of adverse events (regardless of symptoms), ICA—complemented by invasive functional measures (FFR/iFR) when appropriate—is recommended, with the aim of refining risk stratification and improving symptoms and cardiovascular outcomes by revascularization.	I	A
Recommendations for cardiovascular risk reduction, lifestyle changes, and exercise interventions in patients with established chronic coronary syndrome		
An informed discussion on CVD risk and treatment benefits tailored to individual patient needs is recommended.	I	C
Multidisciplinary behavioural approaches to help patients achieve healthy lifestyles, in addition to appropriate pharmacological management, are recommended.	I	A
A multidisciplinary exercise-based programme to improve cardiovascular risk profile and reduce cardiovascular mortality is recommended.	I	A
Aerobic physical activity of at least 150–300 min per week of moderate intensity or 75–150 min per week of vigorous intensity and reduction in sedentary time are recommended.	I	B
Recommendations for antianginal drugs in patients with chronic coronary syndrome		
It is recommended to tailor the selection of antianginal drugs to the patient's characteristics, comorbidities, concomitant medications, treatment tolerability, and underlying pathophysiology of angina, also considering local drug availability and cost.	I	C
Short-acting nitrates are recommended for immediate relief of angina.	I	B
Initial treatment with beta-blockers and/or CCBs to control heart rate and symptoms is recommended for most patients with CCS.	I	B
Ivabradine is not recommended as add-on therapy in patients with CCS, LVEF >40%, and no clinical heart failure.	III	B
Combination of ivabradine with non-DHP-CCB or other strong CYP3A4 inhibitors is not recommended.	III	B
Nitrates are not recommended in patients with hypertrophic cardiomyopathy or in co-administration with phosphodiesterase inhibitors.	III	B
Recommendations for antithrombotic therapy in patients with chronic coronary syndrome		
In CCS patients with a prior MI or remote PCI, aspirin 75–100 mg daily is recommended lifelong after an initial period of DAPT.	I	A
In CCS patients with a prior MI or remote PCI, clopidogrel 75 mg daily is recommended as a safe and effective alternative to aspirin monotherapy.	I	A
After CABG, aspirin 75–100 mg daily is recommended lifelong.	I	A
In patients <i>without</i> prior MI or revascularization but with evidence of significant obstructive CAD, aspirin 75–100 mg daily is recommended lifelong.	I	B
In CCS patients with no indication for oral anticoagulation, DAPT consisting of aspirin 75–100 mg and clopidogrel 75 mg daily for up to 6 months is recommended as the default antithrombotic strategy after PCI-stenting.	I	A
In patients at high bleeding risk, but not at high ischaemic risk, it is recommended to discontinue DAPT 1–3 months after PCI and to continue with single antiplatelet therapy.	I	A
In CCS patients with a long-term indication for OAC, an AF therapeutic dose of VKA alone or, preferably, of DOAC alone (unless contraindicated) is recommended lifelong.	I	B
In patients with an indication for OAC who undergo PCI, initial low-dose aspirin once daily is recommended (loading dose when not on maintenance dose) in addition to OAC and clopidogrel.	I	C

Continued

In patients who are eligible for OAC, DOAC (unless contraindicated) is recommended in preference to VKA.	I	A
After uncomplicated PCI in CCS patients with concomitant indication for OAC: <ul style="list-style-type: none"> • early cessation of aspirin (≤ 1 week); • followed by continuation of OAC and clopidogrel: <ul style="list-style-type: none"> ◦ up to 6 months in patients not at high ischaemic risk; or ◦ up to 12 months in patients at high ischaemic risk; • followed by OAC alone; is recommended.	I	A
The use of ticagrelor or prasugrel is generally not recommended as part of triple antithrombotic therapy with aspirin and an OAC.	III	C
It is recommended to initiate aspirin post-operatively as soon as there is no concern over bleeding.	I	B
A proton pump inhibitor is recommended in patients at increased risk of gastrointestinal bleeding for the duration of combined antithrombotic therapy (antiplatelet therapy and/or OAC).	I	A
Recommendations for lipid-lowering drugs in patients with chronic coronary syndrome		
Lipid-lowering treatment with an LDL-C goal of < 1.4 mmol/L (55 mg/dL) and a $\geq 50\%$ reduction in LDL-C vs. baseline is recommended.	I	A
A high-intensity statin up to the highest tolerated dose to reach the LDL-C goals is recommended for all patients with CCS.	I	A
If a patient's goal is not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.	I	B
For patients who are statin intolerant and do not achieve their goal on ezetimibe, combination with bempedoic acid is recommended.	I	B
For patients who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with a PCSK9 inhibitor is recommended.	I	A
Recommendations for sodium–glucose cotransporter 2 inhibitors and/or glucagon-like peptide-1 receptor agonists in patients with chronic coronary syndrome		
CCS patients with type 2 diabetes		
SGLT2 inhibitors with proven CV benefit are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A
GLP-1 receptor agonists with proven CV benefit are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A
Recommendations for angiotensin-converting enzyme inhibitors in patients with chronic coronary syndrome		
In CCS patients, ACE-Is (or ARBs) are recommended in the presence of specific comorbidities, such as hypertension, diabetes, or heart failure.	I	A
Recommendations for revascularization in patients with chronic coronary syndrome		
It is recommended that patients scheduled for percutaneous or surgical revascularization receive complete information about the benefits, risks, therapeutic consequences, and alternatives to revascularization, as part of shared clinical decision-making.	I	C
For complex clinical cases, to define the optimal treatment strategy, in particular when CABG and PCI hold the same level of recommendation, a Heart Team discussion is recommended, including representatives from interventional cardiology, cardiac surgery, non-interventional cardiology, and other specialties if indicated, aimed at selecting the most appropriate treatment to improve patient outcomes and quality of life.	I	C
It is recommended to communicate the proposal of the Heart Team in a very balanced way and in a language that the patient can understand.	I	C
It is recommended that the decision for revascularization and its modality be patient-centred, considering patient preferences, health literacy, cultural circumstances, and social support.	I	C
It is recommended that the Heart Team (on site or with a partner institution) develop institutional protocols to implement the appropriate revascularization strategy in accordance with current guidelines.	I	C
In CCS patients with LVEF $> 35\%$, myocardial revascularization is recommended, in addition to guideline-directed medical therapy, for patients with functionally significant left main stem stenosis to improve survival.	I	A
In CCS patients with LVEF $> 35\%$, myocardial revascularization is recommended, in addition to guideline-directed medical therapy, for patients with functionally significant three-vessel disease to improve long-term survival and to reduce long-term cardiovascular mortality and the risk of spontaneous myocardial infarction.	I	A
In CCS patients with LVEF $> 35\%$, myocardial revascularization is recommended, in addition to guideline-directed medical therapy, for patients with functionally significant single- or two-vessel disease involving the proximal LAD, to reduce long-term cardiovascular mortality and the risk of spontaneous myocardial infarction.	I	B
In CCS patients with LVEF $\leq 35\%$, it is recommended to choose between revascularization or medical therapy alone, after careful evaluation, preferably by the Heart Team, of coronary anatomy, correlation between coronary artery disease and LV dysfunction, comorbidities, life expectancy, individual risk-to-benefit ratio, and patient perspectives.	I	C

Continued

In surgically eligible CCS patients with multivessel CAD and LVEF $\leq 35\%$, myocardial revascularization with CABG is recommended over medical therapy alone to improve long-term survival.	I	B
In CCS patients with persistent angina or anginal equivalent, despite guideline-directed medical treatment, myocardial revascularization of functionally significant obstructive CAD is recommended to improve symptoms.	I	A
In patients with complex CAD in whom revascularization is being considered, it is recommended to assess procedural risks and post-procedural outcomes to guide shared clinical decision-making.	I	C
Calculation of the STS score is recommended to estimate in-hospital morbidity and 30-day mortality after CABG.	I	B
In patients with multivessel obstructive CAD, calculation of the SYNTAX score is recommended to assess the anatomical complexity of disease.	I	B
Intracoronary imaging guidance by IVUS or OCT is recommended when performing PCI on anatomically complex lesions, in particular left main stem, true bifurcations, and long lesions.	I	A
Intracoronary pressure measurement (FFR or iFR) or computation (QFR) is recommended to guide lesion selection for intervention in patients with multivessel disease.	I	A
It is recommended that physicians select the most appropriate revascularization modality based on patient profile, coronary anatomy, procedural factors, LVEF, preferences, and outcome expectations.	I	C
Recommendations for mode of revascularization in patients with chronic coronary syndrome		
Left main disease		
In CCS patients at low surgical risk with significant left main coronary stenosis, CABG:	I	A
• is recommended over medical therapy alone to improve survival		
• is recommended as the overall preferred revascularization mode over PCI, given the lower risk of spontaneous myocardial infarction and repeat revascularization	I	A
In CCS patients with significant left main coronary stenosis of low complexity (SYNTAX score ≤ 22), in whom PCI can provide equivalent completeness of revascularization to that of CABG, PCI is recommended as an alternative to CABG, given its lower invasiveness and non-inferior survival.	I	A
Left main with multivessel disease		
In CCS patients at low surgical risk with suitable anatomy, CABG is recommended over medical therapy alone to improve survival.	I	A
Multivessel disease and diabetes		
In CCS patients with significant multivessel disease and diabetes, with insufficient response to guideline-directed medical therapy, CABG is recommended over medical therapy alone and over PCI to improve symptoms and outcomes.	I	A
Three-vessel disease, without diabetes		
In CCS patients with significant three-vessel disease, preserved LVEF, no diabetes, and insufficient response to guideline-directed medical therapy, CABG is recommended over medical therapy alone to improve symptoms, survival, and other outcomes.	I	A
In CCS patients with preserved LVEF, no diabetes, insufficient response to guideline-directed medical therapy, and significant three-vessel disease of low-to-intermediate anatomic complexity in whom PCI can provide similar completeness of revascularization to that of CABG, PCI is recommended, given its lower invasiveness, and generally non-inferior survival.	I	A
Single- or double-vessel disease involving the proximal LAD		
In CCS patients with significant single- or double-vessel disease involving the proximal LAD and insufficient response to guideline-directed medical therapy, CABG or PCI is recommended over medical therapy alone to improve symptoms and outcomes.	I	A
In CCS patients with complex significant single- or double-vessel disease involving the proximal LAD, less amenable to PCI, and insufficient response to guideline-directed medical therapy, CABG is recommended over PCI to improve symptoms and reduce revascularization rates.	I	B
Single- or double-vessel disease not involving the proximal LAD		
In symptomatic CCS patients with single- or double-vessel disease not involving the proximal LAD and with insufficient response to guideline-directed medical therapy, PCI is recommended to improve symptoms.	I	B
Recommendations for management of chronic coronary syndrome patients with chronic heart failure		
Managing CCS in heart failure patients		
In HF patients with LVEF $\leq 35\%$ in whom obstructive CAD is suspected, ICA is recommended with a view towards improving prognosis by CABG, taking into account the risk-to-benefit ratio of the procedures.	I	B
In HF patients with LVEF $> 35\%$ and suspected CCS with low or moderate ($> 5\%$ – 50%) pre-test likelihood of obstructive CAD, CCTA or functional imaging is recommended.	I	C
In HF patients with LVEF $> 35\%$ and suspected CCS with very high ($> 85\%$) pre-test likelihood of obstructive CAD, ICA (with FFR, iFR, or QFR when needed) is recommended.	I	C

Continued

Managing heart failure in CCS patients		
It is recommended that CCS patients with HF be enrolled in a multidisciplinary HF management programme to reduce the risk of HF hospitalization and to improve survival.	I	A
An ACE-I, an MRA, an SGLT2 inhibitor (dapagliflozin or empagliflozin), and, in stable conditions, a beta-blocker are recommended for CCS patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HF with mildly reduced ejection fraction (HFmrEF) or HFpEF to reduce the risk of HF hospitalization or cardiovascular death.	I	A
An ARB is recommended in symptomatic patients with CCS and HFrEF unable to tolerate an ACE-I or ARNI to reduce the risk of HF hospitalization and cardiovascular death.	I	B
Sacubitril/valsartan is recommended as a replacement for an ACE-I or ARB in CCS patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B
Diuretics are recommended in CCS patients with HF and signs and/or symptoms of congestion to alleviate symptoms, improve exercise capacity, and reduce HF hospitalizations.	I	B
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of ischaemic aetiology (unless they have had an MI in the prior 40 days), and an LVEF $\leq 35\%$ despite ≥ 3 months of optimized GDMT, provided they are expected to survive substantially longer than 1 year with good functional status.	I	A
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status, in the absence of reversible causes or unless the ventricular arrhythmia has occurred <48 h after an MI.	I	A
CRT is recommended for CCS patients with symptomatic HF, sinus rhythm, LVEF $\leq 35\%$ despite GDMT, and a QRS duration ≥ 150 ms with an LBBB QRS morphology to improve symptoms and survival and to reduce morbidity.	I	A
CRT rather than right ventricular pacing is recommended for patients with HFrEF regardless of NYHA class or QRS width who have an indication for ventricular pacing for high-degree AV block in order to reduce morbidity. This includes patients with AF.	I	A
Recommendations for diagnosis and management of patients with angina with non-obstructive coronary arteries/ischaemia with non-obstructive coronary arteries		
In persistently symptomatic patients despite medical treatment with suspected ANOCA/INOCA (i.e. anginal symptoms with normal coronary arteries or non-obstructive lesions at non-invasive imaging, or intermediate stenoses with normal FFR/IFR at coronary arteriography) and poor quality of life, invasive coronary functional testing is recommended to identify potentially treatable endotypes and to improve symptoms and quality of life, considering patient choices and preferences.	I	B
In individuals with suspected vasospastic angina, a resting 12-lead ECG recording during angina is recommended.	I	C
In patients with suspected vasospastic angina and repetitive episodes of rest angina associated with ST-segment changes that resolve with nitrates and/or calcium antagonists, invasive functional angiography is recommended to confirm the diagnosis and to determine the severity of underlying atherosclerotic disease.	I	C
For the treatment of isolated vasospastic angina: • calcium channel blockers are recommended to control symptoms and to prevent ischaemia and potentially fatal complications.	I	A
Recommendations for older, female, high bleeding risk, comorbid, and socially/geographically diverse patients		
In older adults (≥ 75 years), particular attention to drug side effects, intolerance, drug–drug interactions, overdosing, and procedural complications is recommended.	I	C
In older, as in younger, individuals, diagnostic and revascularization decisions based on symptoms, extent of ischaemia, frailty, life expectancy, comorbidities, and patient preferences are recommended.	I	C
Similar guideline-directed cardiovascular preventive therapy is recommended in women and men.	I	C
Systemic post-menopausal hormone therapy is not recommended in women with CCS, given the lack of cardiovascular benefit and an increased risk of thrombo-embolic complications.	III	A
Bleeding risk assessment is recommended using the PRECISE-DAPT score, the qualitative ARC-HBR tool or other, validated method.	I	B
Attention to interaction between antiretroviral treatment and statins is recommended in patients with HIV.	I	B
Continued targeted efforts are recommended: • to increase delivery of safe and effective cardiac care to all CCS patients, especially those of lower socioeconomic classes; and • to enhance inclusion in future clinical trials of geographical, social, or other groups that are currently underrepresented.	I	C
Recommendations for screening for coronary artery disease in asymptomatic individuals		
Opportunistic screening of healthy individuals for cardiovascular risk factors and to estimate the risk of future cardiovascular events using scoring systems, e.g. SCORE2 and SCORE-OP, is recommended to detect individuals at high risk and guide treatment decisions.	I	C

Continued

Recommendations for adherence to medical therapy and lifestyle changes		
Mobile health interventions (e.g. using text messages, apps, wearable devices) are recommended to improve patient adherence to healthy lifestyles and medical therapy.	I	A
Behavioural interventions are recommended to improve adherence.	I	B
Simplifying medication regimens (e.g. using fixed-dose drug combinations) is recommended to increase patient adherence to medications.	I	B
Multiprofessional and family involvement is recommended to promote adherence, in addition to patient education and involvement.	I	C
Recommendations for diagnosis of disease progression in patients with established chronic coronary syndrome		
Regardless of symptoms, periodic visits (e.g. annual) to a general practitioner or cardiovascular healthcare professional are recommended to evaluate cardiovascular risk factor control and to assess changes in risk status, disease status, and comorbidities that may require lifestyle, medical, or procedural interventions.	I	C
Reassessment of CAD status is recommended in patients with deteriorating LV systolic function that cannot be attributed to a reversible cause (e.g. longstanding tachycardia or myocarditis).	I	C
Risk stratification is recommended in patients with new or worsening symptoms, preferably using stress imaging.	I	C
In patients with symptoms refractory to medical treatment or at high risk of adverse events, invasive coronary angiography (with FFR/iFR when necessary) is recommended for risk stratification and for possible revascularization aimed at improving symptoms and prognosis.	I	C
Recommendations for treatment of revascularization failure		
DES is recommended over drug-coated balloons for treatment of in-DES restenosis.	I	A
LIMA is indicated as the conduit of choice for redo CABG in patients in whom the LIMA was not used previously.	I	B
Recommendations for recurrent or refractory angina/ischæmia		
In patients with refractory angina leading to poor quality of life and with documented or suspected ANOCA/INOCA, invasive coronary function testing is recommended to define ANOCA/INOCA endotypes and appropriate treatment, considering patient choices and preferences.	I	B

ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AF, atrial fibrillation; ANOCA, angina with non-obstructive coronary arteries; ARB, angiotensin receptor blocker; ARC-HBR, Academic Research Consortium for High Bleeding; ARNI, angiotensin receptor neprilysin inhibitor; AV, atrioventricular; BP, blood pressure; CABG, coronary artery bypass grafting; CACS, coronary artery calcium score; CAD, coronary artery disease; CCB, calcium channel blocker; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CKD, chronic kidney disease; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; CT, computed tomography; CV, cardiovascular; CVD, cardiovascular disease; CYP3A4, cytochrome P450 3A4; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DHP, dihydropyridine; DOAC, direct oral anticoagulant; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; FFR-CT, coronary computed tomography angiography-derived fractional flow reserve; GDMT, guideline-directed medical therapy; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HIV, human immunodeficiency virus; ICA, invasive coronary angiography; ICD, implantable cardioverter defibrillator; iFR, instantaneous wave-free ratio; INOCA, ischaemia with non-obstructive coronary arteries; IVUS, intravascular ultrasound; LAD, left anterior descending; LBBB, left bundle branch block; LDL-C, low-density lipoprotein cholesterol; LIMA, left internal mammary artery; LV, left ventricular; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; OAC, oral anticoagulant; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; PET, positron emission tomography; PRECISE-DAPT, PREdicting bleeding Complications In patients undergoing Stent implantation and subSequent Dual AntiPlatelet Therapy; QFR, quantitative flow ratio; SCORE2, Systematic Coronary Risk Estimation 2; SCORE-OP, Systematic Coronary Risk Estimation 2—Older Persons; SGLT2, sodium–glucose cotransporter 2; SPECT, single-photon emission computed tomography; STS, Society of Thoracic Surgeons; SYNTAX, SYnergy Between PCI with TAXUS and Cardiac Surgery; T2DM, type 2 diabetes mellitus; VKA, vitamin K antagonist.

^aClass of recommendation.

^bLevel of evidence.

10. Evidence tables

Evidence tables are available at *European Heart Journal* online.

11. Data availability statement

No new data were generated or analysed in support of this research.

12. Author information

Author/task force Member Affiliations: Konstantinos

C. Koskinas, Department of Cardiology, Bern University Hospital—INSELSPIITAL, University of Bern, Bern, Switzerland; **Xavier**

Rossello, Cardiology Department Hospital Universitari Son Espases, Palma de Mallorca, Spain, Health Research Institute of the Balearic Islands (IdISBa), Universitat de les Illes Balears (UIB), Palma de Mallorca, Spain, and Clinical Research Department, Centro Nacional

de Investigaciones Cardiovasculares (CNIC), Madrid, Spain; **Marianna Adamo**, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, Institute of Cardiology, ASST Spedali Civili di Brescia and University of Brescia, Brescia, Italy; **James Ainslie**, ESC Patient Forum, Sophia Antipolis, France; **Adrian Paul Banning**, Oxford Heart Centre, Oxford University Hospitals, Oxford, United Kingdom; **Andrzej Budaj**, Department of Cardiology, Centre of Postgraduate Medical Education, Warsaw, Poland; **Ronny R. Buechel**, Department of Nuclear Medicine, Cardiac Imaging, University and University Hospital Zurich, Zurich, Switzerland; **Giovanni Alfonso Chiariello**, Department of Cardiovascular Sciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, and Università Cattolica del Sacro Cuore, Rome, Italy; **Alaide Chieffo**, Vita Salute San Raffaele University, Milan, Italy, and Interventional Cardiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; **Ruxandra Maria Christodorescu**, Department V Internal Medicine, University of Medicine and Pharmacy V Babes, Timisoara, Romania, and Research

Center, Institute of Cardiovascular Diseases, Timisoara, Romania; **Christi Deaton**, Public Health and Primary Care, Cambridge University School of Clinical Medicine, Cambridge, United Kingdom; **Torsten Doenst**, Department of cardiothoracic surgery, Friedrich-Schiller-University Jena, university hospital, Jena, Germany; Hywel W. Jones, ESC Patient Forum, Sophia Antipolis, France; **Vijay Kunadian**, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University and Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; **Julinda Mehilli**, Medizinische Klinik I, Landshut-Achdorf Hospital, Landshut, Germany, and Klinikum der Universität München Ludwig-Maximilians University, Munich, Germany; **Milan Milojevic**, Department of Cardiac Surgery and Cardiovascular Research, Dedinje Cardiovascular Institute, Belgrade, Serbia; **Jan J. Piek**, Heart Center, Department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands; **Francesca Pugliese**, Centre for Advanced Cardiovascular Imaging, The William Harvey Research Institute, Queen Mary University of London, London, United Kingdom, Barts Health NHS Trust, London, United Kingdom, and Heart Vascular and Thoracic Institute, Cleveland Clinic London, London, United Kingdom; **Andrea Rubboli**, Department of Emergency, Internal Medicine, and Cardiology, Division of Cardiology, S. Maria delle Croci Hospital, Ravenna, Italy; **Anne Grete Semb**, Preventive cardio-rheuma clinic, Diakonhjemmet Hospital, Oslo, Norway, and REMEDY Centre Diakonhjemmet Hospital, Oslo, Norway; **Roxy Senior**, Cardiology Royal Brompton Hospital and Imperial College London, London, United Kingdom, and Cardiology, Northwick Park Hospital, Harrow, United Kingdom; **Jurrien M. ten Berg**, Cardiology, St Antonius Hospital, Nieuwegein, Netherlands, and Cardiology, Maastricht University Medical Centre, Maastricht, Netherlands; **Eric van Belle**, Cardiology, Institut Cour Poumon—CHU de Lille, Lille, France, and Equipe 2, INSERM U 1011, Lille, France; **Emeline M. Van Craenenbroeck**, Cardiology department, Antwerp University Hospital, Edegem, Belgium, and GENCOR, University of Antwerp, Antwerp, Belgium; **Rafael Vidal-Perez**, Cardiology, Cardiac Imaging Unit, Complejo Hospitalario Universitario de A Coruña (CHUAC), A Coruña, Spain, and Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain; and **Simon Winther**, Department of cardiology, Gødstrup hospital, Herning, Denmark, and Institute of clinical medicine, Aarhus university, Aarhus, Denmark.

13. Appendix

ESC Scientific Document Group

Includes Document Reviewers and ESC National Cardiac Societies.

Document Reviewers: Michael Borger (CPG Review Co-ordinator) (Germany); Ingibjörg J. Gudmundsdóttir (CPG Review Co-ordinator) (Iceland); Juhani Knuuti (CPG Review Co-ordinator) (Finland); Ingo Ahrens (Germany); Michael Böhm (Germany); Davide Capodanno (Italy); Evald Høj Christiansen (Denmark); Jean-Philippe Collet[†] (France); Kenneth Dickstein (Norway); Christian Eek (Norway); Volkmar Falk (Germany); Peter A. Henriksen (United Kingdom); Borja Ibanez (Spain); Stefan James (Sweden); Sasko Kedev (Macedonia); Lars Køber (Denmark); Martha Kyriakou (Cyprus); Emma F. Magavern (United Kingdom); Angelia McInerney (Ireland); Caius Ovidiu Mersha (Romania); Borislava Mihaylova (United

Kingdom); Richard Mindham (United Kingdom); Lis Neubeck (United Kingdom); Franz-Josef Neumann (Germany); Jens Cosedis Nielsen (Denmark); Pasquale Paolisso (Italy); Valeria Paradies (Netherlands); Agnes A. Pasquet (Belgium); Massimo Piepoli (Italy); Eva Prescott (Denmark); Amina Rakisheva (Kazakhstan); Bianca Rocca (Italy); Marc Ruel (Canada); Sigrid Sandner (Austria); Antti Saraste (Finland); Karolina Szummer (Sweden); Ilonca Vaartjes (Netherlands); William Wijns (Ireland); Stephan Windecker (Switzerland); Adam Witkowski (Poland); Marija Zdrakovic (Serbia); and Katja Zeppenfeld (Netherlands).

[†]Professor Jean-Philippe Collet sadly passed away during the development of these guidelines. Professor Collet's contribution to these guidelines was, as always, highly valued.

ESC National Cardiac Societies actively involved in the review process of the 2024 ESC Guidelines on the management of chronic coronary syndromes:

Albania: Albanian Society of Cardiology, Naltin Shuka; **Algeria:** Algerian Society of Cardiology, Mohamed Abed Bouraghda; **Armenia:** Armenian Cardiologists Association, Hamlet G. Hayrapetyan; **Austria:** Austrian Society of Cardiology, Sebastian J. Reinstadler; **Azerbaijan:** Azerbaijan Society of Cardiology, Ogtay Musayev; **Belgium:** Belgian Society of Cardiology, Michel De Pauw; **Bosnia and Herzegovina:** Association of Cardiologists of Bosnia and Herzegovina, Zumreta Kušljugić; **Bulgaria:** Bulgarian Society of Cardiology, Valeri Gelev; **Croatia:** Croatian Cardiac Society, Bosko Skoric; **Cyprus:** Cyprus Society of Cardiology, Maria Karakyriou; **Czechia:** Czech Society of Cardiology, Tomas Kovarnik; **Denmark:** Danish Society of Cardiology, Lene H. Nielsen; **Egypt:** Egyptian Society of Cardiology, Islam Sh. Abdel-Aziz; **Estonia:** Estonian Society of Cardiology, Tiia Ainla; **Finland:** Finnish Cardiac Society, Pekka Porela; **France:** French Society of Cardiology, Hakim Benamer; **Georgia:** Georgian Society of Cardiology, Kakha Nadaraia; **Germany:** German Cardiac Society, Gert Richardt; **Greece:** Hellenic Society of Cardiology, Michail I. Papafaklis; **Hungary:** Hungarian Society of Cardiology, Dávid Becker; **Iceland:** Icelandic Society of Cardiology, Ingibjörg J. Gudmundsdóttir; **Israel:** Israel Heart Society, Arik Wolak; **Italy:** Italian Federation of Cardiology, Carmine Riccio; **Kazakhstan:** Association of Cardiologists of Kazakhstan, Bekbolat Kulzhanovich Zholdin; **Kosovo (Republic of):** Kosovo Society of Cardiology, Shpend Elezi; **Kyrgyzstan:** Kyrgyz Society of Cardiology, Saamay Abilova; **Latvia:** Latvian Society of Cardiology, Iveta Mintale; **Lebanon:** Lebanese Society of Cardiology, Bachir Allam; **Lithuania:** Lithuanian Society of Cardiology, Jolita Badarienė; **Luxembourg:** Luxembourg Society of Cardiology, Bruno Pereira; **Malta:** Maltese Cardiac Society, Philip Dingli; **Moldova (Republic of):** Moldavian Society of Cardiology, Valeriu Revenco; **Montenegro:** Montenegro Society of Cardiology, Nebojsa Bulatovic; **Morocco:** Moroccan Society of Cardiology, El Ghali Mohamed Benouna; **Netherlands:** Netherlands Society of Cardiology, Admir Dedic; **North Macedonia:** National Society of Cardiology of North Macedonia, Irena Mitevaska; **Norway:** Norwegian Society of Cardiology, Kristin Angel; **Poland:** Polish Cardiac Society, Krzysztof Bryniarski; **Portugal:** Portuguese Society of Cardiology, André Miguel Coimbra Luz; **Romania:** Romanian Society of Cardiology, Bogdan Alexandru Popescu; **San Marino:** San Marino Society of Cardiology, Luca Bertelli; **Serbia:** Cardiology Society of Serbia, Branko Dušan Beleslin; **Slovakia:** Slovak Society of Cardiology, Martin Hudec; **Slovenia:** Slovenian Society of Cardiology, Zlatko Fras; **Spain:** Spanish Society of Cardiology, Román Freixa-Pamias; **Sweden:** Swedish Society of Cardiology,

Anna Holm; **Switzerland:** Swiss Society of Cardiology, Raban Jeger; **Syrian Arab Republic:** Syrian Cardiovascular Association, Mhd Yassin Bani Marjeh; **Tunisia:** Tunisian Society of Cardiology and Cardiovascular Surgery, Rania Hammami; **Türkiye:** Turkish Society of Cardiology, Vedat Aytekin; **Ukraine:** Ukrainian Association of Cardiology, Elena G. Nesukay; **United Kingdom:** British Cardiovascular Society, Neil Swanson; and **Uzbekistan:** Association of Cardiologists of Uzbekistan, Aleksandr Borisovich Shek.

ESC Clinical Practice Guidelines (CPG) Committee: Eva Prescott (Chairperson) (Denmark), Stefan James (Co-Chairperson) (Sweden), Elena Arbelo (Spain), Colin Baigent (United Kingdom), Michael A. Borger (Germany), Sergio Buccheri (Sweden), Borja Ibanez (Spain), Lars Køber (Denmark), Konstantinos C. Koskinas (Switzerland), John William McEvoy (Ireland), Borislava Mihaylova (United Kingdom), Richard Mindham (United Kingdom), Lis Neubeck (United Kingdom), Jens Cosedis Nielsen (Denmark), Agnes A. Pasquet (Belgium), Amina Rakisheva (Kazakhstan), Bianca Rocca (Italy), Xavier Rossello (Spain), Ilonca Vaartjes (Netherlands), Christiaan Vrints (Belgium), Adam Witkowski (Poland), Katja Zeppenfeld (Netherlands), and Alexia Rossi[§] (Italy).

[§]Contributor either stepped down or was engaged in only a part of the review process.

14. References

- Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–77. <https://doi.org/10.1093/eurheartj/ehz425>
- Collet C, Sonck J, Vandeloos B, Mizukami T, Roosens B, Lochy S, et al. Measurement of hyperemic pullback pressure gradients to characterize patterns of coronary atherosclerosis. *J Am Coll Cardiol* 2019;**74**:1772–84. <https://doi.org/10.1016/j.jacc.2019.07.072>
- Scarsini R, Fezzi S, Leone AM, De Maria GL, Pighi M, Marcoli M, et al. Functional patterns of coronary disease: diffuse, focal, and serial lesions. *JACC Cardiovasc Interv* 2022;**15**:2174–91. <https://doi.org/10.1016/j.jcin.2022.07.015>
- Sternheim D, Power DA, Samtani R, Kini A, Fuster V, Sharma S. Myocardial bridging: diagnosis, functional assessment, and management: JACC state-of-the-art review. *J Am Coll Cardiol* 2021;**78**:2196–212. <https://doi.org/10.1016/j.jacc.2021.09.859>
- Gentile F, Castiglione V, De Caterina R. Coronary artery anomalies. *Circulation* 2021;**144**:983–96. <https://doi.org/10.1161/CIRCULATIONAHA.121.055347>
- Del Buono MG, Montone RA, Camilli M, Carbone S, Narula J, Lavie CJ, et al. Coronary microvascular dysfunction across the spectrum of cardiovascular diseases: JACC state-of-the-art review. *J Am Coll Cardiol* 2021;**78**:1352–71. <https://doi.org/10.1016/j.jacc.2021.07.042>
- Marzilli M, Crea F, Morrone D, Bonow RO, Brown DL, Camici PG, et al. Myocardial ischemia: from disease to syndrome. *Int J Cardiol* 2020;**314**:32–5. <https://doi.org/10.1016/j.ijcard.2020.04.074>
- Gutierrez E, Flammer AJ, Lerman LO, Elizaga J, Lerman A, Fernandez-Aviles F. Endothelial dysfunction over the course of coronary artery disease. *Eur Heart J* 2013;**34**:3175–81. <https://doi.org/10.1093/eurheartj/ehz351>
- Allaqaband H, Gutterman DD, Kadlec AO. Physiological consequences of coronary arteriolar dysfunction and its influence on cardiovascular disease. *Physiology (Bethesda)* 2018;**33**:338–47. <https://doi.org/10.1152/physiol.00019.2018>
- Alexander Y, Osto E, Schmidt-Trucksäss A, Shechter M, Trifunovic D, Duncker DJ, et al. Endothelial function in cardiovascular medicine: a consensus paper of the European Society of Cardiology Working Groups on Atherosclerosis and Vascular Biology, Aorta and Peripheral Vascular Diseases, Coronary Pathophysiology and Microcirculation, and Thrombosis. *Cardiovasc Res* 2021;**117**:29–42. <https://doi.org/10.1093/cvr/cvaa085>
- Trask AJ, Katz PS, Kelly AP, Galantowicz ML, Cismowski MJ, West TA, et al. Dynamic micro- and macrovascular remodeling in coronary circulation of obese Ossabaw pigs with metabolic syndrome. *J Appl Physiol* 2012;**113**:1128–40. <https://doi.org/10.1152/jappphysiol.00604.2012>
- Campbell DJ, Somaratne JB, Prior DL, Yui M, Kenny JF, Newcomb AE, et al. Obesity is associated with lower coronary microvascular density. *PLoS One* 2013;**8**:e81798. <https://doi.org/10.1371/journal.pone.0081798>
- Hinkel R, Howe A, Renner S, Ng J, Lee S, Klett K, et al. Diabetes mellitus-induced microvascular destabilization in the myocardium. *J Am Coll Cardiol* 2017;**69**:131–43. <https://doi.org/10.1016/j.jacc.2016.10.058>
- Bajaj Navkanbir S, Osborne MT, Gupta A, Tavakkoli A, Bravo PE, Vita T, et al. Coronary microvascular dysfunction and cardiovascular risk in obese patients. *J Am Coll Cardiol* 2018;**72**:707–17. <https://doi.org/10.1016/j.jacc.2018.05.049>
- Seitz A, Martínez Pereyra V, Sechtem U, Ong P. Update on coronary artery spasm 2022—a narrative review. *Int J Cardiol* 2022;**359**:1–6. <https://doi.org/10.1016/j.ijcard.2022.04.011>
- Vissers FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**:3227–337. <https://doi.org/10.1093/eurheartj/ehab484>
- Sandhu AT, Rodriguez F, Ngo S, Patel BN, Mastrodocasa D, Eng D, et al. Incidental coronary artery calcium: opportunistic screening of previous nongated chest computed tomography scans to improve statin rates (NOTIFY-1 project). *Circulation* 2023;**147**:703–14. <https://doi.org/10.1161/CIRCULATIONAHA.122.062746>
- Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol* 2006;**47**:S21–9. <https://doi.org/10.1016/j.jacc.2004.12.084>
- Andreotti F, Marchese N. Women and coronary disease. *Heart* 2008;**94**:108–16. <https://doi.org/10.1136/hrt.2005.072769>
- Ferrari R, Abergel H, Ford I, Fox KM, Greenlaw N, Steg PG, et al. Gender- and age-related differences in clinical presentation and management of outpatients with stable coronary artery disease. *Int J Cardiol* 2013;**167**:2938–43. <https://doi.org/10.1016/j.ijcard.2012.08.013>
- Mehta PK, Bess C, Elias-Smale S, Vaccarino V, Quyyumi A, Pepine CJ, et al. Gender in cardiovascular medicine: chest pain and coronary artery disease. *Eur Heart J* 2019;**40**:3819–26. <https://doi.org/10.1093/eurheartj/ehz784>
- Ford ES, Capewell S. Proportion of the decline in cardiovascular mortality disease due to prevention versus treatment: public health versus clinical care. *Annu Rev Public Health* 2011;**32**:5–22. <https://doi.org/10.1146/annurev-publhealth-031210-101211>
- Safiri S, Karamzad N, Singh K, Carson-Chahhoud K, Adams C, Nejadghaderi SA, et al. Burden of ischemic heart disease and its attributable risk factors in 204 countries and territories, 1990–2019. *Eur J Prev Cardiol* 2022;**29**:420–31. <https://doi.org/10.1093/eurjpc/zwab213>
- Andreotti F, Crea F, Sechtem U. Diagnoses and outcomes in patients with suspected angina: what are they trying to tell us? *Eur Heart J* 2019;**40**:1436–9. <https://doi.org/10.1093/eurheartj/ehz032>
- Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979;**300**:1350–8. <https://doi.org/10.1056/NEJM197906143002402>
- Genders TS, Steyerberg EW, Alkadi H, Leschka S, Desbiolles L, Nieman K, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J* 2011;**32**:1316–30. <https://doi.org/10.1093/eurheartj/ehz014>
- Reeh J, Thering CB, Heitmann M, Højberg S, Sørum C, Bech J, et al. Prediction of obstructive coronary artery disease and prognosis in patients with suspected stable angina. *Eur Heart J* 2019;**40**:1426–35. <https://doi.org/10.1093/eurheartj/ehy806>
- Gerber Y, Gibbons RJ, Weston SA, Fabbri M, Herrmann J, Manemann SM, et al. Coronary disease surveillance in the community: angiography and revascularization. *J Am Heart Assoc* 2020;**9**:e015231. <https://doi.org/10.1161/jaha.119.015231>
- Juarez-Orozco LE, Saraste A, Capodanno D, Prescott E, Ballo H, Bax JJ, et al. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease. *Eur Heart J Cardiovasc Imaging* 2019;**20**:1198–207. <https://doi.org/10.1093/ehjci/jez054>
- Winther S, Schmidt SE, Rasmussen LD, Juárez Orozco LE, Steffensen FH, Bøtker HE, et al. Validation of the European Society of Cardiology pre-test probability model for obstructive coronary artery disease. *Eur Heart J* 2021;**42**:1401–11. <https://doi.org/10.1093/eurheartj/ehaa755>
- Serruys PW, Hara H, Garg S, Kawashima H, Nørgaard BL, Dweck MR, et al. Coronary computed tomographic angiography for complete assessment of coronary artery disease: JACC state-of-the-art review. *J Am Coll Cardiol* 2021;**78**:713–36. <https://doi.org/10.1016/j.jacc.2021.06.019>
- Serruys WP, Kotoku N, Nørgaard LB, Garg S, Nieman K, Dweck MR, et al. Computed tomographic angiography in coronary artery disease. *EurIntervention* 2023;**18**:e1307–27. <https://doi.org/10.4244/EIJ-D-22-00776>
- Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med* 2015;**372**:1291–300. <https://doi.org/10.1056/NEJMoa1415516>
- SCOT-HEART Investigators; Newby DE, Adamson PD, Berry C, Boon NA, Dweck MR, et al. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med* 2018;**379**:924–33. <https://doi.org/10.1056/NEJMoa1805971>
- Mezquita AJV, Biavati F, Falk V, Alkadi H, Hajhosseiny R, Maurovich-Horvat P, et al. Clinical quantitative coronary artery stenosis and coronary atherosclerosis imaging: a consensus statement from the Quantitative Cardiovascular Imaging Study Group. *Nat Rev Cardiol* 2023;**20**:696–714. <https://doi.org/10.1038/s41569-023-00880-4>

36. Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas AHEM, et al. An EAPCI expert consensus document on ischaemia with non-obstructive coronary arteries in collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. *Eur Heart J* 2020;**41**:3504–20. <https://doi.org/10.1093/eurheartj/ehaa503>
37. Ong P, Athanasiadis A, Borgulya G, Vokshi I, Bastiaenen R, Kubik S, et al. Clinical usefulness, angiographic characteristics, and safety evaluation of intracoronary acetylcholine provocation testing among 921 consecutive white patients with unobstructed coronary arteries. *Circulation* 2014;**129**:1723–30. <https://doi.org/10.1161/CIRCULATIONAHA.113.004096>
38. Feenstra RGT, Boerhout CKM, Woudstra J, Vink CEM, Wittekoek ME, de Waard GA, et al. Presence of coronary endothelial dysfunction, coronary vasospasm, and adenosine-mediated vasodilatory disorders in patients with ischemia and nonobstructive coronary arteries. *Circ Cardiovasc Interv* 2022;**15**:e012017. <https://doi.org/10.1161/circinterventions.122.012017>
39. Samuels BA, Shah SM, Widmer RJ, Kobayashi Y, Miner SES, Taqueti VR, et al. Comprehensive management of ANOCA, Part 1—definition, patient population, and diagnosis: JACC state-of-the-art review. *J Am Coll Cardiol* 2023;**82**:1245–63. <https://doi.org/10.1016/j.jacc.2023.06.043>
40. Smilowitz NR, Prasad M, Widmer RJ, Toleva O, Quesada O, Sutton NR, et al. Comprehensive management of ANOCA, Part 2—program development, treatment, and research initiatives: JACC state-of-the-art review. *J Am Coll Cardiol* 2023;**82**:1264–79. <https://doi.org/10.1016/j.jacc.2023.06.044>
41. Ong P, Safdar B, Seitz A, Hubert A, Beltrame JF, Prescott E. Diagnosis of coronary microvascular dysfunction in the clinic. *Cardiovasc Res* 2020;**116**:841–55. <https://doi.org/10.1093/cvr/cvz339>
42. Feenstra RGT, Seitz A, Boerhout CKM, de Winter RJ, Ong P, Beijl MAM, et al. Reference values for intracoronary Doppler flow velocity-derived hyperaemic microvascular resistance index. *Int J Cardiol* 2023;**371**:16–20. <https://doi.org/10.1016/j.ijcard.2022.09.054>
43. Jansen TPJ, Konst RE, Elias-Smale SE, van den Oord SC, Ong P, de Vos AMJ, et al. Assessing microvascular dysfunction in angina with unobstructed coronary arteries: JACC review topic of the week. *J Am Coll Cardiol* 2021;**78**:1471–9. <https://doi.org/10.1016/j.jacc.2021.08.028>
44. Taqueti VR, Hachamovitch R, Murthy VL, Naya M, Foster CR, Hainer J, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. *Circulation* 2015;**131**:19–27. <https://doi.org/10.1161/CIRCULATIONAHA.114.011939>
45. Schindler TH, Fearon WF, Pelletier-Galarneau M, Ambrosio G, Sechtem U, Ruddy TD, et al. PET for detection and reporting coronary microvascular dysfunction. *JACC Cardiovasc Imaging* 2023;**16**:536–48. <https://doi.org/10.1016/j.jcmg.2022.12.015>
46. Ong P, Seitz A. Advances in risk stratification of patients with coronary microvascular dysfunction: usefulness of stress perfusion CMR. *JACC Cardiovasc Imaging* 2021;**14**:612–4. <https://doi.org/10.1016/j.jcmg.2020.09.036>
47. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, et al. Initial invasive or conservative strategy for stable coronary disease. *New Engl J Med* 2020;**382**:1395–407. <https://doi.org/10.1056/NEJMoa1915922>
48. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;**356**:1503–16. <https://doi.org/10.1056/NEJMoa070829>
49. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PAL, Piroth Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;**367**:991–1001. <https://doi.org/10.1056/NEJMoa1205361>
50. Spertus JA, Jones PG, Maron DJ, O'Brien SM, Reynolds HR, Rosenberg Y, et al. Health-status outcomes with invasive or conservative care in coronary disease. *N Engl J Med* 2020;**382**:1408–19. <https://doi.org/10.1056/NEJMoa1916370>
51. Creber RM, Dimagli A, Spadaccio C, Myers A, Moscarelli M, Demetres M, et al. Effect of coronary artery bypass grafting on quality of life: a meta-analysis of randomized trials. *Eur Heart J Qual Care Clin Outcomes* 2022;**8**:259–68. <https://doi.org/10.1093/ehjqcco/qcab075>
52. Rajkumar CA, Foley MJ, Ahmed-Jushuf F, Nowbar AN, Simader FA, Davies JR, et al. A placebo-controlled trial of percutaneous coronary intervention for stable angina. *New Engl J Med* 2023;**389**:2319–30. <https://doi.org/10.1056/NEJMoa2310610>
53. Velazquez EJ, Lee KL, DeJa MA, Jain A, Sopko G, Marchenko A, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med* 2011;**364**:1607–16. <https://doi.org/10.1056/NEJMoa1100356>
54. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med* 2016;**374**:1511–20. <https://doi.org/10.1056/NEJMoa1602001>
55. Navarese EP, Lansky AJ, Kereiakes DJ, Kubica J, Gurbel PA, Gorog DA, et al. Cardiac mortality in patients randomised to elective coronary revascularisation plus medical therapy or medical therapy alone: a systematic review and meta-analysis. *Eur Heart J* 2021;**42**:4638–51. <https://doi.org/10.1093/eurheartj/ehab246>
56. Hochman JS, Anthonopolos R, Reynolds HR, Bangalore S, Xu Y, O'Brien SM, et al. Survival after invasive or conservative management of stable coronary disease. *Circulation* 2023;**147**:8–19. <https://doi.org/10.1161/CIRCULATIONAHA.122.062714>
57. Douglas PS, Nanna MG, Kelsey MD, Yow E, Mark DB, Patel MR, et al. Comparison of an initial risk-based testing strategy vs usual testing in stable symptomatic patients with suspected coronary artery disease: the PRECISE randomized clinical trial. *JAMA Cardiol* 2023;**8**:904–14. <https://doi.org/10.1001/jamacardio.2023.2595>
58. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. *New Engl J Med* 1996;**334**:1311–5. <https://doi.org/10.1056/nejm199605163342007>
59. Hemal K, Pagidipati NJ, Coles A, Dolor RJ, Mark DB, Pelikka PA, et al. Sex differences in demographics, risk factors, presentation, and noninvasive testing in stable outpatients with suspected coronary artery disease: insights from the PROMISE trial. *JACC Cardiovasc Imaging* 2016;**9**:337–46. <https://doi.org/10.1016/j.jcmg.2016.02.001>
60. Garcia M, Mulvagh SL, Bairey Merz CN, Buring JE, Manson JE. Cardiovascular disease in women: clinical perspectives. *Circ Res* 2016;**118**:1273–93. <https://doi.org/10.1161/CIRCRESAHA.116.307547>
61. Stepinska J, Lettino M, Ahrens I, Bueno H, Garcia-Castrillo L, Khoury A, et al. Diagnosis and risk stratification of chest pain patients in the emergency department: focus on acute coronary syndromes. A position paper of the Acute Cardiovascular Care Association. *Eur Heart J Acute Cardiovasc Care* 2020;**9**:76–89. <https://doi.org/10.1177/2048872619885346>
62. Hoorweg BB, Willemsen RT, Cleef LE, Boogaerts T, Buntinx F, Glatz JFC, et al. Frequency of chest pain in primary care, diagnostic tests performed and final diagnoses. *Heart* 2017;**103**:1727–32. <https://doi.org/10.1136/heartjnl-2016-310905>
63. Reynolds HR, Shaw LJ, Min JK, Spertus JA, Chaitman BR, Berman DS, et al. Association of sex with severity of coronary artery disease, ischemia, and symptom burden in patients with moderate or severe ischemia: secondary analysis of the ISCHEMIA randomized clinical trial. *JAMA Cardiol* 2020;**5**:773–86. <https://doi.org/10.1001/jamacardio.2020.0822>
64. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**:111–88. <https://doi.org/10.1093/eurheartj/ehz455>
65. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of patients with acute coronary syndromes. *Eur Heart J* 2023;**44**:3720–826. <https://doi.org/10.1093/eurheartj/ehad191>
66. Campeau L. Letter: grading of angina pectoris. *Circulation* 1976;**54**:522–3. <https://doi.org/10.1161/circ.54.3.947585>
67. Fiol-Sala M, Birnbaum J, Nikus K, Bayés de Luna A. *Electrocardiography in Ischemic Heart Disease*. Hoboken, NJ: Wiley Blackwell, 2019.
68. Kannel WB, Abbott RD, Savage DD, McNamara PM. Coronary heart disease and atrial fibrillation: the Framingham study. *Am Heart J* 1983;**106**:389–96. [https://doi.org/10.1016/0002-8703\(83\)90208-9](https://doi.org/10.1016/0002-8703(83)90208-9)
69. Cohn PF, Fox KM, Daly C. Silent myocardial ischemia. *Circulation* 2003;**108**:1263–77. <https://doi.org/10.1161/01.CIR.0000088001.59265.EE>
70. Androulakis A, Aznaouridis KA, Aggeli CJ, Roussakis GN, Michaelides AP, Kartalis AN, et al. Transient ST-segment depression during paroxysms of atrial fibrillation in otherwise normal individuals: relation with underlying coronary artery disease. *J Am Coll Cardiol* 2007;**50**:1909–11. <https://doi.org/10.1016/j.jacc.2007.08.005>
71. Guo Y, Zhang L, Wang C, Zhao Y, Chen W, Gao M, et al. Medical treatment and long-term outcome of chronic atrial fibrillation in the aged with chest distress: a retrospective analysis versus sinus rhythm. *Clin Interv Aging* 2011;**6**:193–8. <https://doi.org/10.2147/CI.A.521775>
72. Nucifora G, Schuijff JD, van Werkhoven JM, Trines SA, Kajander S, Tops LF, et al. Relationship between obstructive coronary artery disease and abnormal stress testing in patients with paroxysmal or persistent atrial fibrillation. *Int J Cardiovasc Imaging* 2011;**27**:777–85. <https://doi.org/10.1007/s10554-010-9725-x>
73. Beltrame JF, Crea F, Kaski JC, Ogawa H, Ong P, Sechtem U, et al. International standardization of diagnostic criteria for vasospastic angina. *Eur Heart J* 2017;**38**:2565–8. <https://doi.org/10.1093/eurheartj/ehv351>
74. Forslund L, Hjemdahl P, Held C, Björkander I, Eriksson SV, Rehnqvist N. Ischaemia during exercise and ambulatory monitoring in patients with stable angina pectoris and healthy controls. Gender differences and relationships to catecholamines. *Eur Heart J* 1998;**19**:578–87. <https://doi.org/10.1053/ehj.1997.0819>
75. Davies RF, Goldberg AD, Forman S, Pepine CJ, Knatterud GL, Geller N, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. *Circulation* 1997;**95**:2037–43. <https://doi.org/10.1161/01.cir.95.8.2037>
76. Stone PH, Chaitman BR, Forman S, Andrews TC, Bittner V, Bourassa MG, et al. Prognostic significance of myocardial ischemia detected by ambulatory electrocardiography, exercise treadmill testing, and electrocardiogram at rest to predict cardiac events by one year (the Asymptomatic Cardiac Ischemia Pilot [ACIP] study). *Am J Cardiol* 1997;**80**:1395–401. [https://doi.org/10.1016/s0002-9149\(97\)00706-6](https://doi.org/10.1016/s0002-9149(97)00706-6)
77. Shaw LJ, Bairey Merz CN, Pepine CJ, Reis SE, Bittner V, Kelsey SF, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and

- gender-optimized diagnostic strategies. *J Am Coll Cardiol* 2006;**47**:S4–20. <https://doi.org/10.1016/j.jacc.2005.01.072>
78. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009;**361**:858–67. <https://doi.org/10.1056/NEJMoa0900428>
 79. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med* 2009;**361**:868–77. <https://doi.org/10.1056/NEJMoa0903515>
 80. Nelson SD, Kou WH, Annesley T, de Buitre M, Morady F. Significance of ST segment depression during paroxysmal supraventricular tachycardia. *J Am Coll Cardiol* 1988;**12**:383–7. [https://doi.org/10.1016/0735-1097\(88\)90410-x](https://doi.org/10.1016/0735-1097(88)90410-x)
 81. Imrie JR, Yee R, Klein GJ, Sharma AD. Incidence and clinical significance of ST segment depression in supraventricular tachycardia. *Can J Cardiol* 1990;**6**:323–6. <https://doi.org/10.1016/j.amjmed.2017.01.002>
 82. Riva SI, Della Bella P, Fassini G, Carbuicchio C, Tondo C. Value of analysis of ST segment changes during tachycardia in determining type of narrow QRS complex tachycardia. *J Am Coll Cardiol* 1996;**27**:1480–5. [https://doi.org/10.1016/0735-1097\(96\)00013-7](https://doi.org/10.1016/0735-1097(96)00013-7)
 83. Rivera S, De La Paz Ricapito M, Conde D, Verdu M, Roux J, Paredes F. The retrograde P-wave theory: explaining ST segment depression in supraventricular tachycardia by retrograde AV node conduction. *Pacing Clin Electrophysiol* 2014;**37**:1100–5. <https://doi.org/10.1111/pace.12394>
 84. Mercik J, Radziejewska J, Pach K, Zawadzki G, Zyško D, Gajek J, et al. ST-segment depression in atrioventricular nodal reentrant tachycardia: important finding or just an artifact? *Medicine (Baltimore)* 2022;**101**:e31806. <https://doi.org/10.1097/md.00000000000031806>
 85. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2019;**41**:255–323. <https://doi.org/10.1093/eurheartj/ehz486>
 86. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes: developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC). *Eur Heart J* 2023;**44**:4043–140. <https://doi.org/10.1093/eurheartj/ehad192>
 87. Nordestgaard BG, Langsted A, Mora S, Kolovou G, Baum H, Bruckert E, et al. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points—a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. *Eur Heart J* 2016;**37**:1944–58. <https://doi.org/10.1093/eurheartj/ehw152>
 88. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and improved cardiovascular risk prediction. *J Am Coll Cardiol* 2013;**61**:1146–56. <https://doi.org/10.1016/j.jacc.2012.12.023>
 89. Rossello X. Lifetime risk estimation in atherosclerotic cardiovascular disease: where inflammation meets lipoprotein(a). *J Am Coll Cardiol* 2021;**78**:1095–6. <https://doi.org/10.1016/j.jacc.2021.07.035>
 90. Boffa MB, Stranges S, Klar N, Moriarty PM, Watts GF, Koschinsky ML. Lipoprotein(a) and secondary prevention of atherothrombotic events: a critical appraisal. *J Clin Lipidol* 2018;**12**:1358–66. <https://doi.org/10.1016/j.jacl.2018.08.012>
 91. Malick WA, Goonewardena SN, Koenig W, Rosenson RS. Clinical trial design for lipoprotein(a)-lowering therapies: JACC focus seminar 2/3. *J Am Coll Cardiol* 2023;**81**:1633–45. <https://doi.org/10.1016/j.jacc.2023.02.033>
 92. Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. *Eur Heart J* 2022;**43**:3925–46. <https://doi.org/10.1093/eurheartj/ehac361>
 93. Lopes NH, da Silva Paulitsch F, Pereira A, Garzillo CL, Ferreira JF, Stolf N, et al. Mild chronic kidney dysfunction and treatment strategies for stable coronary artery disease. *J Thorac Cardiovasc Surg* 2009;**137**:1443–9. <https://doi.org/10.1016/j.jtcvs.2008.11.028>
 94. Di Angelantonio E, Chowdhury R, Sarwar N, Aspelund T, Danesh J, Gudnason V. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. *BMJ* 2010;**341**:c4986. <https://doi.org/10.1136/bmj.c4986>
 95. Nitsch D, Grams M, Sang Y, Black C, Cirillo M, Djurdjev O, et al. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. *BMJ* 2013;**346**:f324. <https://doi.org/10.1136/bmj.f324>
 96. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med* 2009;**361**:2538–47. <https://doi.org/10.1056/NEJMoa0805299>
 97. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khara A, Rohatgi A, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA* 2010;**304**:2503–12. <https://doi.org/10.1001/jama.2010.1768>
 98. Omland T, Pfeffer MA, Solomon SD, de Lemos JA, Røsjø H, Šaltytė Benth J, et al. Prognostic value of cardiac troponin I measured with a highly sensitive assay in patients with stable coronary artery disease. *J Am Coll Cardiol* 2013;**61**:1240–9. <https://doi.org/10.1016/j.jacc.2012.12.026>
 99. van Holten TC, Waanders LF, de Groot PG, Vissers J, Hoefer IE, Pasterkamp G, et al. Circulating biomarkers for predicting cardiovascular disease risk; a systematic review and comprehensive overview of meta-analyses. *PLoS One* 2013;**8**:e62080. <https://doi.org/10.1371/journal.pone.0062080>
 100. Everett BM, Brooks MM, Vlachos HE, Chaitman BR, Frye RL, Bhatt DL, et al. Troponin and cardiac events in stable ischemic heart disease and diabetes. *N Engl J Med* 2015;**373**:610–20. <https://doi.org/10.1056/NEJMoa1415921>
 101. Laufer EM, Mingels AM, Winkens MH, Joosen IAPG, Schellings MWM, Leiner T, et al. The extent of coronary atherosclerosis is associated with increasing circulating levels of high sensitive cardiac troponin T. *Arterioscler Thromb Vasc Biol* 2010;**30**:1269–75. <https://doi.org/10.1161/ATVBAHA.109.200394>
 102. Madsen DM, Diederichsen ACP, Hosbond SE, Gerke O, Mickley H. Diagnostic and prognostic value of a careful symptom evaluation and high sensitive troponin in patients with suspected stable angina pectoris without prior cardiovascular disease. *Atherosclerosis* 2017;**258**:131–7. <https://doi.org/10.1016/j.atherosclerosis.2016.11.030>
 103. Adamson PD, Hunter A, Madsen DM, Shah ASV, McAllister DA, Pawade TA, et al. High-sensitivity cardiac troponin I and the diagnosis of coronary artery disease in patients with suspected angina pectoris. *Circ Cardiovasc Qual Outcomes* 2018;**11**:e004227. <https://doi.org/10.1161/circoutcomes.117.004227>
 104. Januzzi JL Jr, Suchindran S, Coles A, Ferencik M, Patel MR, Hoffmann U, et al. High-sensitivity troponin I and coronary computed tomography in symptomatic outpatients with suspected CAD: insights from the PROMISE trial. *JACC Cardiovasc Imaging* 2019;**12**:1047–55. <https://doi.org/10.1016/j.jcmg.2018.01.021>
 105. Vavassori C, Cipriani E, Colombo GI. Circulating microRNAs as novel biomarkers in risk assessment and prognosis of coronary artery disease. *Eur Heart J* 2022;**43**:e06. <https://doi.org/10.15420/ehj.2021.47>
 106. Hoogeveen RM, Pereira JPB, Nurmohamed NS, Zampolieri V, Bom MJ, Baragetti A, et al. Improved cardiovascular risk prediction using targeted plasma proteomics in primary prevention. *Eur Heart J* 2020;**41**:3998–4007. <https://doi.org/10.1093/eurheartj/ehaa648>
 107. Ibrahim NE, Januzzi JL Jr, Magaret CA, Gaggini HK, Rhyne RF, Gandhi PU, et al. A clinical and biomarker scoring system to predict the presence of obstructive coronary artery disease. *J Am Coll Cardiol* 2017;**69**:1147–56. <https://doi.org/10.1016/j.jacc.2016.12.021>
 108. Hilvo M, Meikle PJ, Pedersen ER, Tell GS, Dhar I, Brenner H, et al. Development and validation of a ceramide- and phospholipid-based cardiovascular risk estimation score for coronary artery disease patients. *Eur Heart J* 2020;**41**:371–80. <https://doi.org/10.1093/eurheartj/ehz387>
 109. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;**342**:836–43. <https://doi.org/10.1056/nejm200003233421202>
 110. Danesh J, Wheeler JG, Hirschfeld GM, Eda S, Eiriksdottir G, Rumley A, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004;**350**:1387–97. <https://doi.org/10.1056/NEJMoa032804>
 111. Sinning JM, Bickel C, Messow CM, Schnabel R, Lubos E, Rupprecht HJ, et al. Impact of C-reactive protein and fibrinogen on cardiovascular prognosis in patients with stable angina pectoris: the AtheroGene study. *Eur Heart J* 2006;**27**:2962–8. <https://doi.org/10.1093/eurheartj/ehl362>
 112. Jia RF, Li L, Li H, Cao X-J, Ruan Y, Meng S, et al. Meta-analysis of C-reactive protein and risk of angina pectoris. *Am J Cardiol* 2020;**125**:1039–45. <https://doi.org/10.1016/j.amjcard.2020.01.005>
 113. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;**336**:973–9. <https://doi.org/10.1056/nejm199704033361401>
 114. Thompson SG, Kienast J, Pyke SD, Haverkate F, van de Loo JC. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *N Engl J Med* 1995;**332**:635–41. <https://doi.org/10.1056/nejm199503093321003>
 115. De Luca G, Verdoia M, Cassetti E, Schaffer A, Cavallino C, Bolzani V, et al. High fibrinogen level is an independent predictor of presence and extent of coronary artery disease among Italian population. *J Thromb Thrombolysis* 2011;**31**:458–63. <https://doi.org/10.1007/s11239-010-0531-z>
 116. Ndrepepa G, Braun S, King L, Fusaro M, Keta D, Cassese S, et al. Relation of fibrinogen level with cardiovascular events in patients with coronary artery disease. *Am J Cardiol* 2013;**111**:804–10. <https://doi.org/10.1016/j.amjcard.2012.11.060>
 117. Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardiovascular disease: the Framingham study. *JAMA* 1987;**258**:1183–6. <https://doi.org/10.1001/jama.1987.03400090067035>
 118. Appiah D, Schreiner PJ, MacLehose RF, Folsom AR. Association of plasma γ fibrinogen with incident cardiovascular diseases: the Atherosclerosis Risk in Communities (ARIC)

- study. *Arterioscler Thromb Vasc Biol* 2015;**35**:2700–6. <https://doi.org/10.1161/atvbaha.115.306284>
119. Ridker PM, Bhatt DL, Pradhan AD, Glynn RJ, MacFadyen JG, Nissen SE, et al. Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials. *Lancet* 2023;**401**:1293–301. [https://doi.org/10.1016/S0140-6736\(23\)00215-5](https://doi.org/10.1016/S0140-6736(23)00215-5)
 120. Ridker PM, Lei L, Louie MJ, Haddad T, Nicholls SJ, Lincoff AM, et al. Inflammation and cholesterol as predictors of cardiovascular events among 13 970 contemporary high-risk patients with statin intolerance. *Circulation* 2024;**149**:28–35. <https://doi.org/10.1161/CIRCULATIONAHA.123.066213>
 121. Bohula EA, Giugliano RP, Leiter LA, Verma S, Park J-G, Sever PS, et al. Inflammatory and cholesterol risk in the FOURIER trial. *Circulation* 2018;**138**:131–40. <https://doi.org/10.1161/circulationaha.118.034032>
 122. Tokgözoğlu L, Libby P. The dawn of a new era of targeted lipid-lowering therapies. *Eur Heart J* 2022;**43**:3198–208. <https://doi.org/10.1093/eurheartj/ehab841>
 123. Byrne P, Demasi M, Jones M, Smith SM, O'Brien KK, DuBroff R. Evaluating the association between low-density lipoprotein cholesterol reduction and relative and absolute effects of statin treatment: a systematic review and meta-analysis. *JAMA Intern Med* 2022;**182**:474–81. <https://doi.org/10.1001/jamainternmed.2022.0134>
 124. Nurmohamed NS, Navar AM, Kastelein JJP. New and emerging therapies for reduction of LDL-cholesterol and apolipoprotein B: JACC focus seminar 1/4. *J Am Coll Cardiol* 2021;**77**:1564–75. <https://doi.org/10.1016/j.jacc.2020.11.079>
 125. Pradhan AD, Aday AV, Rose LM, Ridker PM. Residual inflammatory risk on treatment with PCSK9 inhibition and statin therapy. *Circulation* 2018;**138**:141–9. <https://doi.org/10.1161/CIRCULATIONAHA.118.034645>
 126. Waksman R, Merdler I, Case BC, Waksman O, Porto I. Targeting inflammation in atherosclerosis: overview, strategy and directions. *EuroIntervention* 2024;**20**:32–44. <https://doi.org/10.4244/EIJ-D-23-00606>
 127. Ridker PM, Devalaraja M, Baeres FMM, Engelmann MDM, Hovingh GK, Ivkovic M, et al. IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet* 2021;**397**:2060–9. [https://doi.org/10.1016/S0140-6736\(21\)00520-1](https://doi.org/10.1016/S0140-6736(21)00520-1)
 128. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA* 2016;**316**:1289–97. <https://doi.org/10.1001/jama.2016.13985>
 129. Arant CB, Wessel TR, Olson MB, Bairey Merz CN, Sopko G, Rogers WJ, et al. Hemoglobin level is an independent predictor for adverse cardiovascular outcomes in women undergoing evaluation for chest pain: results from the National Heart, Lung, and Blood Institute Women's Ischemia Syndrome Evaluation Study. *J Am Coll Cardiol* 2004;**43**:2009–14. <https://doi.org/10.1016/j.jacc.2004.01.038>
 130. da Silveira AD, Ribeiro RA, Rossini AP, Stella SF, Ritta HAR, Stein R, et al. Association of anemia with clinical outcomes in stable coronary artery disease. *Coron Artery Dis* 2008;**19**:21–6. <https://doi.org/10.1097/MCA.0b013e3282f27c0a>
 131. Muzzarelli S, Pfisterer M; Time Investigators. Anemia as independent predictor of major events in elderly patients with chronic angina. *Am Heart J* 2006;**152**:991–6. <https://doi.org/10.1016/j.ahj.2006.06.014>
 132. Kalra PR, Greenlaw N, Ferrari R, Ford I, Tardif J-C, Tendera M, et al. Hemoglobin and change in hemoglobin status predict mortality, cardiovascular events, and bleeding in stable coronary artery disease. *Am J Med* 2017;**130**:720–30. <https://doi.org/10.1016/j.amjmed.2017.01.002>
 133. Asif A, Wei J, Lauzon M, Sopko G, Reis SE, Handberg E, et al. Anemia and long-term cardiovascular outcomes in women with suspected ischemia—the Women's Ischemia Syndrome Evaluation (WISE). *Am Heart J Plus Cardiol Res Pract* 2021;**10**:100059. <https://doi.org/10.1016/j.ahjo.2021.100059>
 134. Di Angelantonio E, Danesh J, Eiriksdottir G, Gudnason V. Renal function and risk of coronary heart disease in general populations: new prospective study and systematic review. *PLoS Med* 2007;**4**:e270. <https://doi.org/10.1371/journal.pmed.0040270>
 135. Bartnik M, Ryden L, Malmberg K, Ohrvik J, Pyörälä K, Standl E, et al. Oral glucose tolerance test is needed for appropriate classification of glucose regulation in patients with coronary artery disease: a report from the Euro Heart Survey on Diabetes and the Heart. *Heart* 2007;**93**:72–7. <https://doi.org/10.1136/hrt.2005.086975>
 136. Gyberg V, De Bacquer D, Kotseva K, De Backer G, Schnell O, Sundvall J, et al. Screening for dysglycaemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test, and HbA1c: a report from EUROASPIRE IV—a survey from the European Society of Cardiology. *Eur Heart J* 2015;**36**:1171–7. <https://doi.org/10.1093/eurheartj/ehv008>
 137. Corona G, Croce L, Sparano C, Petrone L, Sforza A, Maggi M, et al. Thyroid and heart, a clinically relevant relationship. *J Endocrinol Invest* 2021;**44**:2535–44. <https://doi.org/10.1007/s40618-021-01590-9>
 138. Sohn SY, Lee E, Lee MK, Lee JH. The association of overt and subclinical hyperthyroidism with the risk of cardiovascular events and cardiovascular mortality: meta-analysis and systematic review of cohort studies. *Endocrinol Metab (Seoul)* 2020;**35**:786–800. <https://doi.org/10.3803/EnM.2020.728>
 139. Winther S, Schmidt SE, Mayrhofer T, Bøtker HE, Hoffmann U, Douglas PS, et al. Incorporating coronary calcification into pre-test assessment of the likelihood of coronary artery disease. *J Am Coll Cardiol* 2020;**76**:2421–32. <https://doi.org/10.1016/j.jacc.2020.09.585>
 140. Genders TS, Steyerberg EW, Hunink MG, Nieman K, Galema TW, Mollet NR, et al. Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. *BMJ* 2012;**344**:e3485. <https://doi.org/10.1136/bmj.e3485>
 141. Zhou J, Zhao J, Li Z, Cong H, Wang C, Zhang H, et al. Coronary calcification improves the estimation for clinical likelihood of obstructive coronary artery disease and avoids unnecessary testing in patients with borderline pretest probability. *Eur J Prev Cardiol* 2022;**29**:e105–7. <https://doi.org/10.1093/eurjpc/zwab036>
 142. Winther S, Murphy T, Schmidt SE, Bax JJ, Wijns W, Knuuti J, et al. Performance of the American Heart Association/American College of Cardiology guideline-recommended pretest probability model for the diagnosis of obstructive coronary artery disease. *J Am Heart Assoc* 2022:e027260. <https://doi.org/10.1161/JAHA.122.027260>
 143. Winther S, Schmidt SE, Foldyna B, Mayrhofer T, Rasmussen LD, Dahl JN, et al. Coronary calcium scoring improves risk prediction in patients with suspected obstructive coronary artery disease. *J Am Coll Cardiol* 2022;**80**:1965–77. <https://doi.org/10.1016/j.jacc.2022.08.805>
 144. Rasmussen LD, Schmidt SE, Knuuti J, Newby DE, Singh T, Nieman K, et al. Exercise electrocardiography for pre-test assessment of the likelihood of coronary artery disease. *Heart* 2023;**110**:263–70. <https://doi.org/10.1136/heartjnl-2023-322970>
 145. McKavanagh P, Lusk L, Ball PA, Verghis RM, Agus AM, Trinick TR, et al. A comparison of cardiac computerized tomography and exercise stress electrocardiogram test for the investigation of stable chest pain: the clinical results of the CAPP randomized prospective trial. *Eur Heart J Cardiovasc Imaging* 2015;**16**:441–8. <https://doi.org/10.1093/ehjci/jeu284>
 146. Lubbers M, Dedic A, Coenen A, Galema T, Akkerhuis J, Bruning T, et al. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. *Eur Heart J* 2016;**37**:1232–43. <https://doi.org/10.1093/eurheartj/ehv700>
 147. Banerjee A, Newman DR, Van den Bruel A, Heneghan C. Diagnostic accuracy of exercise stress testing for coronary artery disease: a systematic review and meta-analysis of prospective studies. *Int J Clin Pract* 2012;**66**:477–92. <https://doi.org/10.1111/j.1742-1241.2012.02900.x>
 148. Knuuti J, Ballo H, Juárez-Orozco LE, Saraste A, Kolh P, Rutjes AWS, et al. The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. *Eur Heart J* 2018;**39**:3322–30. <https://doi.org/10.1093/eurheartj/ehy267>
 149. Cole JP, Ellestad MH. Significance of chest pain during treadmill exercise: correlation with coronary events. *Am J Cardiol* 1978;**41**:227–32. [https://doi.org/10.1016/0002-9149\(78\)90161-3](https://doi.org/10.1016/0002-9149(78)90161-3)
 150. Lindow T, Ekström M, Brudin L, Carlén A, Elmberg V, Hedman K. Typical angina during exercise stress testing improves the prediction of future acute coronary syndrome. *Clin Physiol Funct Imaging* 2021;**41**:281–91. <https://doi.org/10.1111/cpf.12695>
 151. Agha AM, Pacor J, Grandhi GR, Mszar R, Khan SU, Parikh R, et al. The prognostic value of CAC zero among individuals presenting with chest pain. *JACC Cardiovasc Imaging* 2022;**15**:1745–57. <https://doi.org/10.1016/j.jcmg.2022.03.031>
 152. Mortensen MB, Gaur S, Frimmer A, Bøtker HE, Sørensen HT, Kragholm KH, et al. Association of age with the diagnostic value of coronary artery calcium score for ruling out coronary stenosis in symptomatic patients. *JAMA Cardiol* 2022;**7**:36–44. <https://doi.org/10.1001/jamacardio.2021.4406>
 153. Lubbers M, Coenen A, Kofflard M, Bruning T, Kietselaer B, Galema T, et al. Comprehensive cardiac CT with myocardial perfusion imaging versus functional testing in suspected coronary artery disease: the multicenter, randomized CRESCENT-II trial. *JACC Cardiovasc Imaging* 2018;**11**:1625–36. <https://doi.org/10.1016/j.jcmg.2017.10.010>
 154. Zhou J, Li C, Cong H, Duan L, Wang H, Wang C, et al. Comparison of different investigation strategies to defer cardiac testing in patients with stable chest pain. *JACC Cardiovasc Imaging* 2022;**15**:91–104. <https://doi.org/10.1016/j.jcmg.2021.08.022>
 155. Heald CL, Fowkes FG, Murray GD, Price JF. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: systematic review. *Atherosclerosis* 2006;**189**:61–9. <https://doi.org/10.1016/j.atherosclerosis.2006.03.011>
 156. Molnár S, Kerényi L, Ritter MA, Magyar MT, Ida Y, Szöllösi Z, et al. Correlations between the atherosclerotic changes of femoral, carotid and coronary arteries: a post mortem study. *J Neurol Sci* 2009;**287**:241–5. <https://doi.org/10.1016/j.jns.2009.06.001>
 157. Fernandez-Friera L, Penalvo JL, Fernandez-Ortiz A, Ibañez B, López-Melgar B, Laclaustra M, et al. Prevalence, vascular distribution, and multiterritorial extent of sub-clinical atherosclerosis in a middle-aged cohort: the PESA (Progression of Early Subclinical Atherosclerosis) study. *Circulation* 2015;**131**:2104–13. <https://doi.org/10.1161/CIRCULATIONAHA.114.014310>
 158. Laclaustra M, Casasnovas JA, Fernández-Ortiz A, Fuster V, León-Latre M, Jiménez-Borreguero LJ, et al. Femoral and carotid subclinical atherosclerosis association with risk factors and coronary calcium: the AWHHS study. *J Am Coll Cardiol* 2016;**67**:1263–74. <https://doi.org/10.1016/j.jacc.2015.12.056>

159. Gepner AD, Young R, Delaney JA, Budoff MJ, Polak JF, Blaha MJ, et al. Comparison of carotid plaque score and coronary artery calcium score for predicting cardiovascular disease events: the multi-ethnic study of atherosclerosis. *J Am Heart Assoc* 2017;**6**: e005179. <https://doi.org/10.1161/jaha.116.005179>
160. Colledanchise KN, Mantella LE, Héту MF, Liblik K, Abunassar JG, Johri AM. Femoral plaque burden by ultrasound is a better indicator of significant coronary artery disease over ankle brachial index. *Int J Cardiovasc Imaging* 2021;**37**:2965–73. <https://doi.org/10.1007/s10554-021-02334-9>
161. Bjerking LH, Winther S, Hansen KW, Galatius S, Böttcher M, Prescott E. Prediction models as gatekeepers for diagnostic testing in angina patients with suspected chronic coronary syndrome. *Eur Heart J Qual Care Clin Outcomes* 2022;**8**:630–9. <https://doi.org/10.1093/ehjqcco/qcac025>
162. Rasmussen LD, Karim SR, Westra J, et al. Clinical likelihood prediction of hemodynamically obstructive coronary artery disease in patients with stable chest pain. *JACC Cardiovasc Imaging* 2024; In press. <https://doi.org/10.1016/j.jcmg.2024.04.015>
163. Winther S, Nissen L, Westra J, Schmidt SE, Bouteldja N, Knudsen LL, et al. Pre-test probability prediction in patients with a low to intermediate probability of coronary artery disease: a prospective study with a fractional flow reserve endpoint. *Eur Heart J Cardiovasc Imaging* 2019;**20**:1208–18. <https://doi.org/10.1093/ehjci/jez058>
164. Winther S, Schmidt Samuel E, Knuuti J, Böttcher M. Comparison of pretest probability models of obstructive coronary artery disease. *JACC Cardiovasc Imaging* 2022;**15**: 173–5. <https://doi.org/10.1016/j.jcmg.2021.11.019>
165. Brix GS, Rasmussen LD, Rohde PD, Schmidt SE, Nyegaard M, Douglas PS, et al. Calcium scoring improves clinical management in patients with low clinical likelihood of coronary artery disease. *JACC Cardiovasc Imaging* 2024;**17**:625–39. <https://doi.org/10.1016/j.jcmg.2023.11.008>
166. Christman MP, Bittencourt MS, Hulten E, Saksena E, Hainer J, Skali H, et al. Yield of downstream tests after exercise treadmill testing: a prospective cohort study. *J Am Coll Cardiol* 2014;**63**:1264–74. <https://doi.org/10.1016/j.jacc.2013.11.052>
167. Daly CA, De Stavola B, Sendon JL, Tavazzi L, Boersma E, Clemens F, et al. Predicting prognosis in stable angina—results from the Euro heart survey of stable angina: prospective observational study. *BMJ* 2006;**332**:262–7. <https://doi.org/10.1136/bmj.38695.605440.AE>
168. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;**105**:539–42. <https://doi.org/10.1161/hc0402.102975>
169. Eek C, Grenne B, Brunvand H, Aakhus S, Endresen K, Hol PK, et al. Strain echocardiography and wall motion score index predicts final infarct size in patients with non-ST-segment-elevation myocardial infarction. *Circ Cardiovasc Imaging* 2010;**3**: 187–94. <https://doi.org/10.1161/CIRCIMAGING.109.910521>
170. Smedsrud MK, Sarvari S, Haugaa KH, Gjesdal O, Ørn S, Aaberge L, et al. Duration of myocardial early systolic lengthening predicts the presence of significant coronary artery disease. *J Am Coll Cardiol* 2012;**60**:1086–93. <https://doi.org/10.1016/j.jacc.2012.06.022>
171. Biering-Sorensen T, Hoffmann S, Mogelvang R, Zeeberg Iversen A, Galatius S, Fritzhansen T, et al. Myocardial strain analysis by 2-dimensional speckle tracking echocardiography improves diagnostics of coronary artery stenosis in stable angina pectoris. *Circ Cardiovasc Imaging* 2014;**7**:58–65. <https://doi.org/10.1161/CIRCIMAGING.113.000989>
172. Smedsrud MK, Graving J, Omland T, Eek C, Mørkrid L, Skulstad H, et al. Sensitive cardiac troponins and N-terminal pro-B-type natriuretic peptide in stable coronary artery disease: correlation with left ventricular function as assessed by myocardial strain. *Int J Cardiovasc Imaging* 2015;**31**:967–73. <https://doi.org/10.1007/s10554-015-0646-6>
173. Edwards NFA, Scalia GM, Shiino K, Sabapathy S, Anderson B, Chamberlain R, et al. Global myocardial work is superior to global longitudinal strain to predict significant coronary artery disease in patients with normal left ventricular function and wall motion. *J Am Soc Echocardiogr* 2019;**32**:947–57. <https://doi.org/10.1016/j.echo.2019.02.014>
174. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. *J Am Coll Cardiol* 2009;**54**:1561–75. <https://doi.org/10.1016/j.jacc.2009.04.098>
175. Galderisi M, Cosyns B, Edvardsen T, Cardim N, Delgado V, Di Salvo G, et al. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2017;**18**:1301–10. <https://doi.org/10.1093/ehjci/jev244>
176. Steeds RP, Garbi M, Cardim N, Kasprzak JD, Sade E, Nihoyannopoulos P, et al. EACVI appropriateness criteria for the use of transthoracic echocardiography in adults: a report of literature and current practice review. *Eur Heart J Cardiovasc Imaging* 2017;**18**: 1191–204. <https://doi.org/10.1093/ehjci/jev333>
177. Senior R, Becher H, Monaghan M, Agati L, Zamorano J, Vanoverschelde JL, et al. Clinical practice of contrast echocardiography: recommendation by the European Association of Cardiovascular Imaging (EACVI) 2017. *Eur Heart J Cardiovasc Imaging* 2017;**18**: 1205–1205af. <https://doi.org/10.1093/ehjci/jev182>
178. Greenwood JP, Ripley DP, Berry C, McCann GP, Plein S, Bucciarelli-Ducci C, et al. Effect of care guided by cardiovascular magnetic resonance, myocardial perfusion scintigraphy, or NICE guidelines on subsequent unnecessary angiography rates: the CE-MARC 2 randomized clinical trial. *JAMA* 2016;**316**:1051–60. <https://doi.org/10.1001/jama.2016.12680>
179. Motwani M, Swoboda PP, Plein S, Greenwood JP. Role of cardiovascular magnetic resonance in the management of patients with stable coronary artery disease. *Heart* 2018;**104**:888–94. <https://doi.org/10.1136/heartjnl-2017-311658>
180. Kim RJ, Wu E, Rafael A, Chen E-L, Parker MA, Simonetti O, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000;**343**:1445–53. <https://doi.org/10.1056/NEJM200011163432003>
181. Gómez-Revelles S, Rossello X, Díaz-Villanueva J, López-Lima I, Sciarresi E, Estofán M, et al. Prognostic value of a new semiquantitative score system for adenosine stress myocardial perfusion by CMR. *Eur Radiol* 2019;**29**:2263–71. <https://doi.org/10.1007/s00330-018-5774-7>
182. Emond M, Mock MB, Davis KB, Fisher LD, Holmes DR, Chaitman BR, et al. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) registry. *Circulation* 1994;**90**:2645–57. <https://doi.org/10.1161/01.cir.90.6.2645>
183. Daly C, Norrie J, Murdoch DL, Ford I, Dargie HJ, Fox K, et al. The value of routine non-invasive tests to predict clinical outcome in stable angina. *Eur Heart J* 2003;**24**:532–40. [https://doi.org/10.1016/s1095-668x\(02\)00820-5](https://doi.org/10.1016/s1095-668x(02)00820-5)
184. Vitarelli A, Tiukinhoy S, Di Luzio S, Zampino M, Gheorghiane M. The role of echocardiography in the diagnosis and management of heart failure. *Heart Fail Rev* 2003;**8**: 181–9. <https://doi.org/10.1023/a:1023001104207>
185. Petersen SE, Khanji MY, Plein S, Lancellotti P, Bucciarelli-Ducci C. European Association of Cardiovascular Imaging expert consensus paper: a comprehensive review of cardiovascular magnetic resonance normal values of cardiac chamber size and aortic root in adults and recommendations for grading severity. *Eur Heart J Cardiovasc Imaging* 2019;**20**:1321–31. <https://doi.org/10.1093/ehjci/jev232>
186. Hoffmann R, von Bardeleben S, Kasprzak JD, Borges AC, ten Cate F, Firsck C, et al. Analysis of regional left ventricular function by cineventriculography, cardiac magnetic resonance imaging, and unenhanced and contrast-enhanced echocardiography: a multicenter comparison of methods. *J Am Coll Cardiol* 2006;**47**:121–8. <https://doi.org/10.1016/j.jacc.2005.10.012>
187. Williams MC, Hunter A, Shah ASV, Assi V, Lewis S, Smith J, et al. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. *J Am Coll Cardiol* 2016;**67**:1759–68. <https://doi.org/10.1016/j.jacc.2016.02.026>
188. Singh T, Bing R, Dweck MR, van Beek EJR, Mills NL, Williams MC, et al. Exercise electrocardiography and computed tomography coronary angiography for patients with suspected stable angina pectoris: a post hoc analysis of the randomized SCOT-HEART trial. *JAMA Cardiol* 2020;**5**:920–8. <https://doi.org/10.1001/jamacardio.2020.1567>
189. Zacharias K, Ahmed A, Shah BN, Gurunathan S, Young G, Acosta D, et al. Relative clinical and economic impact of exercise echocardiography vs. exercise electrocardiography, as first line investigation in patients without known coronary artery disease and new stable angina: a randomized prospective study. *Eur Heart J Cardiovasc Imaging* 2017;**18**:195–202. <https://doi.org/10.1093/ehjci/jev049>
190. Shaw LJ, Mieres JH, Hendel RH, Boden WE, Gulati M, Veledar E, et al. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. *Circulation* 2011;**124**:1239–49. <https://doi.org/10.1161/CIRCULATIONAHA.111.029660>
191. Mark DB, Shaw L, Harrell FE Jr, Hlatky MA, Lee KL, Bengtson JR, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med* 1991;**325**:849–53. <https://doi.org/10.1056/NEJM199109193251204>
192. Araki H, Koiwaya Y, Nakagaki O, Nakamura M. Diurnal distribution of ST-segment elevation and related arrhythmias in patients with variant angina: a study by ambulatory ECG monitoring. *Circulation* 1983;**67**:995–1000. <https://doi.org/10.1161/01.cir.67.5.995>
193. Onaka H, Hirota Y, Shimada S, Kita Y, Sakai Y, Kawakami Y, et al. Clinical observation of spontaneous anginal attacks and multivessel spasm in variant angina pectoris with normal coronary arteries: evaluation by 24-hour 12-lead electrocardiography with computer analysis. *J Am Coll Cardiol* 1996;**27**:38–44. [https://doi.org/10.1016/0735-1097\(95\)00423-8](https://doi.org/10.1016/0735-1097(95)00423-8)
194. Beijk MA, Vlastra WV, Delewi R, van de Hoef TP, Boekholdt SM, Sjaun KD, et al. Myocardial infarction with non-obstructive coronary arteries: a focus on vasospastic angina. *Neth Heart J* 2019;**27**:237–45. <https://doi.org/10.1007/s12471-019-1232-7>
195. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol* 2010;**55**:2816–21. <https://doi.org/10.1016/j.jacc.2009.11.096>

196. Schuijff JD, Wijns W, Jukema JW, Atsma DE, de Roos A, Lamb HJ, et al. Relationship between noninvasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging. *J Am Coll Cardiol* 2006;**48**:2508–14. <https://doi.org/10.1016/j.jacc.2006.05.080>
197. Siontis GC, Mavridis D, Greenwood JP, Coles B, Nikolakopoulou A, Jüni P, et al. Outcomes of non-invasive diagnostic modalities for the detection of coronary artery disease: network meta-analysis of diagnostic randomised controlled trials. *BMJ* 2018;**360**:k504. <https://doi.org/10.1136/bmj.k504>
198. Neglia D, Liga R, Gimelli A, Podlesnikar T, Cvijic M, Pontone G, et al. Use of cardiac imaging in chronic coronary syndromes: the EURECA Imaging registry. *Eur Heart J* 2023;**44**:142–58. <https://doi.org/10.1093/eurheartj/ehac640>
199. Celeng C, Leiner T, Maurovich-Horvat P, Merkely B, de Jong P, Dankbaar JW, et al. Anatomical and functional computed tomography for diagnosing hemodynamically significant coronary artery disease: a meta-analysis. *JACC Cardiovasc Imaging* 2019;**12**:1316–25. <https://doi.org/10.1016/j.jcmg.2018.07.022>
200. Curzen N, Nicholas Z, Stuart B, Wilding S, Hill K, Shambrook J, et al. Fractional flow reserve derived from computed tomography coronary angiography in the assessment and management of stable chest pain: the FORECAST randomized trial. *Eur Heart J* 2021;**42**:3844–52. <https://doi.org/10.1093/eurheartj/ehab444>
201. Mickley H, Veien KT, Gerke O, Lambrechtsen J, Rohold A, Steffensen FH, et al. Diagnostic and clinical value of FFR(CT) in stable chest pain patients with extensive coronary calcification: the FACC study. *JACC Cardiovasc Imaging* 2022;**15**:1046–58. <https://doi.org/10.1016/j.jcmg.2021.12.010>
202. Nørgaard BL, Terkelsen CJ, Mathiasen ON, Grove EL, Bøtker HE, Parner E, et al. Coronary CT angiographic and flow reserve-guided management of patients with stable ischemic heart disease. *J Am Coll Cardiol* 2018;**72**:2123–34. <https://doi.org/10.1016/j.jacc.2018.07.043>
203. Pontone G, Weir-McCall JR, Baggiano A, Del Torto A, Fusini L, Guglielmo M, et al. Determinants of rejection rate for coronary CT angiography fractional flow reserve analysis. *Radiology* 2019;**292**:597–605. <https://doi.org/10.1148/radiol.2019182673>
204. Andreini D, Belmonte M, Penicka M, Van Hoe L, Mileva N, Paolisso P, et al. Impact of coronary CT image quality on the accuracy of the FFR(CT) planner. *Eur Radiol* 2023;**34**:2677–88. <https://doi.org/10.1007/s00330-023-10228-8>
205. Rochitte CE, George RT, Chen MY, Arbab-Zadeh A, Dewey M, Miller JM, et al. Computed tomography angiography and perfusion to assess coronary artery stenosis causing perfusion defects by single photon emission computed tomography: the CORE320 study. *Eur Heart J* 2014;**35**:1120–30. <https://doi.org/10.1093/eurheartj/eh488>
206. Nous FMA, Geisler T, Kruk MBP, Alkadhhi H, Kitagawa K, Vliegenthart R, et al. Dynamic myocardial perfusion CT for the detection of hemodynamically significant coronary artery disease. *JACC Cardiovasc Imaging* 2022;**15**:75–87. <https://doi.org/10.1016/j.jcmg.2021.07.021>
207. Rossi A, Merkus D, Klotz E, Mollet N, de Feyter PJ, Krestin GP. Stress myocardial perfusion: imaging with multidetector CT. *Radiology* 2014;**270**:25–46. <https://doi.org/10.1148/radiol.13112739>
208. Hoffmann U, Ferencik M, Udelson JE, Picard MH, Truong QA, Patel MR, et al. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). *Circulation* 2017;**135**:2320–32. <https://doi.org/10.1161/CIRCULATIONAHA.116.024360>
209. Adamson PD, Williams MC, Dweck MR, Mills NL, Boon NA, Daghmagh M, et al. Guiding therapy by coronary CT angiography improves outcomes in patients with stable chest pain. *J Am Coll Cardiol* 2019;**74**:2058–70. <https://doi.org/10.1016/j.jacc.2019.07.085>
210. Williams MC, Moss AJ, Dweck M, Adamson PD, Alam S, Hunter A, et al. Coronary artery plaque characteristics associated with adverse outcomes in the SCOT-HEART study. *J Am Coll Cardiol* 2019;**73**:291–301. <https://doi.org/10.1016/j.jacc.2018.10.066>
211. Foy AJ, Dhruva SS, Peterson B, Mandrola JM, Morgan DJ, Redberg RF. Coronary computed tomography angiography vs functional stress testing for patients with suspected coronary artery disease: a systematic review and meta-analysis. *JAMA Intern Med* 2017;**177**:1623–31. <https://doi.org/10.1001/jamainternmed.2017.4772>
212. SCOT-HEART Investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet* 2015;**385**:2383–91. [https://doi.org/10.1016/S0140-6736\(15\)60291-4](https://doi.org/10.1016/S0140-6736(15)60291-4)
213. Cury RC, Leipsic J, Abbara S, Achenbach S, Berman D, Bittencourt M, et al. CAD-RADS 2.0—2022 Coronary Artery Disease—Reporting and Data System an expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Cardiology (ACC), the American College of Radiology (ACR) and the North America Society of Cardiovascular Imaging (NASCI). *J Cardiovasc Comput Tomogr* 2022;**16**:536–57. <https://doi.org/10.1016/j.jcct.2022.07.002>
214. Meijboom WB, Meijis MF, Schuijff JD, Cramer MJ, Mollet NR, van Mieghem CAG, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *J Am Coll Cardiol* 2008;**52**:2135–44. <https://doi.org/10.1016/j.jacc.2008.08.058>
215. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008;**359**:2324–36. <https://doi.org/10.1056/NEJMoa0806576>
216. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol* 2008;**52**:1724–32. <https://doi.org/10.1016/j.jacc.2008.07.031>
217. Min JK, Koduru S, Dunning AM, Cole JH, Hines JL, Greenwell D, et al. Coronary CT angiography versus myocardial perfusion imaging for near-term quality of life, cost and radiation exposure: a prospective multicenter randomized pilot trial. *J Cardiovasc Comput Tomogr* 2012;**6**:274–83. <https://doi.org/10.1016/j.jcct.2012.06.002>
218. Douglas PS, Pontone G, Hlatky MA, Patel MR, Nørgaard BL, Byrne RA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFRCT: outcome and resource impacts study. *Eur Heart J* 2015;**36**:3359–67. <https://doi.org/10.1093/eurheartj/ehv444>
219. Dewey M, Rief M, Martus P, Kendziora B, Feger S, Dreger H, et al. Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial. *BMJ* 2016;**355**:i5441. <https://doi.org/10.1136/bmj.i5441>
220. Chang HJ, Lin FY, Gebow D, An HY, Andreini D, Bathina R, et al. Selective referral using CCTA versus direct referral for individuals referred to invasive coronary angiography for suspected CAD: a randomized, controlled, open-label trial. *JACC Cardiovasc Imaging* 2019;**12**:1303–12. <https://doi.org/10.1016/j.jcmg.2018.09.018>
221. Sharma A, Coles A, Sekaran NK, Pagidipati NJ, Lu MT, Mark DB, et al. Stress testing versus CT angiography in patients with diabetes and suspected coronary artery disease. *J Am Coll Cardiol* 2019;**73**:893–902. <https://doi.org/10.1016/j.jacc.2018.11.056>
222. The Discharge Trial Group; Maurovich-Horvat P, Bossert M, Kofoed KF, Rieckmann N, Benedek T, et al. CT or invasive coronary angiography in stable chest pain. *N Engl J Med* 2022;**386**:1591–602. <https://doi.org/10.1056/NEJMoa2200963>
223. Smulders MW, Jaarsma C, Nelemans PJ, Bekkers SCAM, Bucnerius J, Leiner T, et al. Comparison of the prognostic value of negative non-invasive cardiac investigations in patients with suspected or known coronary artery disease—a meta-analysis. *Eur Heart J Cardiovasc Imaging* 2017;**18**:980–7. <https://doi.org/10.1093/ehjci/jex014>
224. Picano E, Mathias W Jr, Pingitore A, Bigi R, Previtali M. Safety and tolerability of dobutamine-atropine stress echocardiography: a prospective, multicentre study. Echo Dobutamine International Cooperative Study Group. *Lancet* 1994;**344**:1190–2. [https://doi.org/10.1016/s0140-6736\(94\)90508-8](https://doi.org/10.1016/s0140-6736(94)90508-8)
225. Varga A, Garcia MA, Picano E. Safety of stress echocardiography (from the International Stress Echo Complication Registry). *Am J Cardiol* 2006;**98**:541–3. <https://doi.org/10.1016/j.amjcard.2006.02.064>
226. Lorenzoni V, Bellelli S, Caselli C, Knuuti J, Underwood SR, Neglia D, et al. Cost-effectiveness analysis of stand-alone or combined non-invasive imaging tests for the diagnosis of stable coronary artery disease: results from the EVINCI study. *Eur J Health Econ* 2019;**20**:1437–49. <https://doi.org/10.1007/s10198-019-01096-5>
227. Pellikka PA, Arruda-Olson A, Chaudhry FA, Chen MH, Marshall JE, Porter TR, et al. Guidelines for performance, interpretation, and application of stress echocardiography in ischemic heart disease: from the American Society of Echocardiography. *J Am Soc Echocardiogr* 2020;**33**:1–41.e8. <https://doi.org/10.1016/j.echo.2019.07.001>
228. Marwick TH. Stress echocardiography. *Heart* 2003;**89**:113–8. <https://doi.org/10.1136/heart.89.1.113>
229. Plana JC, Mikati IA, Dokainish H, Lakkis N, Abukhalil J, Davis R, et al. A randomized cross-over study for evaluation of the effect of image optimization with contrast on the diagnostic accuracy of dobutamine echocardiography in coronary artery disease The OPTIMIZE Trial. *JACC Cardiovasc Imaging* 2008;**1**:145–52. <https://doi.org/10.1016/j.jcmg.2007.10.014>
230. Qian L, Xie F, Xu D, Porter TR. Long-term prognostic value of stress myocardial perfusion echocardiography in patients with coronary artery disease: a meta-analysis. *Eur Heart J Cardiovasc Imaging* 2021;**22**:553–62. <https://doi.org/10.1093/ehjci/jeaa026>
231. Abdelmoneim SS, Dhoble A, Bernier M, Erwin PJ, Korosoglou G, Senior R, et al. Quantitative myocardial contrast echocardiography during pharmacological stress for diagnosis of coronary artery disease: a systematic review and meta-analysis of diagnostic accuracy studies. *Eur J Echocardiogr* 2009;**10**:813–25. <https://doi.org/10.1093/ejchocard/jep084>
232. Porter TR, Smith LM, Wu J, Thomas D, Haas JT, Mathers DH, et al. Patient outcome following 2 different stress imaging approaches: a prospective randomized comparison. *J Am Coll Cardiol* 2013;**61**:2446–55. <https://doi.org/10.1016/j.jacc.2013.04.019>
233. Rinkevich D, Belcik T, Gupta NC, Cannard E, Alkayed NJ, Kaul S. Coronary autoregulation is abnormal in syndrome X: insights using myocardial contrast echocardiography. *J Am Soc Echocardiogr* 2013;**26**:290–6. <https://doi.org/10.1016/j.echo.2012.12.008>
234. Kutty S, Bisselou Moukagna KS, Craft M, Shostrom V, Xie F, Porter TR. Clinical outcome of patients with inducible capillary blood flow abnormalities during demand

- stress in the presence or absence of angiographic coronary disease. *Circ Cardiovasc Imaging* 2018;**11**:e007483. <https://doi.org/10.1161/CIRCIMAGING.117.007483>
235. Taqui S, Ferencik M, Davidson BP, Belcik JT, Moccetti F, Layoun M, et al. Coronary microvascular dysfunction by myocardial contrast echocardiography in nonelderly patients referred for computed tomographic coronary angiography. *J Am Soc Echocardiogr* 2019;**32**:817–25. <https://doi.org/10.1016/j.echo.2019.03.001>
 236. Porter TR, Mulvagh SL, Abdelmoneim SS, Becher H, Belcik JT, Bierig M, et al. Clinical applications of ultrasonic enhancing agents in echocardiography: 2018 American Society of Echocardiography Guidelines update. *J Am Soc Echocardiogr* 2018;**31**: 241–74. <https://doi.org/10.1016/j.echo.2017.11.013>
 237. Hu C, Feng Y, Huang P, Jin J. Adverse reactions after the use of SonoVue contrast agent: characteristics and nursing care experience. *Medicine* 2019;**98**:e17745. <https://doi.org/10.1097/md.00000000000017745>
 238. Ciampi Q, Zagatina A, Cortigiani L, Gaibazzi N, Borguezan Daros C, Zhuravskaya N, et al. Functional, anatomical, and prognostic correlates of coronary flow velocity reserve during stress echocardiography. *J Am Coll Cardiol* 2019;**74**:2278–91. <https://doi.org/10.1016/j.jacc.2019.08.1046>
 239. Ahmadvazir S, Shah BN, Zacharias K, Senior R. Incremental prognostic value of stress echocardiography with carotid ultrasound for suspected CAD. *JACC Cardiovasc Imaging* 2018;**11**:173–80. <https://doi.org/10.1016/j.jcmg.2016.12.020>
 240. Ahmadvazir S, Pradhan J, Khattar RS, Senior R. Long-term prognostic value of simultaneous assessment of atherosclerosis and ischemia in patients with suspected angina: implications for routine use of carotid ultrasound during stress echocardiography. *J Am Soc Echocardiogr* 2020;**33**:559–69. <https://doi.org/10.1016/j.echo.2019.11.019>
 241. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. *JAMA* 1998;**280**:913–20. <https://doi.org/10.1001/jama.280.10.913>
 242. Marwick TH, Case C, Vasey C, Allen S, Short L, Thomas JD. Prediction of mortality by exercise echocardiography: a strategy for combination with the Duke treadmill score. *Circulation* 2001;**103**:2566–71. <https://doi.org/10.1161/01.cir.103.21.2566>
 243. Shaw LJ, Vasey C, Sawada S, Rimmerman C, Marwick TH. Impact of gender on risk stratification by exercise and dobutamine stress echocardiography: long-term mortality in 4234 women and 6898 men. *Eur Heart J* 2005;**26**:447–56. <https://doi.org/10.1093/eurheartj/ehi102>
 244. Gurunathan S, Zacharias K, Akhtar M, Ahmed A, Mehta V, Karogiannis N, et al. Cost-effectiveness of a management strategy based on exercise echocardiography versus exercise electrocardiography in patients presenting with suspected angina during long term follow up: a randomized study. *Int J Cardiol* 2018;**259**:1–7. <https://doi.org/10.1016/j.ijcard.2018.01.112>
 245. Vamvakidou A, Danylenko O, Pradhan J, Kelshiker M, Jones T, Whiteside D, et al. Relative clinical value of coronary computed tomography and stress echocardiography-guided management of stable chest pain patients: a propensity-matched analysis. *Eur Heart J Cardiovasc Imaging* 2020;**22**:1473–81. <https://doi.org/10.1093/ehjci/jeaa303>
 246. Woodward W, Dockerill C, McCourt A, Upton R, O'Driscoll J, Balkhausen K, et al. Real-world performance and accuracy of stress echocardiography: the EVAREST observational multi-centre study. *Eur Heart J Cardiovasc Imaging* 2022;**23**:689–98. <https://doi.org/10.1093/ehjci/jeab092>
 247. Senior R, Andersson O, Caidahl K, Carlens P, Herregods MC, Jenni R, et al. Enhanced left ventricular endocardial border delineation with an intravenous injection of SonoVue, a new echocardiographic contrast agent: a European multicenter study. *Echocardiography* 2000;**17**:705–11. <https://doi.org/10.1111/j.1540-8175.2000.tb01223.x>
 248. Edwardsen T, Asch FM, Davidson B, Delgado V, DeMaria A, Dilsizian V, et al. Non-invasive imaging in coronary syndromes: recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography, in collaboration with the American Society of Nuclear Cardiology, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *Eur Heart J Cardiovasc Imaging* 2022;**23**:e6–33. <https://doi.org/10.1093/ehjci/jeab244>
 249. Tsutsui JM, Elhendy A, Anderson JR, Xie F, McGrain AC, Porter TR. Prognostic value of dobutamine stress myocardial contrast perfusion echocardiography. *Circulation* 2005;**112**:1444–50. <https://doi.org/10.1161/circulationaha.105.537134>
 250. Jeetley P, Hickman M, Kamp O, Lang RM, Thomas JD, Vannan MA, et al. Myocardial contrast echocardiography for the detection of coronary artery stenosis: a prospective multicenter study in comparison with single-photon emission computed tomography. *J Am Coll Cardiol* 2006;**47**:141–5. <https://doi.org/10.1016/j.jacc.2005.08.054>
 251. Dolan MS, Gala SS, Dodla S, Abdelmoneim SS, Xie F, Cloutier D, et al. Safety and efficacy of commercially available ultrasound contrast agents for rest and stress echocardiography: a multicenter experience. *J Am Coll Cardiol* 2009;**53**:32–8. <https://doi.org/10.1016/j.jacc.2008.08.066>
 252. Gaibazzi N, Reverberi C, Lorenzoni V, Molinaro S, Porter TR. Prognostic value of high-dose dipyridamole stress myocardial contrast perfusion echocardiography. *Circulation* 2012;**126**:1217–24. <https://doi.org/10.1161/circulationaha.112.110031>
 253. Gaibazzi N, Rigo F, Lorenzoni V, Molinaro S, Bartolomucci F, Reverberi C, et al. Comparative prediction of cardiac events by wall motion, wall motion plus coronary flow reserve, or myocardial perfusion analysis: a multicenter study of contrast stress echocardiography. *JACC Cardiovasc Imaging* 2013;**6**:1–12. <https://doi.org/10.1016/j.jcmg.2012.08.009>
 254. Senior R, Moreo A, Gaibazzi N, Agati L, Tiemann K, Shivalkar B, et al. Comparison of sulfur hexafluoride microbubble (SonoVue)-enhanced myocardial contrast echocardiography with gated single-photon emission computed tomography for detection of significant coronary artery disease: a large European multicenter study. *J Am Coll Cardiol* 2013;**62**:1353–61. <https://doi.org/10.1016/j.jacc.2013.04.082>
 255. Schroder J, Prescott E. Doppler echocardiography assessment of coronary microvascular function in patients with angina and no obstructive coronary artery disease. *Front Cardiovasc Med* 2021;**8**:723542. <https://doi.org/10.3389/fcvm.2021.723542>
 256. Yang Z, Zheng H, Zhou T, Yang L-F, Hu X-F, Peng Z-H, et al. Diagnostic performance of myocardial perfusion imaging with SPECT, CT and MR compared to fractional flow reserve as reference standard. *Int J Cardiol* 2015;**190**:103–5. <https://doi.org/10.1016/j.ijcard.2015.04.091>
 257. Takx RA, Blomberg BA, El Aidi H, Habets J, de Jong PA, Nagel E, et al. Diagnostic accuracy of stress myocardial perfusion imaging compared to invasive coronary angiography with fractional flow reserve meta-analysis. *Circ Cardiovasc Imaging* 2015;**8**:e002666. <https://doi.org/10.1161/circimaging.114.002666>
 258. Dai N, Zhang X, Zhang Y, Hou L, Li W, Fan B, et al. Enhanced diagnostic utility achieved by myocardial blood analysis: a meta-analysis of noninvasive cardiac imaging in the detection of functional coronary artery disease. *Int J Cardiol* 2016;**221**:665–73. <https://doi.org/10.1016/j.ijcard.2016.07.031>
 259. Mowatt G, Brazzelli M, Gemmell H, Hillis GS, Metcalfe M, Vale L, et al. Systematic review of the prognostic effectiveness of SPECT myocardial perfusion scintigraphy in patients with suspected or known coronary artery disease and following myocardial infarction. *Nucl Med Commun* 2005;**26**:217–29. <https://doi.org/10.1097/00006231-200503000-00006>
 260. Cantoni V, Green R, Acampa W, Zampella E, Assante R, Nappi C, et al. Diagnostic performance of myocardial perfusion imaging with conventional and CZT single-photon emission computed tomography in detecting coronary artery disease: a meta-analysis. *J Nucl Cardiol* 2021;**28**:698–715. <https://doi.org/10.1007/s12350-019-01747-3>
 261. Panjer M, Dobrolinska M, Wagenaar NRL, Slart R. Diagnostic accuracy of dynamic CZT-SPECT in coronary artery disease. A systematic review and meta-analysis. *J Nucl Cardiol* 2022;**29**:1686–97. <https://doi.org/10.1007/s12350-021-02721-8>
 262. Juárez-Orozco LE, Tio RA, Alexanderson E, Dweck M, Vliegenthart R, El Mounmi M, et al. Quantitative myocardial perfusion evaluation with positron emission tomography and the risk of cardiovascular events in patients with coronary artery disease: a systematic review of prognostic studies. *Eur Heart J Cardiovasc Imaging* 2018;**19**:1179–87. <https://doi.org/10.1093/ehjci/jex331>
 263. Green R, Cantoni V, Acampa W, Assante R, Zampella E, Nappi C, et al. Prognostic value of coronary flow reserve in patients with suspected or known coronary artery disease referred to PET myocardial perfusion imaging: a meta-analysis. *J Nucl Cardiol* 2021;**28**:904–18. <https://doi.org/10.1007/s12350-019-02000-7>
 264. Groenenhoff F, Klaassen RGM, Valstar GB, Bots SH, Onland-Moret NC, Den Ruijter HM, et al. Evaluation of non-invasive imaging parameters in coronary microvascular disease: a systematic review. *BMC Med Imaging* 2021;**21**:5. <https://doi.org/10.1186/s12880-020-00535-7>
 265. Yang K, Yu SQ, Lu MJ, Zhao SH. Comparison of diagnostic accuracy of stress myocardial perfusion imaging for detecting hemodynamically significant coronary artery disease between cardiac magnetic resonance and nuclear medical imaging: a meta-analysis. *Int J Cardiol* 2019;**293**:278–85. <https://doi.org/10.1016/j.ijcard.2019.06.054>
 266. Mc Ardle BA, Dowsley TF, deKemp RA, Wells GA, Beanlands RS. Does rubidium-82 PET have superior accuracy to SPECT perfusion imaging for the diagnosis of obstructive coronary disease?: a systematic review and meta-analysis. *J Am Coll Cardiol* 2012;**60**: 1828–37. <https://doi.org/10.1016/j.jacc.2012.07.038>
 267. Parker MW, Iskandar A, Limone B, Perugini A, Kim H, Jones C, et al. Diagnostic accuracy of cardiac positron emission tomography versus single photon emission computed tomography for coronary artery disease: a bivariate meta-analysis. *Circ Cardiovasc Imaging* 2012;**5**:700–7. <https://doi.org/10.1161/circimaging.112.978270>
 268. Danad I, Rajmakers PG, Driessen RS, Leipsic J, Raju R, Naoum C, et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. *JAMA Cardiol* 2017;**2**:1100–7. <https://doi.org/10.1001/jamacardio.2017.2471>
 269. Rasmussen LD, Winther S, Eftekhari A, Karim SR, Westra J, Isaksen C, et al. Second-line myocardial perfusion imaging to detect obstructive stenosis: head-to-head comparison of CMR and PET. *JACC Cardiovasc Imaging* 2023;**16**:642–55. <https://doi.org/10.1016/j.jcmg.2022.11.015>
 270. Patel KK, Al Badarin F, Chan PS, Spertus JA, Courter S, Kennedy KF, et al. Randomized comparison of clinical effectiveness of pharmacologic SPECT and PET MPI in symptomatic CAD patients. *JACC Cardiovasc Imaging* 2019;**12**:1821–31. <https://doi.org/10.1016/j.jcmg.2019.04.020>
 271. Patel KK, Spertus JA, Chan PS, Sperry BW, Al Badarin F, Kennedy KF, et al. Myocardial blood flow reserve assessed by positron emission tomography myocardial perfusion

- imaging identifies patients with a survival benefit from early revascularization. *Eur Heart J* 2020;**41**:759–68. <https://doi.org/10.1093/eurheartj/ehz389>
272. van Dijk R, van Assen M, Vliegenthart R, de Bock GH, van der Harst P, Oudkerk M. Diagnostic performance of semi-quantitative and quantitative stress CMR perfusion analysis: a meta-analysis. *J Cardiovasc Magn Reson* 2017;**19**:92. <https://doi.org/10.1186/s12968-017-0393-z>
 273. Gargiulo P, Dellegrottaglie S, Bruzzese D, Savarese G, Scala O, Ruggiero D, et al. The prognostic value of normal stress cardiac magnetic resonance in patients with known or suspected coronary artery disease: a meta-analysis. *Circ Cardiovasc Imaging* 2013;**6**:574–82. <https://doi.org/10.1161/circimaging.113.000035>
 274. Iwata K, Nakagawa S, Ogasawara K. The prognostic value of normal stress cardiovascular magnetic resonance imaging. *J Comput Assist Tomogr* 2014;**38**:36–43. <https://doi.org/10.1097/RCT.0b013e3182a474a0>
 275. Ricci F, Khanji MY, Bisaccia G, Cipriani A, Di Cesare A, Ceriello L, et al. Diagnostic and prognostic value of stress cardiovascular magnetic resonance imaging in patients with known or suspected coronary artery disease: a systematic review and meta-analysis. *JAMA Cardiol* 2023;**8**:662–73. <https://doi.org/10.1001/jamacardio.2023.1290>
 276. Nagel E, Greenwood JP, McCann GP, Bettencourt N, Shah AM, Hussain ST, et al. Magnetic resonance perfusion or fractional flow reserve in coronary disease. *N Engl J Med* 2019;**380**:2418–28. <https://doi.org/10.1056/NEJMoa1716734>
 277. Nagel E, Lehmkuhl HB, Bocksch W, Klein C, Vogel U, Frantz E, et al. Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. *Circulation* 1999;**99**:763–70. <https://doi.org/10.1161/01.cir.99.6.763>
 278. Ripley DP, Motwani M, Brown JM, Nixon J, Everett CC, Bijsterveld P, et al. Individual component analysis of the multi-parametric cardiovascular magnetic resonance protocol in the CE-MARC trial. *J Cardiovasc Magn Reson* 2015;**17**:59. <https://doi.org/10.1186/s12968-015-0169-2>
 279. Di Leo G, Fisci E, Secchi F, Ali M, Ambrogi F, Sconfienza LM, et al. Diagnostic accuracy of magnetic resonance angiography for detection of coronary artery disease: a systematic review and meta-analysis. *Eur Radiol* 2016;**26**:3706–18. <https://doi.org/10.1007/s00330-015-4134-0>
 280. Feger S, Rief M, Zimmermann E, Richter F, Roehle R, Dewey M, et al. Patient satisfaction with coronary CT angiography, myocardial CT perfusion, myocardial perfusion MRI, SPECT myocardial perfusion imaging and conventional coronary angiography. *Eur Radiol* 2015;**25**:2115–24. <https://doi.org/10.1007/s00330-015-3604-8>
 281. Shaw LJ, Weintraub WS, Maron DJ, Hartigan PM, Hachamovitch R, Min JK, et al. Baseline stress myocardial perfusion imaging results and outcomes in patients with stable ischemic heart disease randomized to optimal medical therapy with or without percutaneous coronary intervention. *Am Heart J* 2012;**164**:243–50. <https://doi.org/10.1016/j.ahj.2012.05.018>
 282. Dorbala S, Di Carli MF, Beanlands RS, Merhige ME, Williams BA, Veledar E, et al. Prognostic value of stress myocardial perfusion positron emission tomography: results from a multicenter observational registry. *J Am Coll Cardiol* 2013;**61**:176–84. <https://doi.org/10.1016/j.jacc.2012.09.043>
 283. Kay J, Dorbala S, Goyal A, Fazel R, Di Carli MF, Einstein AJ, et al. Influence of sex on risk stratification with stress myocardial perfusion Rb-82 positron emission tomography: results from the PET (Positron Emission Tomography) Prognosis Multicenter Registry. *J Am Coll Cardiol* 2013;**62**:1866–76. <https://doi.org/10.1016/j.jacc.2013.06.017>
 284. Uretsky S, Rozanski A. Long-term outcomes following a normal stress myocardial perfusion scan. *J Nucl Cardiol* 2013;**20**:715–8. <https://doi.org/10.1007/s12350-013-9769-0>
 285. Rozanski A, Gransar H, Min JK, Hayes SV, Friedman JD, Thomson LEJ, et al. Long-term mortality following normal exercise myocardial perfusion SPECT according to coronary disease risk factors. *J Nucl Cardiol* 2014;**21**:341–50. <https://doi.org/10.1007/s12350-013-9830-z>
 286. Zellweger MJ, Fahrni G, Ritter M, Jeger RV, Wild D, Buser P, et al. Prognostic value of “routine” cardiac stress imaging 5 years after percutaneous coronary intervention: the prospective long-term observational BASKET (Basel Stent Kosteneffektivitäts Trial) LATE IMAGING study. *JACC Cardiovasc Interv* 2014;**7**:615–21. <https://doi.org/10.1016/j.jcin.2014.01.161>
 287. Patel KK, Spertus JA, Arnold SV, Chan PS, Kennedy KF, Jones PG, et al. Ischemia on PET MPI may identify patients with improvement in angina and health status post-revascularization. *J Am Coll Cardiol* 2019;**74**:1734–6. <https://doi.org/10.1016/j.jacc.2019.06.074>
 288. Bom MJ, van Diemen PA, Driessen RS, Everaars H, Schumacher SP, Wijmenga J-T, et al. Prognostic value of [¹⁵O]H₂O positron emission tomography-derived global and regional myocardial perfusion. *Eur Heart J Cardiovasc Imaging* 2020;**21**:777–86. <https://doi.org/10.1093/ehjci/jez258>
 289. Schepis T, Gaemperli O, Koepfli P, Namdar M, Valenta I, Scheffel H, et al. Added value of coronary artery calcium score as an adjunct to gated SPECT for the evaluation of coronary artery disease in an intermediate-risk population. *J Nucl Med* 2007;**48**:1424–30. <https://doi.org/10.2967/jnumed.107.040758>
 290. Schenker MP, Dorbala S, Hong EC, Rybicki FJ, Hachamovitch R, Kwong RY, et al. Interrelation of coronary calcification, myocardial ischemia, and outcomes in patients with intermediate likelihood of coronary artery disease: a combined positron emission tomography/computed tomography study. *Circulation* 2008;**117**:1693–700. <https://doi.org/10.1161/CIRCULATIONAHA.107.717512>
 291. Chang SM, Nabi F, Xu J, Peterson LE, Achari A, Pratt CM, et al. The coronary artery calcium score and stress myocardial perfusion imaging provide independent and complementary prediction of cardiac risk. *J Am Coll Cardiol* 2009;**54**:1872–82. <https://doi.org/10.1016/j.jacc.2009.05.071>
 292. Ghadri JR, Pazhenkottal AP, Nkoulou RN, Goetti R, Buechel RR, Husmann L, et al. Very high coronary calcium score unmasks obstructive coronary artery disease in patients with normal SPECT MPI. *Heart* 2011;**97**:998–1003. <https://doi.org/10.1136/hrt.2010.217281>
 293. Brodov Y, Gransar H, Dey D, Shalev A, Germano G, Friedman JD, et al. Combined quantitative assessment of myocardial perfusion and coronary artery calcium score by hybrid 82Rb PET/CT improves detection of coronary artery disease. *J Nucl Med* 2015;**56**:1345–50. <https://doi.org/10.2967/jnumed.114.153429>
 294. Hamon M, Fau G, Nee G, Ehtisham J, Morello R, Hamon M. Meta-analysis of the diagnostic performance of stress perfusion cardiovascular magnetic resonance for detection of coronary artery disease. *J Cardiovasc Magn Reson* 2010;**12**:29. <https://doi.org/10.1186/1532-429X-12-29>
 295. Jiang B, Cai W, Lv X, Liu H. Diagnostic performance and clinical utility of myocardial perfusion MRI for coronary artery disease with fractional flow reserve as the standard reference: a meta-analysis. *Heart Lung Circ* 2016;**25**:1031–8. <https://doi.org/10.1016/j.hlc.2016.02.018>
 296. Heitner JF, Kim RJ, Kim HW, Klem I, Shah DJ, Debs D, et al. Prognostic value of vasodilator stress cardiac magnetic resonance imaging: a multicenter study with 48 000 patient-years of follow-up. *JAMA Cardiol* 2019;**4**:256–64. <https://doi.org/10.1001/jamacardio.2019.0035>
 297. Arai AE, Schulz-Menger J, Shah DJ, Han Y, Bandettini WP, Abraham A, et al. Stress perfusion cardiac magnetic resonance vs SPECT imaging for detection of coronary artery disease. *J Am Coll Cardiol* 2023;**82**:1828–38. <https://doi.org/10.1016/j.jacc.2023.08.046>
 298. Ford TJ, Stanley B, Good R, Rocchiccioli P, McEntegart M, Watkins S, et al. Stratified medical therapy using invasive coronary function testing in angina: the CorMicA trial. *J Am Coll Cardiol* 2018;**72**:2841–55. <https://doi.org/10.1016/j.jacc.2018.09.006>
 299. Mileva N, Nagumo S, Mizukami T, Sonck J, Berry C, Gallinoro E, et al. Prevalence of coronary microvascular disease and coronary vasospasm in patients with nonobstructive coronary artery disease: systematic review and meta-analysis. *J Am Heart Assoc* 2022;**11**:e023207. <https://doi.org/10.1161/JAHA.121.023207>
 300. Brainin P, Frestad D, Prescott E. The prognostic value of coronary endothelial and microvascular dysfunction in subjects with normal or non-obstructive coronary artery disease: a systematic review and meta-analysis. *Int J Cardiol* 2018;**254**:1–9. <https://doi.org/10.1016/j.ijcard.2017.10.052>
 301. Gdowski MA, Murthy VL, Doering M, Monroy-Gonzalez AG, Slart R, Brown DL. Association of isolated coronary microvascular dysfunction with mortality and major adverse cardiac events: a systematic review and meta-analysis of aggregate data. *J Am Heart Assoc* 2020;**9**:e014954. <https://doi.org/10.1161/JAHA.119.014954>
 302. Hozumi T, Yoshida K, Ogata Y, Akasaka T, Asami Y, Takagi T, et al. Noninvasive assessment of significant left anterior descending coronary artery stenosis by coronary flow velocity reserve with transthoracic color Doppler echocardiography. *Circulation* 1998;**97**:1557–62. <https://doi.org/10.1161/01.CIR.97.16.1557>
 303. Sicari R, Rigo F, Cortigiani L, Gherardi S, Galderisi M, Picano E. Additive prognostic value of coronary flow reserve in patients with chest pain syndrome and normal or near-normal coronary arteries. *Am J Cardiol* 2009;**103**:626–31. <https://doi.org/10.1016/j.amjcard.2008.10.033>
 304. Taqueti VR, Everett BM, Murthy VL, Gaber M, Foster CR, Hainer J, et al. Interaction of impaired coronary flow reserve and cardiomyocyte injury on adverse cardiovascular outcomes in patients without overt coronary artery disease. *Circulation* 2015;**131**:528–35. <https://doi.org/10.1161/CIRCULATIONAHA.114.009716>
 305. Michelson MM, Mygind ND, Pena A, Olsen RH, Christensen TE, Ghotbi AA, et al. Transthoracic Doppler echocardiography compared with positron emission tomography for assessment of coronary microvascular dysfunction: the iPOWER study. *Int J Cardiol* 2017;**228**:435–43. <https://doi.org/10.1016/j.ijcard.2016.11.004>
 306. Cortigiani L, Ciampi Q, Lombardo A, Rigo F, Bovenzi F, Picano E, et al. Age- and gender-specific prognostic cutoff values of coronary flow velocity reserve in vasodilator stress echocardiography. *J Am Soc Echocardiogr* 2019;**32**:1307–17. <https://doi.org/10.1016/j.echo.2019.05.020>
 307. Everaars H, de Waard GA, Driessen RS, Danad I, van de Ven PM, Raijmakers PG, et al. Doppler flow velocity and thermomodulation to assess coronary flow reserve: a head-to-head comparison with [¹⁵O]H₂O PET. *JACC Cardiovasc Interv* 2018;**11**:2044–54. <https://doi.org/10.1016/j.jcin.2018.07.011>
 308. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van 't Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;**360**:213–24. <https://doi.org/10.1056/NEJMoa0807611>
 309. Curzen N, Rana O, Nicholas Z, Golledge P, Zaman A, Oldroyd K, et al. Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain? The RIPCARD study. *Circ Cardiovasc Interv* 2014;**7**:248–55. <https://doi.org/10.1161/CIRCINTERVENTIONS.113.000978>

310. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med* 2017;**376**:1824–34. <https://doi.org/10.1056/NEJMoa1700445>
311. Gotberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med* 2017;**376**:1813–23. <https://doi.org/10.1056/NEJMoa1616540>
312. Faria D, Hennessey B, Shabbir A, Mejía-Rentería H, Wang L, Lee JM, et al. Functional coronary angiography for the assessment of the epicardial vessels and the microcirculation. *EuroIntervention* 2023;**19**:203–21. <https://doi.org/10.4244/EIJ-D-22-00969>
313. Van Belle E, Rioufol G, Pouillot C, Cuisset T, Bougrini K, Teiger E, et al. Outcome impact of coronary revascularization strategy reclassification with fractional flow reserve at time of diagnostic angiography: insights from a large French multicenter fractional flow reserve registry. *Circulation* 2014;**129**:173–85. <https://doi.org/10.1161/CIRCULATIONAHA.113.006646>
314. Lopes RD, Alexander KP, Stevens SR, Reynolds HR, Stone GW, Piña IL, et al. Initial invasive versus conservative management of stable ischemic heart disease in patients with a history of heart failure or left ventricular dysfunction. *Circulation* 2020;**142**:1725–35. <https://doi.org/10.1161/CIRCULATIONAHA.120.050304>
315. Rozanski A, Miller RJH, Gransar H, Han D, Slomka P, Dey D, et al. Benefit of early revascularization based on inducible ischemia and left ventricular ejection fraction. *J Am Coll Cardiol* 2022;**80**:202–15. <https://doi.org/10.1016/j.jacc.2022.04.052>
316. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165. <https://doi.org/10.1093/eurheartj/ehy394>
317. Reynolds HR, Shaw LJ, Min JK, Page CB, Berman DS, Chaitman BR, et al. Outcomes in the ISCHEMIA trial based on coronary artery disease and ischemia severity. *Circulation* 2021;**144**:1024–38. <https://doi.org/10.1161/CIRCULATIONAHA.120.049755>
318. Johnson NP, Toth GG, Lai D, Zhu H, Ager A, Agostoni P, et al. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. *J Am Coll Cardiol* 2014;**64**:1641–54. <https://doi.org/10.1016/j.jacc.2014.07.973>
319. Barbato E, Toth GG, Johnson NP, Pijls NHJ, Fearon WF, Tonino PAL, et al. A prospective natural history study of coronary atherosclerosis using fractional flow reserve. *J Am Coll Cardiol* 2016;**68**:2247–55. <https://doi.org/10.1016/j.jacc.2016.08.055>
320. Ciccarelli G, Barbato E, Toth GG, Gahl B, Xaplanteris P, Fournier S, et al. Angiography versus hemodynamics to predict the natural history of coronary stenoses. *Circulation* 2018;**137**:1475–85. <https://doi.org/10.1161/CIRCULATIONAHA.117.028782>
321. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med* 2014;**371**:1208–17. <https://doi.org/10.1056/NEJMoa1408758>
322. Van Belle E, Baptista SB, Raposo L, Henderson J, Rioufol G, Santos L, et al. Impact of routine fractional flow reserve on management decision and 1-year clinical outcome of patients with acute coronary syndromes: PRIME-FFR (Insights from the POST-IT [Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease] and R3F [French FFR Registry]) integrated multicenter registries—implementation of FFR [Fractional Flow Reserve] in routine practice. *Circ Cardiovasc Interv* 2017;**10**:e004296. <https://doi.org/10.1161/circinterventions.116.004296>
323. Escaned J, Ryan N, Mejía-Rentería H, Cook CM, Dehbi H-M, Alegria-Barrero E, et al. Safety of the deferral of coronary revascularization on the basis of instantaneous wave-free ratio and fractional flow reserve measurements in stable coronary artery disease and acute coronary syndromes. *JACC Cardiovasc Interv* 2018;**11**:1437–49. <https://doi.org/10.1016/j.jcin.2018.05.029>
324. Elguindy M, Stables R, Nicholas Z, Kemp I, Curzen N. Design and rationale of the RIPCORDER 2 Trial (does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain?): a randomized controlled trial to compare routine pressure wire assessment with conventional angiography in the management of patients with coronary artery disease. *Circ Cardiovasc Qual Outcomes* 2018;**11**:e004191. <https://doi.org/10.1161/circoutcomes.117.004191>
325. Xu B, Tu S, Song L, Jin Z, Yu B, Fu G, et al. Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China): a multicentre, randomised, sham-controlled trial. *Lancet* 2021;**398**:2149–59. [https://doi.org/10.1016/s0140-6736\(21\)02248-0](https://doi.org/10.1016/s0140-6736(21)02248-0)
326. Fearon WF, Zimmermann FM, De Bruyne B, Piroth Z, van Straten AHM, Szekely L, et al. Fractional flow reserve-guided PCI as compared with coronary bypass surgery. *N Engl J Med* 2022;**386**:128–37. <https://doi.org/10.1056/NEJMoa2112299>
327. Gargiulo G, Giacoppo D, Jolly SS, Cairns J, Le May M, Bernat I, et al. Effects on mortality and major bleeding of radial versus femoral artery access for coronary angiography or percutaneous coronary intervention: meta-analysis of individual patient data from 7 multicenter randomized clinical trials. *Circulation* 2022;**146**:1329–43. <https://doi.org/10.1161/CIRCULATIONAHA.122.061527>
328. Ferrante G, Rao SV, Juni P, Da Costa BR, Reimers B, Condorelli G, et al. Radial versus femoral access for coronary interventions across the entire spectrum of patients with coronary artery disease: a meta-analysis of randomized trials. *JACC Cardiovasc Interv* 2016;**9**:1419–34. <https://doi.org/10.1016/j.jcin.2016.04.014>
329. Kolkailah AA, Alreshq RS, Muhammed AM, Zahran ME, Anas El-Wegoud M, Nabhan AF. Transradial versus transfemoral approach for diagnostic coronary angiography and percutaneous coronary intervention in people with coronary artery disease. *Cochrane Database Syst Rev* 2018;**4**:CD012318. <https://doi.org/10.1002/14651858.CD012318.pub2>
330. Chiarito M, Cao D, Nicolas J, Roumeliotis A, Power D, Chandiramani R, et al. Radial versus femoral access for coronary interventions: an updated systematic review and meta-analysis of randomized trials. *Catheter Cardiovasc Interv* 2021;**97**:1387–96. <https://doi.org/10.1002/ccd.29486>
331. Hamilos M, Muller O, Cuisset T, Ntalianis A, Chlouverakis G, Sarno G, et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation* 2009;**120**:1505–12. <https://doi.org/10.1161/CIRCULATIONAHA.109.850073>
332. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J* 2015;**36**:3182–8. <https://doi.org/10.1093/eurheartj/ehv452>
333. Warisawa T, Cook CM, Rajkumar C, Howard JP, Seligman H, Ahmad Y, et al. Safety of revascularization deferral of left main stenosis based on instantaneous wave-free ratio evaluation. *JACC Cardiovasc Interv* 2020;**13**:1655–64. <https://doi.org/10.1016/j.jcin.2020.02.035>
334. Mallidi J, Atreya AR, Cook J, Garb J, Jeremias A, Klein LW, et al. Long-term outcomes following fractional flow reserve-guided treatment of angiographically ambiguous left main coronary artery disease: a meta-analysis of prospective cohort studies. *Catheter Cardiovasc Interv* 2015;**86**:12–8. <https://doi.org/10.1002/ccd.25894>
335. Modi BN, van de Hoef TP, Piek JJ, Perera D. Physiological assessment of left main coronary artery disease. *EuroIntervention* 2017;**13**:820–7. <https://doi.org/10.4244/eij-d-17-00135>
336. Cerrato E, Echavarría-Pinto M, D'Ascenzo F, Gonzalo N, Quadri G, Quirós A, et al. Safety of intermediate left main stenosis revascularization deferral based on fractional flow reserve and intravascular ultrasound: a systematic review and meta-regression including 908 deferred left main stenosis from 12 studies. *Int J Cardiol* 2018;**271**:42–8. <https://doi.org/10.1016/j.ijcard.2018.04.032>
337. Stone GW, Christiansen EH, Ali ZA, Andreasen LN, Maehara A, Ahmad Y, et al. Intravascular imaging-guided coronary drug-eluting stent implantation: an updated network meta-analysis. *Lancet* 2024;**403**:824–37. [https://doi.org/10.1016/S0140-6736\(23\)02454-6](https://doi.org/10.1016/S0140-6736(23)02454-6)
338. Park S-J, Kang S-J, Ahn J-M, Shim EB, Kim Y-T, Yun S-C, et al. Visual-functional mismatch between coronary angiography and fractional flow reserve. *JACC Cardiovasc Interv* 2012;**5**:1029–36. <https://doi.org/10.1016/j.jcin.2012.07.007>
339. Toth G, Hamilos M, Pyxaras S, Mangiacapra F, Nelis O, De Vroey F, et al. Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. *Eur Heart J* 2014;**35**:2831–8. <https://doi.org/10.1093/eurheartj/ehu094>
340. Baptista SB, Raposo L, Santos L, Ramos R, Calé R, Jorge E, et al. Impact of routine fractional flow reserve evaluation during coronary angiography on management strategy and clinical outcome: one-year results of the POST-IT. *Circ Cardiovasc Interv* 2016;**9**:e003288. <https://doi.org/10.1161/CIRCINTERVENTIONS.115.003288>
341. Van Belle E, Gil R, Klaus V, Balghith M, Meuwissen M, Clerc J, et al. Impact of routine invasive physiology at time of angiography in patients with multivessel coronary artery disease on reclassification of revascularization strategy: results from the DEFINE REAL study. *JACC Cardiovasc Interv* 2018;**11**:354–65. <https://doi.org/10.1016/j.jcin.2017.11.030>
342. Van Belle E, Dupouy P, Rioufol G. Routine fractional flow reserve combined to diagnostic coronary angiography as a one-stop procedure: episode 3. *Circ Cardiovasc Interv* 2016;**9**:e004137. <https://doi.org/10.1161/CIRCINTERVENTIONS.116.004137>
343. Eftekhari A, Holck EN, Westra J, Olsen NT, Bruun NH, Jensen LO, et al. Instantaneous wave free ratio vs. fractional flow reserve and 5-year mortality: iFR-SWEDEHEART and DEFINE FLAIR. *Eur Heart J* 2023;**44**:4376–84. <https://doi.org/10.1093/eurheartj/ehad582>
344. Berry C, McClure JD, Oldroyd KG. Coronary revascularization guided by instantaneous wave-free ratio compared to fractional flow reserve: pooled 5-year mortality in the DEFINE-FLAIR and iFR-SWEDEHEART trials. *Eur Heart J* 2023;**44**:4388–90. <https://doi.org/10.1093/eurheartj/ehad552>
345. Berntorp K, Rylance R, Yndigegn T, Koul S, Fröbert O, Christiansen EH, et al. Clinical outcome of revascularization deferral with instantaneous wave-free ratio and fractional flow reserve: a 5-year follow-up substudy from the iFR-SWEDEHEART Trial. *J Am Heart Assoc* 2023;**12**:e028423. <https://doi.org/10.1161/jaha.122.028423>
346. Rioufol G, Derimay F, Roubille F, Perret T, Motreff P, Angoulvant D, et al. Fractional flow reserve to guide treatment of patients with multivessel coronary artery disease. *J Am Coll Cardiol* 2021;**78**:1875–85. <https://doi.org/10.1016/j.jacc.2021.08.061>
347. Stables RH, Mullen LJ, Elguindy M, Nicholas Z, Aboul-Enien YH, Kemp I, et al. Routine pressure wire assessment versus conventional angiography in the management of patients with coronary artery disease: the RIPCORDER 2 trial. *Circulation* 2022;**146**:687–98. <https://doi.org/10.1161/circulationaha.121.057793>
348. Nijjer SS, Sen S, Petraco R, Escaned J, Echavarría-Pinto M, Broyd C, et al. Pre-angioplasty instantaneous wave-free ratio pullback provides virtual intervention and predicts hemodynamic outcome for serial lesions and diffuse coronary artery disease. *JACC Cardiovasc Interv* 2014;**7**:1386–96. <https://doi.org/10.1016/j.jcin.2014.06.015>

349. Kikuta Y, Cook CM, Sharp ASP, Salinas P, Kawase Y, Shiono Y, et al. Pre-angioplasty instantaneous wave-free ratio pullback predicts hemodynamic outcome in humans with coronary artery disease. *JACC Cardiovasc Interv* 2018;**11**:757–67. <https://doi.org/10.1016/j.jcin.2018.03.005>
350. Jeremias A, Davies JE, Maehara A, Matsumura M, Schneider J, Tang K, et al. Blinded physiological assessment of residual ischemia after successful angiographic percutaneous coronary intervention: the DEFINE PCI study. *JACC Cardiovasc Interv* 2019;**12**:1991–2001. <https://doi.org/10.1016/j.jcin.2019.05.054>
351. Lee SH, Shin D, Lee JM, Lefieux A, Molony D, Choi KH, et al. Automated algorithm using pre-intervention fractional flow reserve pullback curve to predict post-intervention physiological results. *JACC Cardiovasc Interv* 2020;**13**:2670–84. <https://doi.org/10.1016/j.jcin.2020.06.062>
352. Omori H, Kawase Y, Mizukami T, Tanigaki T, Hirata T, Kikuchi J, et al. Comparisons of nonhyperemic pressure ratios: predicting functional results of coronary revascularization using longitudinal vessel interrogation. *JACC Cardiovasc Interv* 2020;**13**:2688–98. <https://doi.org/10.1016/j.jcin.2020.06.060>
353. Masdjedi K, Tanaka N, Van Belle E, Porouchani S, Linke A, Woitek FW, et al. Vessel fractional flow reserve (vFFR) for the assessment of stenosis severity: the FAST II study. *EuroIntervention* 2022;**17**:1498–505. <https://doi.org/10.4244/eij-d-21-00471>
354. Scoccia A, Byrne RA, Banning AP, Landmesser U, Van Belle E, Amat-Santos IJ, et al. Fractional flow reserve or 3D-quantitative-coronary-angiography based vessel-FFR guided revascularization. Rationale and study design of the prospective randomized fast III trial. *Am Heart J* 2023;**260**:1–8. <https://doi.org/10.1016/j.ahj.2023.02.003>
355. Song L, Xu B, Tu S, Guan C, Jin Z, Yu B, et al. 2-Year outcomes of angiographic quantitative flow ratio-guided coronary interventions. *J Am Coll Cardiol* 2022;**80**:2089–101. <https://doi.org/10.1016/j.jacc.2022.09.007>
356. Johnson NP, Matsuo H, Nakayama M, Eftekhari A, Kakuta T, Tanaka N, et al. Combined pressure and flow measurements to guide treatment of coronary stenoses. *JACC Cardiovasc Interv* 2021;**14**:1904–13. <https://doi.org/10.1016/j.jcin.2021.07.041>
357. van de Hoef TP, Lee JM, Boerhout CKM, de Waard GA, Jung J-H, Lee SH, et al. Combined assessment of FFR and CFR for decision making in coronary revascularization: from the multicenter international ILIAS registry. *JACC Cardiovasc Interv* 2022;**15**:1047–56. <https://doi.org/10.1016/j.jcin.2022.03.016>
358. van de Hoef TP, Stegehuis VE, Madera-Cambero MI, van Royen N, van der Hoeven NVW, de Waard GA, et al. Impact of core laboratory assessment on treatment decisions and clinical outcomes using combined fractional flow reserve and coronary flow reserve measurements—DEFINE-FLOW core laboratory sub-study. *Int J Cardiol* 2023;**377**:9–16. <https://doi.org/10.1016/j.ijcard.2023.01.009>
359. Meuwissen M, Siebes M, Chamuleau SA, van Eck-Smit BLF, Koch KT, de Winter RJ, et al. Hyperemic stenosis resistance index for evaluation of functional coronary lesion severity. *Circulation* 2002;**106**:441–6. <https://doi.org/10.1161/01.cir.0000023041.26199.29>
360. Boerhout CKM, Echavarría-Pinto M, de Waard GA, et al. Impact of hyperemic stenosis resistance (HSR) on long-term outcomes of stable angina. *Eurointervention* 2024;**20**:e699–706. <https://doi.org/10.4244/EIJ-D-23-00713>
361. De Bruyne B, Pijls NHJ, Gallinoro E, Candrea A, Fournier S, Keulards DCJ, et al. Microvascular resistance reserve for assessment of coronary microvascular function: JACC technology corner. *J Am Coll Cardiol* 2021;**78**:1541–9. <https://doi.org/10.1016/j.jacc.2021.08.017>
362. Candrea A, Gallinoro E, Fernandez Peregrina E, Sonck J, Keulards DCJ, van't Veer M, et al. Automation of intracoronary continuous thermodilution for absolute coronary flow and microvascular resistance measurements. *Catheter Cardiovasc Interv* 2022;**100**:199–206. <https://doi.org/10.1002/ccd.30244>
363. De Bruyne B, Belmonte M, Jabbour JR, Curzen N. Invasive functional testing in the cath lab as a routine investigation in INOCA: pros and cons. *EuroIntervention* 2023;**19**:23–5. <https://doi.org/10.4244/EIJ-E-23-00008>
364. de Vos A, Jansen TPJ, van 't Veer M, Dimitriu-Leen A, Konst RE, Elias-Smale S, et al. Microvascular resistance reserve to assess microvascular dysfunction in ANOCA patients. *JACC Cardiovasc Interv* 2023;**16**:470–81. <https://doi.org/10.1016/j.jcin.2022.12.012>
365. Johnson NP, Gould KL. Integrating noninvasive absolute flow, coronary flow reserve, and ischemic thresholds into a comprehensive map of physiological severity. *JACC Cardiovasc Imaging* 2012;**5**:430–40. <https://doi.org/10.1016/j.jcmg.2011.12.014>
366. van de Hoef TP, Echavarría-Pinto M, van Lavieren MA, Meuwissen M, Serruys PWJ, Tijssen JGP, et al. Diagnostic and prognostic implications of coronary flow capacity: a comprehensive cross-modality physiological concept in ischemic heart disease. *JACC Cardiovasc Interv* 2015;**8**:1670–80. <https://doi.org/10.1016/j.jcin.2015.05.032>
367. Murai T, Stegehuis VE, van de Hoef TP, Wijntjens GWM, Hoshino M, Kanaji Y, et al. Coronary flow capacity to identify stenosis associated with coronary flow improvement after revascularization: a combined analysis from DEFINE FLOW and IDEAL. *J Am Heart Assoc* 2020;**9**:e016130. <https://doi.org/10.1161/JAHA.120.016130>
368. de Winter RW, Jukema RA, van Diemen PA, Schumacher SP, Driessen RS, Stuijzand WJ, et al. The impact of coronary revascularization on vessel-specific coronary flow capacity and long-term outcomes: a serial [¹⁵O]H₂O positron emission tomography perfusion imaging study. *Eur Heart J Cardiovasc Imaging* 2022;**23**:743–52. <https://doi.org/10.1093/ehjci/jeab263>
369. Park SJ, Ahn JM, Kang SJ, Yoon S-H, Koo B-K, Lee J-Y, et al. Intravascular ultrasound-derived minimal lumen area criteria for functionally significant left main coronary artery stenosis. *JACC Cardiovasc Interv* 2014;**7**:868–74. <https://doi.org/10.1016/j.jcin.2014.02.015>
370. Ziedes des Plantes AC, Scoccia A, Gijzen F, van Soest G, Daemen J. Intravascular imaging-derived physiology-basic principles and clinical application. *Interv Cardiol Clin* 2023;**12**:83–94. <https://doi.org/10.1016/j.iccl.2022.09.008>
371. Noguchi M, Gkargkoulas F, Matsumura M, Kotinkaduwa LN, Hu X, Usui E, et al. Impact of nonobstructive left main coronary artery atherosclerosis on long-term mortality. *JACC Cardiovasc Interv* 2022;**15**:2206–17. <https://doi.org/10.1016/j.jcin.2022.08.024>
372. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech J-W, van't Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol* 2007;**49**:2105–11. <https://doi.org/10.1016/j.jacc.2007.01.087>
373. Van Belle E, Cosenza A, Baptista SB, Vincent F, Henderson J, Santos L, et al. Usefulness of routine fractional flow reserve for clinical management of coronary artery disease in patients with diabetes. *JAMA Cardiol* 2020;**5**:272–81. <https://doi.org/10.1001/jamacardio.2019.5097>
374. Xu B, Tu S, Qiao S, Qu X, Chen Y, Yang J, et al. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. *J Am Coll Cardiol* 2017;**70**:3077–87. <https://doi.org/10.1016/j.jacc.2017.10.035>
375. Westra J, Andersen BK, Campo G, Matsuo H, Koltowski L, Eftekhari A, et al. Diagnostic performance of in-procedure angiography-derived quantitative flow reserve compared to pressure-derived fractional flow reserve: the FAVOR II Europe-Japan study. *J Am Heart Assoc* 2018;**7**:e009603. <https://doi.org/10.1161/JAHA.118.009603>
376. Johnson NP, Gould KL, De Bruyne B. Autoregulation of coronary blood supply in response to demand: JACC review topic of the week. *J Am Coll Cardiol* 2021;**77**:2335–45. <https://doi.org/10.1016/j.jacc.2021.03.293>
377. Masdjedi K, van Zandvoort LJC, Balbi MM, Gijzen FJH, Ligthart JMR, Rutten MCM, et al. Validation of a three-dimensional quantitative coronary angiography-based software to calculate fractional flow reserve: the FAST study. *EuroIntervention* 2020;**16**:591–9. <https://doi.org/10.4244/eij-d-19-00466>
378. Pijls NH, De Bruyne B, Smith L, Aarnoudse W, Barbato E, Bartunek J, et al. Coronary thermodilution to assess flow reserve: validation in humans. *Circulation* 2002;**105**:2482–6. <https://doi.org/10.1161/01.cir.0000017199.09457.3d>
379. Barbato E, Aarnoudse W, Aengevaeren WR, Werner G, Klaus V, Bojara W, et al. Validation of coronary flow reserve measurements by thermodilution in clinical practice. *Eur Heart J* 2004;**25**:219–23. <https://doi.org/10.1016/j.ehj.2003.11.009>
380. Fearon WF, Balsam LB, Farouque HM, Robbins RC, Fitzgerald PJ, Yock PG, et al. Novel index for invasively assessing the coronary microcirculation. *Circulation* 2003;**107**:3129–32. <https://doi.org/10.1161/01.Cir.0000080700.98607.D1>
381. Fearon WF, Kobayashi Y. Invasive assessment of the coronary microvasculature: the index of microcirculatory resistance. *Circ Cardiovasc Interv* 2017;**10**:e005361. <https://doi.org/10.1161/circinterventions.117.005361>
382. Gallinoro E, Bertolone DT, Fernandez-Peregrina E, Paolisso P, Bermpeis K, Esposito G, et al. Reproducibility of bolus versus continuous thermodilution for assessment of coronary microvascular function in patients with ANOCA. *EuroIntervention* 2023;**19**:e155–66. <https://doi.org/10.4244/eij-d-22-00772>
383. Mejía-Rentería H, Wang L, Chipayo-Gonzales D, van de Hoef TP, Travieso A, Espejo C, et al. Angiography-derived assessment of coronary microcirculatory resistance in patients with suspected myocardial ischemia and non-obstructive coronary arteries. *EuroIntervention* 2023;**18**:e1348–56. <https://doi.org/10.4244/EIJ-D-22-00579>
384. Ford TJ, Ong P, Sechtem U, Beltrame J, Camici PG, Crea F, et al. Assessment of vascular dysfunction in patients without obstructive coronary artery disease: why, how, and when. *JACC Cardiovasc Interv* 2020;**13**:1847–64. <https://doi.org/10.1016/j.jcin.2020.05.052>
385. Radico F, Cicchitti V, Zimarino M, De Caterina R. Angina pectoris and myocardial ischemia in the absence of obstructive coronary artery disease: practical considerations for diagnostic tests. *JACC Cardiovasc Interv* 2014;**7**:453–63. <https://doi.org/10.1016/j.jcin.2014.01.157>
386. Boerhout CKM, Feenstra RGT, Somsen GA, Appelman Y, Ong P, Beijl MAM, et al. Coronary computed tomographic angiography as gatekeeper for new-onset stable angina. *Neth Heart J* 2021;**29**:551–6. <https://doi.org/10.1007/s12471-021-01639-7>
387. Jukema R, Maaniitty T, van Diemen P, Berkhof H, Raijmakers PG, Sprengers R, et al. Warranty period of coronary computed tomography angiography and [¹⁵O]H₂O positron emission tomography in symptomatic patients. *Eur Heart J Cardiovasc Imaging* 2022;**24**:304–11. <https://doi.org/10.1093/ehjci/jeac258>
388. Haberkorn SM, Haberkorn SI, Bonner F, Kelm M, Hopkin G, Petersen SE. Vasodilator myocardial perfusion cardiac magnetic resonance imaging is superior to dobutamine stress echocardiography in the detection of relevant coronary artery stenosis: a systematic review and meta-analysis on their diagnostic accuracy. *Front Cardiovasc Med* 2021;**8**:630846. <https://doi.org/10.3389/fcvm.2021.630846>
389. van der Molen AJ, Reimer P, Dekkers IA, Bongartz G, Bellin M-F, Bertolotto M, et al. Post-contrast acute kidney injury—Part 1: definition, clinical features, incidence, role of contrast medium and risk factors : recommendations for updated ESUR Contrast

- Medium Safety Committee guidelines. *Eur Radiol* 2018;**28**:2845–55. <https://doi.org/10.1007/s00330-017-5246-5>
390. Bittencourt MS, Hulthen EA, Murthy VL, Cheezum M, Rochitte CE, Carli MFD, et al. Clinical outcomes after evaluation of stable chest pain by coronary computed tomographic angiography versus usual care: a meta-analysis. *Circ Cardiovasc Imaging* 2016;**9**: e004419. <https://doi.org/10.1161/CIRCIMAGING.115.004419>
 391. Reis JF, Ramos RB, Marques H, Daniel PM, Aguiar SR, Morais LA, et al. Cardiac computed tomographic angiography after abnormal ischemia test as a gatekeeper to invasive coronary angiography. *Int J Cardiovasc Imaging* 2022;**38**:883–93. <https://doi.org/10.1007/s10554-021-02426-6>
 392. Maaniitty T, Stenstrom I, Bax JJ, Uusitalo V, Ukkonen H, Kajander S, et al. Prognostic value of coronary CT angiography with selective PET perfusion imaging in coronary artery disease. *JACC Cardiovasc Imaging* 2017;**10**:1361–70. <https://doi.org/10.1016/j.jcmg.2016.10.025>
 393. Pezel T, Hovasse T, Sanguineti F, Untersee T, Champagne S, et al. Prognostic value of stress CMR in symptomatic patients with coronary stenosis on CCTA. *JACC Cardiovasc Imaging* 2022;**15**:1408–22. <https://doi.org/10.1016/j.jcmg.2022.03.008>
 394. Winther S, Andersen IT, Gormsen LC, Steffensen FH, Nielsen LH, Grove EL, et al. Prognostic value of myocardial perfusion imaging after first-line coronary computed tomography angiography: a multi-center cohort study. *J Cardiovasc Comput Tomogr* 2022;**16**:34–40. <https://doi.org/10.1016/j.jcct.2021.08.001>
 395. Min JK, Leipsic J, Pencina MJ, Berman DS, Koo B-K, van Mieghem C, et al. Diagnostic accuracy of fractional flow reserve from anatomical CT angiography. *JAMA* 2012;**308**: 1237–45. <https://doi.org/10.1001/2012.jama.11274>
 396. Douglas PS, De Bruyne B, Pontone G, Patel MR, Norgaard BL, Byrne RA, et al. 1-Year outcomes of FFRCT-guided care in patients with suspected coronary disease: the PLATFORM study. *J Am Coll Cardiol* 2016;**68**:435–45. <https://doi.org/10.1016/j.jacc.2016.05.057>
 397. Fairbairn TA, Nieman K, Akasaka T, Norgaard BL, Berman DS, Raff G, et al. Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: lessons from the ADVANCE registry. *Eur Heart J* 2018;**39**:3701–11. <https://doi.org/10.1093/eurheartj/ehy530>
 398. Andreini D, Modolo R, Katagiri Y, Mushtaq S, Sonck J, Collet C, et al. Impact of fractional flow reserve derived from coronary computed tomography angiography on heart team treatment decision-making in patients with multivessel coronary artery disease: insights from the SYNTAX III REVOLUTION trial. *Circ Cardiovasc Interv* 2019;**12**: e007607. <https://doi.org/10.1161/CIRCINTERVENTIONS.118.007607>
 399. Patel MR, Norgaard BL, Fairbairn TA, Nieman K, Akasaka T, Berman DS, et al. 1-year impact on medical practice and clinical outcomes of FFR(CT): the ADVANCE registry. *JACC Cardiovasc Imaging* 2020;**13**:97–105. <https://doi.org/10.1016/j.jcmg.2019.03.003>
 400. Riedl KA, Jensen JM, Ko BS, Leipsic J, Grove EL, Mathiassen ON, et al. Coronary CT angiography derived FFR in patients with left main disease. *Int J Cardiovasc Imaging* 2021;**37**:3299–308. <https://doi.org/10.1007/s10554-021-02371-4>
 401. Norgaard BL, Gaur S, Fairbairn TA, Douglas PS, Jensen JM, Patel MR, et al. Prognostic value of coronary computed tomography angiography derived fractional flow reserve: a systematic review and meta-analysis. *Heart* 2022;**108**:194–202. <https://doi.org/10.1136/heartjnl-2021-319773>
 402. Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet* 2018;**391**:31–40. [https://doi.org/10.1016/S0140-6736\(17\)32714-9](https://doi.org/10.1016/S0140-6736(17)32714-9)
 403. Foley M, Rajkumar CA, Shun-Shin M, Ganesanathan S, Seligman H, Howard J, et al. Achieving optimal medical therapy: insights from the ORBITA trial. *J Am Heart Assoc* 2021;**10**:e017381. <https://doi.org/10.1161/JAHA.120.017381>
 404. Mesnier J, Ducrocq G, Danchin N, Ferrari R, Ford I, Tardif J-C, et al. International observational analysis of evolution and outcomes of chronic stable angina: the multi-national CLARIFY study. *Circulation* 2021;**144**:512–23. <https://doi.org/10.1161/CIRCULATIONAHA.121.054567>
 405. Task Force Members; Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC Guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**:2949–3003. <https://doi.org/10.1093/eurheartj/eht296>
 406. Rapsomaniki E, Shah A, Perel P, Denaxas S, George J, Nicholas O, et al. Prognostic models for stable coronary artery disease based on electronic health record cohort of 102 023 patients. *Eur Heart J* 2014;**35**:844–52. <https://doi.org/10.1093/eurheartj/ehz533>
 407. Barbero U, D'Ascenzo F, Nijhoff F, Moretti C, Biondi-Zoccai G, Mennuni M, et al. Assessing risk in patients with stable coronary disease: when should we intensify care and follow-up? Results from a meta-analysis of observational studies of the COURAGE and FAME era. *Scientifica (Cairo)* 2016;**2016**:3769152. <https://doi.org/10.1155/2016/3769152>
 408. Sorbets E, Fox KM, Elbez Y, Danchin N, Dorian P, Ferrari R, et al. Long-term outcomes of chronic coronary syndrome worldwide: insights from the international CLARIFY registry. *Eur Heart J* 2020;**41**:347–56. <https://doi.org/10.1093/eurheartj/ehz660>
 409. Liu Y, Song J, Wang W, Zhang K, Qi Y, Yang J, et al. Association of ejection fraction with mortality and cardiovascular events in patients with coronary artery disease. *ESC Heart Fail* 2022;**9**:3461–8. <https://doi.org/10.1002/ehf2.14063>
 410. Thuijs D, Milojevic M, Stone GW, Puskas JD, Serruys PW, Sabik JF, et al. Impact of left ventricular ejection fraction on clinical outcomes after left main coronary artery revascularization: results from the randomized EXCEL trial. *Eur J Heart Fail* 2020;**22**:871–9. <https://doi.org/10.1002/ehf.1681>
 411. Abidov A, Rozanski A, Hachamovitch R, Hayes SW, Aboul-Enein F, Cohen I, et al. Prognostic significance of dyspnea in patients referred for cardiac stress testing. *N Engl J Med* 2005;**353**:1889–98. <https://doi.org/10.1056/NEJMoa042741>
 412. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002;**346**:793–801. <https://doi.org/10.1056/NEJMoa011858>
 413. Sipilä K, Tikkakoski A, Alanko S, Haarala A, Hernesniemi J, Lyytikäinen L-P, et al. Combination of low blood pressure response, low exercise capacity and slow heart rate recovery during an exercise test significantly increases mortality risk. *Ann Med* 2019;**51**:390–6. <https://doi.org/10.1080/07853890.2019.1684550>
 414. Salokari E, Laukkanen JA, Lehtimäki T, Kurl S, Kunutsor S, Zaccardi F, et al. The Duke treadmill score with bicycle ergometer: exercise capacity is the most important predictor of cardiovascular mortality. *Eur J Prev Cardiol* 2019;**26**:199–207. <https://doi.org/10.1177/2047487318804618>
 415. Williams MC, Kwicinski J, Doris M, McElhinney P, D'Souza MS, Cadet S, et al. Low-attenuation noncalcified plaque on coronary computed tomography angiography predicts myocardial infarction: results from the multicenter SCOT-HEART trial (Scottish Computed Tomography of the HEART). *Circulation* 2020;**141**:1452–62. <https://doi.org/10.1161/CIRCULATIONAHA.119.044720>
 416. Mortensen MB, Dzaye O, Steffensen FH, Botker HE, Jensen JM, Rønnow Sand NP, et al. Impact of plaque burden versus stenosis on ischemic events in patients with coronary atherosclerosis. *J Am Coll Cardiol* 2020;**76**:2803–13. <https://doi.org/10.1016/j.jacc.2020.10.021>
 417. van Rosendaal AR, Bax AM, Smit JM, van den Hoogen IJ, Ma X, Al'Aref S, et al. Clinical risk factors and atherosclerotic plaque extent to define risk for major events in patients without obstructive coronary artery disease: the long-term coronary computed tomography angiography CONFIRM registry. *Eur Heart J Cardiovasc Imaging* 2020;**21**: 479–88. <https://doi.org/10.1093/ehjci/jez322>
 418. Sharir T, Germano G, Kang X, Lewin HC, Miranda R, Cohen I, et al. Prediction of myocardial infarction versus cardiac death by gated myocardial perfusion SPECT: risk stratification by the amount of stress-induced ischemia and the poststress ejection fraction. *J Nucl Med* 2001;**42**:831–7.
 419. Hachamovitch R, Rozanski A, Shaw LJ, Stone GW, Thomson LEJ, Friedman JD, et al. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J* 2011;**32**:1012–24. <https://doi.org/10.1093/eurheartj/ehq500>
 420. Lipinski MJ, McVey CM, Berger JS, Kramer CM, Salerno M. Prognostic value of stress cardiac magnetic resonance imaging in patients with known or suspected coronary artery disease: a systematic review and meta-analysis. *J Am Coll Cardiol* 2013;**62**:826–38. <https://doi.org/10.1016/j.jacc.2013.03.080>
 421. Patel KK, Spertus JA, Chan PS, Sperry BW, Thompson RC, Al Badarin F, et al. Extent of myocardial ischemia on positron emission tomography and survival benefit with early revascularization. *J Am Coll Cardiol* 2019;**74**:1645–54. <https://doi.org/10.1016/j.jacc.2019.07.055>
 422. Azadani PN, Miller RJH, Sharir T, Diniz MA, Hu L-H, Otaki Y, et al. Impact of early revascularization on major adverse cardiovascular events in relation to automatically quantified ischemia. *JACC Cardiovasc Imaging* 2021;**14**:644–53. <https://doi.org/10.1016/j.jcmg.2020.05.039>
 423. Sharir T, Hollander I, Hemo B, Tsamir J, Yefremov N, Bojko A, et al. Survival benefit of coronary revascularization after myocardial perfusion SPECT: the role of ischemia. *J Nucl Cardiol* 2021;**28**:1676–87. <https://doi.org/10.1007/s12350-019-01932-4>
 424. Ciampi Q, Zagatina A, Cortigiani L, Wierzbowska-Drabik K, Kasprzak JD, Haberk M, et al. Prognostic value of stress echocardiography assessed by the ABCDE protocol. *Eur Heart J* 2021;**42**:3869–78. <https://doi.org/10.1093/eurheartj/ehab493>
 425. Picano E, Pierard L, Peteiro J, Djordjevic-Dikic A, Sade LE, Cortigiani L, et al. The clinical use of stress echocardiography in chronic coronary syndromes and beyond coronary artery disease: a clinical consensus statement from the European Association of Cardiovascular Imaging of the ESC. *Eur Heart J Cardiovasc Imaging* 2023;**25**:e65–90. <https://doi.org/10.1093/ehjci/ead250>
 426. Mancini GBJ, Hartigan PM, Shaw LJ, Berman DS, Hayes SW, Bates ER, et al. Predicting outcome in the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation): coronary anatomy versus ischemia. *JACC Cardiovasc Interv* 2014;**7**:195–201. <https://doi.org/10.1016/j.jcin.2013.10.017>
 427. Weintraub WS, Hartigan PM, Mancini GBJ, Teo KK, Maron DJ, Spertus JA, et al. Effect of coronary anatomy and myocardial ischemia on long-term survival in patients with stable ischemic heart disease. *Circ Cardiovasc Qual Outcomes* 2019;**12**:e005079. <https://doi.org/10.1161/circoutcomes.118.005079>

428. Al-Mallah MH, Dilsizian V. The impact of revascularization on mortality: a debate on patient selection bias vs entry bias. *J Am Coll Cardiol* 2022;**80**:216–8. <https://doi.org/10.1016/j.jacc.2022.04.051>
429. Adjedj J, De Bruyne B, Floré V, Di Gioia G, Ferrara A, Pellicano M, et al. Significance of intermediate values of fractional flow reserve in patients with coronary artery disease. *Circulation* 2016;**133**:502–8. <https://doi.org/10.1161/circulationaha.115.018747>
430. Fournier S, Collet C, Xaplanteris P, Zimmermann FM, Toth GG, Tonino PAL, et al. Global fractional flow reserve value predicts 5-year outcomes in patients with coronary atherosclerosis but without ischemia. *J Am Heart Assoc* 2020;**9**:e017729. <https://doi.org/10.1161/jaha.120.017729>
431. Lee JM, Koo BK, Shin ES, Nam C-W, Doh J-H, Hwang D, et al. Clinical implications of three-vessel fractional flow reserve measurement in patients with coronary artery disease. *Eur Heart J* 2018;**39**:945–51. <https://doi.org/10.1093/eurheartj/ehx458>
432. Collet C, Miyazaki Y, Ryan N, Asano T, Tenekcioglu E, Sonck J, et al. Fractional flow reserve derived from computed tomographic angiography in patients with multivessel CAD. *J Am Coll Cardiol* 2018;**71**:2756–69. <https://doi.org/10.1016/j.jacc.2018.02.053>
433. Asano T, Katagiri Y, Chang CC, Kogame N, Chichareon P, Takahashi K, et al. Angiography-derived fractional flow reserve in the SYNTAX II trial: feasibility, diagnostic performance of quantitative flow ratio, and clinical prognostic value of functional SYNTAX score derived from quantitative flow ratio in patients with 3-vessel disease. *JACC Cardiovasc Interv* 2019;**12**:259–70. <https://doi.org/10.1016/j.jcin.2018.09.023>
434. Zhang R, Song C, Guan C, Liu Q, Wang C, Xie L, et al. Prognostic value of quantitative flow ratio based functional SYNTAX score in patients with left main or multivessel coronary artery disease. *Circ Cardiovasc Interv* 2020;**13**:e009155. <https://doi.org/10.1161/circinterventions.120.009155>
435. Shaw LJ, Berman DS, Picard MH, Friedrich MG, Kwong RY, Stone GW, et al. Comparative definitions for moderate-severe ischemia in stress nuclear, echocardiography, and magnetic resonance imaging. *JACC Cardiovasc Imaging* 2014;**7**:593–604. <https://doi.org/10.1016/j.jcmg.2013.10.021>
436. Anderson L, Brown JP, Clark AM, Dalal H, Rossau HKK, Bridges C, et al. Patient education in the management of coronary heart disease. *Cochrane Database Syst Rev* 2017;**6**:CD008895. <https://doi.org/10.1002/14651858.CD008895.pub3>
437. Collado-Mateo D, Lavin-Perez AM, Penacoba C, Del Coso J, Leyton-Román M, Luque-Casado A, et al. Key factors associated with adherence to physical exercise in patients with chronic diseases and older adults: an umbrella review. *Int J Environ Res Public Health* 2021;**18**:2023. <https://doi.org/10.3390/ijerph18042023>
438. Kohler AK, Jaarsma T, Tingstrom P, Nilsson S. The effect of problem-based learning after coronary heart disease—a randomised study in primary health care (COR-PRIM). *BMC Cardiovasc Disord* 2020;**20**:370. <https://doi.org/10.1186/s12872-020-01647-2>
439. Alzaman N, Wartak SA, Friderici J, Rothberg MB. Effect of patients' awareness of CVD risk factors on health-related behaviors. *South Med J* 2013;**106**:606–9. <https://doi.org/10.1097/SMJ.0000000000000013>
440. Riegel B, Jaarsma T, Stromberg A. A middle-range theory of self-care of chronic illness. *ANS Adv Nurs Sci* 2012;**35**:194–204. <https://doi.org/10.1097/ANS.0b013e318261b1ba>
441. Astin F, Lucock M, Jennings CS. Heart and mind: behavioural cardiology demystified for the clinician. *Heart* 2019;**105**:881–8. <https://doi.org/10.1136/heartjnl-2016-310750>
442. Sheeran P, Harris PR, Epton T. Does heightening risk appraisals change people's intentions and behavior? A meta-analysis of experimental studies. *Psychol Bull* 2014;**140**:511–43. <https://doi.org/10.1037/a0033065>
443. Zwack CC, Smith C, Poulsen V, Raffoul N, Redfern J. Information needs and communication strategies for people with coronary heart disease: a scoping review. *Int J Environ Res Public Health* 2023;**20**:1723. <https://doi.org/10.3390/ijerph20031723>
444. Navar AM, Wang TY, Mi X, Robinson JG, Virani SS, Roger VL, et al. Influence of cardiovascular risk communication tools and presentation formats on patient perceptions and preferences. *JAMA Cardiol* 2018;**3**:1192–9. <https://doi.org/10.1001/jamacardio.2018.3680>
445. Whitmore K, Zhou Z, Chapman N, Huynh Q, Magnussen CG, Sharman JE, et al. Impact of patient visualization of cardiovascular images on modification of cardiovascular risk factors: systematic review and meta-analysis. *JACC Cardiovasc Imaging* 2023;**16**:1069–81. <https://doi.org/10.1016/j.jcmg.2023.03.007>
446. Rossello X, Dorresteijn JA, Janssen A, Lambrinou E, Scherrenberg M, Bonnefoy-Cudraz E, et al. Risk prediction tools in cardiovascular disease prevention: a report from the ESC Prevention of CVD Programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). *Eur J Prev Cardiol* 2019;**26**:1534–44. <https://doi.org/10.1177/2047487319846715>
447. Critchley J, Capewell S. Smoking cessation for the secondary prevention of coronary heart disease. *Cochrane Database Syst Rev* 2004;CD003041. <https://doi.org/10.1002/14651858.CD003041.pub2>
448. Barth J, Jacob T, Daha I, Critchley JA. Psychosocial interventions for smoking cessation in patients with coronary heart disease. *Cochrane Database Syst Rev* 2015;**7**:CD006886. <https://doi.org/10.1002/14651858.CD006886.pub2>
449. Prochaska JJ, Benowitz NL. The past, present, and future of nicotine addiction therapy. *Annu Rev Med* 2016;**67**:467–86. <https://doi.org/10.1146/annurev-med-111314-033712>
450. Suissa K, Lariviere J, Eisenberg MJ, Eberg M, Gore GC, Grad R, et al. Efficacy and safety of smoking cessation interventions in patients with cardiovascular disease: a network meta-analysis of randomized controlled trials. *Circ Cardiovasc Qual Outcomes* 2017;**10**:e002458. <https://doi.org/10.1161/CIRCOUTCOMES.115.002458>
451. Lindson N, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2019;**4**:CD013308. <https://doi.org/10.1002/14651858.CD013308>
452. Mills EJ, Thorlund K, Eapen S, Wu P, Prochaska JJ. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. *Circulation* 2014;**129**:28–41. <https://doi.org/10.1161/CIRCULATIONAHA.113.003961>
453. Kavousi M, Pisinger C, Barthelemy JC, De Smedt D, Koskinas K, Marques-Vidal P, et al. Electronic cigarettes and health with special focus on cardiovascular effects: position paper of the European Association of Preventive Cardiology (EAPC). *Eur J Prev Cardiol* 2020;**28**:1552–66. <https://doi.org/10.1177/2047487320941993>
454. Qasim H, Karim ZA, Rivera JO, Khasawneh FT, Alshbool FZ. Impact of electronic cigarettes on the cardiovascular system. *J Am Heart Assoc* 2017;**6**:e006353. <https://doi.org/10.1161/JAHA.117.006353>
455. Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev* 2020;**10**:CD010216. <https://doi.org/10.1002/14651858.CD010216.pub4>
456. Abu Jad AA, Ravanavena A, Ravindra C, Igweonu-Nwakile EO, Ali S, Paul S, et al. Adverse effects of cannabinoids and tobacco consumption on the cardiovascular system: a systematic review. *Cureus* 2022;**14**:e29208. <https://doi.org/10.7759/cureus.29208>
457. Schwartz BG, Rezkalla S, Kloner RA. Cardiovascular effects of cocaine. *Circulation* 2010;**122**:2558–69. <https://doi.org/10.1161/CIRCULATIONAHA.110.940569>
458. Singleton JH, Abner EL, Akpunonu PD, Kucharska-Newton AM. Association of non-opioid use and cardiovascular diseases: a scoping review of the literature. *J Am Heart Assoc* 2021;**10**:e021260. <https://doi.org/10.1161/JAHA.121.021260>
459. DeFilippis EM, Bajaj NS, Singh A, Malloy R, Givertz MM, Blankstein R, et al. Marijuana use in patients with cardiovascular disease: JACC review topic of the week. *J Am Coll Cardiol* 2020;**75**:320–32. <https://doi.org/10.1016/j.jacc.2019.11.025>
460. McNeely J, Cleland CM, Strauss SM, Palamar JJ, Rotrosen J, Saitz R. Validation of self-administered single-item screening questions (SISQS) for unhealthy alcohol and drug use in primary care patients. *J Gen Intern Med* 2015;**30**:1757–64. <https://doi.org/10.1007/s11606-015-3391-6>
461. Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, et al. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. *JAMA Cardiol* 2018;**3**:280–7. <https://doi.org/10.1001/jamacardio.2018.0022>
462. Pack QR, Rodriguez-Escudero JP, Thomas RJ, Ades PA, West CP, Somers VK, et al. The prognostic importance of weight loss in coronary artery disease: a systematic review and meta-analysis. *Mayo Clin Proc* 2014;**89**:1368–77. <https://doi.org/10.1016/j.mayocp.2014.04.033>
463. Strelitz J, Lawlor ER, Wu Y, Estlin A, Nandakumar G, Ahern AL, et al. Association between weight change and incidence of cardiovascular disease events and mortality among adults with type 2 diabetes: a systematic review of observational studies and behavioural intervention trials. *Diabetologia* 2022;**65**:424–39. <https://doi.org/10.1007/s00125-021-05605-1>
464. Rubino DM, Greenway FL, Khalid U, O'Neil PM, Rosenstock J, Sørrig R, et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. *JAMA* 2022;**327**:138–50. <https://doi.org/10.1001/jama.2021.23619>
465. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med* 2023;**389**:2221–32. <https://doi.org/10.1056/NEJMoa2307563>
466. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* 2022;**387**:205–16. <https://doi.org/10.1056/NEJMoa2206038>
467. Garvey WT, Frias JP, Jastreboff AM, le Roux CW, Sattar N, Aizenberg D, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2023;**402**:613–26. [https://doi.org/10.1016/S0140-6736\(23\)01200-X](https://doi.org/10.1016/S0140-6736(23)01200-X)
468. Lopez-Jimenez F, Bhatia S, Collazo-Clavell ML, Sarr MG, Somers VK. Safety and efficacy of bariatric surgery in patients with coronary artery disease. *Mayo Clin Proc* 2005;**80**:1157–62. <https://doi.org/10.4065/80.9.1157>
469. De Bacquer D, Jennings CS, Mirrakhimov E, Lovic D, Bruthans J, De Smedt D, et al. Potential for optimizing management of obesity in the secondary prevention of coronary heart disease. *Eur Heart J Qual Care Clin Outcomes* 2022;**8**:568–76. <https://doi.org/10.1093/ehjqcco/qcab043>
470. Wood AM, Kaptoge S, Butterworth AS, Willeit P, Warnakula S, Bolton T, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet* 2018;**391**:1513–23. [https://doi.org/10.1016/S0140-6736\(18\)30134-X](https://doi.org/10.1016/S0140-6736(18)30134-X)

471. Biddinger KJ, Emdin CA, Haas ME, Wang M, Hindy G, Ellinor PT, et al. Association of habitual alcohol intake with risk of cardiovascular disease. *JAMA Netw Open* 2022;**5**:e223849. <https://doi.org/10.1001/jamanetworkopen.2022.3849>
472. Tully PJ, Ang SY, Lee EJ, Bendig E, Bauereiß N, Bengel J, et al. Psychological and pharmacological interventions for depression in patients with coronary artery disease. *Cochrane Database Syst Rev* 2021;**12**:CD008012. <https://doi.org/10.1002/14651858.CD008012.pub4>
473. Kraus WE, Powell KE, Haskell WL, Janz KF, Campbell WW, Jakicic JM, et al. Physical activity, all-cause and cardiovascular mortality, and cardiovascular disease. *Med Sci Sports Exerc* 2019;**51**:1270–81. <https://doi.org/10.1249/MSS.0000000000001939>
474. Hupin D, Roche F, Gremeaux V, Chatard J-C, Oriol M, Gaspoz J-M, et al. Even a low-dose of moderate-to-vigorous physical activity reduces mortality by 22% in adults aged ≥ 60 years: a systematic review and meta-analysis. *Br J Sports Med* 2015;**49**:1262–7. <https://doi.org/10.1136/bjsports-2014-094306>
475. Arem H, Moore SC, Patel A, Hartge P, Berrington de Gonzalez A, Viswanathan K, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. *JAMA Intern Med* 2015;**175**:959–67. <https://doi.org/10.1001/jamainternmed.2015.0533>
476. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med* 2020;**54**:1451–62. <https://doi.org/10.1136/bjsports-2020-102955>
477. O'Donovan G, Lee IM, Hamer M, Stamatakis E. Association of “weekend warrior” and other leisure time physical activity patterns with risks for all-cause, cardiovascular disease, and cancer mortality. *JAMA Intern Med* 2017;**177**:335–42. <https://doi.org/10.1001/jamainternmed.2016.8014>
478. Jakicic JM, Kraus WE, Powell KE, Campbell WW, Janz KF, Troiano RP, et al. Association between bout duration of physical activity and health: systematic review. *Med Sci Sports Exerc* 2019;**51**:1213–9. <https://doi.org/10.1249/MSS.0000000000001933>
479. Ekelund U, Tarp J, Steene-Johannessen J, Hansen BH, Jefferis B, Fagerland MW, et al. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. *BMJ* 2019;**366**:l4570. <https://doi.org/10.1136/bmj.l4570>
480. Anderson L, Thompson DR, Oldridge N, Zwisler A-D, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2016;**1**:CD001800. <https://doi.org/10.1002/14651858.CD001800.pub3>
481. Santiago de Araujo Pio C, Marzolini S, Pakosh M, Grace SL. Effect of cardiac rehabilitation dose on mortality and morbidity: a systematic review and meta-regression analysis. *Mayo Clin Proc* 2017;**92**:1644–59. <https://doi.org/10.1016/j.mayocp.2017.07.019>
482. Salzwedel A, Jensen K, Rauch B, Doherty P, Metzendorf M-I, Hackbusch M, et al. Effectiveness of comprehensive cardiac rehabilitation in coronary artery disease patients treated according to contemporary evidence based medicine: update of the Cardiac Rehabilitation Outcome Study (CROS-II). *Eur J Prev Cardiol* 2020;**27**:1756–74. <https://doi.org/10.1177/2047487320905719>
483. Dibben G, Faulkner J, Oldridge N, Rees K, Thompson DR, Zwisler A-D, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2021;**11**:CD001800. <https://doi.org/10.1002/14651858.CD001800.pub4>
484. Ambrosetti M, Abreu A, Corra U, Davos CH, Hansen D, Frederix I, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: from knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol* 2020;**28**:460–95. <https://doi.org/10.1177/2047487320913379>
485. Hansen D, Abreu A, Ambrosetti M, Cornelissen V, Gevaert A, Kemps H, et al. Exercise intensity assessment and prescription in cardiovascular rehabilitation and beyond: why and how: a position statement from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol* 2022;**29**:230–45. <https://doi.org/10.1093/eurjpc/zwab007>
486. Hansen D, Niebauer J, Cornelissen V, Barna O, Neunh userer D, Stettler C, et al. Exercise prescription in patients with different combinations of cardiovascular disease risk factors: a consensus statement from the EXPERT working group. *Sports Med* 2018;**48**:1781–97. <https://doi.org/10.1007/s40279-018-0930-4>
487. Abell B, Glasziou P, Hoffmann T. The contribution of individual exercise training components to clinical outcomes in randomised controlled trials of cardiac rehabilitation: a systematic review and meta-regression. *Sports Med Open* 2017;**3**:19. <https://doi.org/10.1186/s40798-017-0086-z>
488. Sanchez-Delgado JC, Camargo Sepulveda DC, Cardona Zapata A, Franco Pico MY, Santos Blanco LM, J c me Hortu a AM, et al. The effects of maintenance cardiac rehabilitation: a systematic review. *J Cardiopulm Rehabil Prev* 2020;**40**:224–44. <https://doi.org/10.1097/HCR.0000000000000520>
489. Piepoli MF, Corra U, Dendale P, Frederix I, Prescott E, Schmid JP, et al. Challenges in secondary prevention after acute myocardial infarction: a call for action. *Eur J Prev Cardiol* 2016;**23**:1994–2006. <https://doi.org/10.1177/2047487316663873>
490. Gomes-Neto M, Duraes AR, Reis H, Neves VR, Martinez BP, Carvalho VO. High-intensity interval training versus moderate-intensity continuous training on exercise capacity and quality of life in patients with coronary artery disease: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2017;**24**:1696–707. <https://doi.org/10.1177/2047487317728370>
491. Franssen WMA, Franssen G, Spaas J, Solmi F, Eijnde BO. Can consumer wearable activity tracker-based interventions improve physical activity and cardiometabolic health in patients with chronic diseases? A systematic review and meta-analysis of randomised controlled trials. *Int J Behav Nutr Phys Act* 2020;**17**:57. <https://doi.org/10.1186/s12966-020-00955-2>
492. Santiago de Araujo Pio C, Chaves GS, Davies P, Taylor RS, Grace SL. Interventions to promote patient utilisation of cardiac rehabilitation. *Cochrane Database Syst Rev* 2019;**2**:CD007131. <https://doi.org/10.1002/14651858.CD007131.pub4>
493. Anderson L, Sharp GA, Norton RJ, Dalal H, Dean SG, Jolly K, et al. Home-based versus centre-based cardiac rehabilitation. *Cochrane Database Syst Rev* 2017;**6**:CD007130. <https://doi.org/10.1002/14651858.CD007130.pub4>
494. Jin K, Khonsari S, Gallagher R, Gallagher P, Clark AM, Freedman B, et al. Telehealth interventions for the secondary prevention of coronary heart disease: a systematic review and meta-analysis. *Eur J Cardiovasc Nurs* 2019;**18**:260–71. <https://doi.org/10.1177/1474515119826510>
495. Cruz-Cobo C, Bernal-Jimenez MA, Vazquez-Garcia R, Santi-Cano MJ. Effectiveness of mHealth interventions in the control of lifestyle and cardiovascular risk factors in patients after a coronary event: systematic review and meta-analysis. *JMIR Mhealth Uhealth* 2022;**10**:e39593. <https://doi.org/10.2196/39593>
496. Hamilton SJ, Mills B, Birch EM, Thompson SC. Smartphones in the secondary prevention of cardiovascular disease: a systematic review. *BMC Cardiovasc Disord* 2018;**1**:25. <https://doi.org/10.1186/s12872-018-0764-x>
497. Kissel CK, Nikolettou D. Cardiac rehabilitation and exercise prescription in symptomatic patients with non-obstructive coronary artery disease—a systematic review. *Curr Treat Options Cardiovasc Med* 2018;**20**:78. <https://doi.org/10.1007/s11936-018-0667-2>
498. Keteyian SJ, Brawner CA, Savage PD, Ehrman JK, Schairer J, Divine G, et al. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. *Am Heart J* 2008;**156**:292–300. <https://doi.org/10.1016/j.ahj.2008.03.017>
499. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. *JAMA* 2003;**290**:86–97. <https://doi.org/10.1001/jama.290.1.86>
500. Held C, Hadziosmanovic N, Aylward PE, Hagstr m E, Hochman JS, Stewart RAH, et al. Body mass index and association with cardiovascular outcomes in patients with stable coronary heart disease—a STABILITY substudy. *J Am Heart Assoc* 2022;**11**:e023667. <https://doi.org/10.1161/JAHA.121.023667>
501. Stewart RA, Wallentin L, Benatar J, Danchin N, Hagstr m E, Held C, et al. Dietary patterns and the risk of major adverse cardiovascular events in a global study of high-risk patients with stable coronary heart disease. *Eur Heart J* 2016;**37**:1993–2001. <https://doi.org/10.1093/eurheartj/ehw125>
502. Stewart RAH, Held C, Hadziosmanovic N, Armstrong PW, Cannon CP, Granger CB, et al. Physical activity and mortality in patients with stable coronary heart disease. *J Am Coll Cardiol* 2017;**70**:1689–700. <https://doi.org/10.1016/j.jacc.2017.08.017>
503. Artinian NT, Fletcher GF, Mozaffarian D, Kris-Etherton P, Van Horn L, Lichtenstein AH, et al. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. *Circulation* 2010;**122**:406–41. <https://doi.org/10.1161/CIR.0b013e3181e8edf1>
504. Ferrari R, Pavaasini R, Camici PG, Crea F, Danchin N, Pinto F, et al. Anti-anginal drugs-beliefs and evidence: systematic review covering 50 years of medical treatment. *Eur Heart J* 2019;**40**:190–4. <https://doi.org/10.1093/eurheartj/ehy504>
505. Belsey J, Savelieva I, Mugelli A, Camm AJ. Relative efficacy of antianginal drugs used as add-on therapy in patients with stable angina: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2015;**22**:837–48. <https://doi.org/10.1177/2047487314533217>
506. Pavaasini R, Camici PG, Crea F, Danchin N, Fox K, Manolis AJ, et al. Anti-anginal drugs: systematic review and clinical implications. *Int J Cardiol* 2019;**283**:55–63. <https://doi.org/10.1016/j.ijcard.2018.12.008>
507. Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K; INITIATIVE Investigators. Efficacy of ivabradine, a new selective I_f inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J* 2005;**26**:2529–36. <https://doi.org/10.1093/eurheartj/ehi586>
508. Ruzyllo W, Tendera M, Ford I, Fox KM. Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial. *Drugs* 2007;**67**:393–405. <https://doi.org/10.2165/00003495-200767030-00005>
509. Fox K, Ford I, Steg PG, Tardif J-C, Tendera M, Ferrari R, et al. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med* 2014;**371**:1091–9. <https://doi.org/10.1056/NEJMoa1406430>
510. Sorbets E, Steg PG, Young R, Danchin N, Greenlaw N, Ford I, et al. Beta-blockers, calcium antagonists, and mortality in stable coronary artery disease: an international cohort study. *Eur Heart J* 2019;**40**:1399–407. <https://doi.org/10.1093/eurheartj/ehy811>
511. Steg PG, Greenlaw N, Tendera M, Tardif J-C, Ferrari R, Al-Zaibag M, et al. Prevalence of anginal symptoms and myocardial ischemia and their effect on clinical outcomes in outpatients with stable coronary artery disease: data from the International Observational CLARIFY Registry. *JAMA Intern Med* 2014;**174**:1651–9. <https://doi.org/10.1001/jamainternmed.2014.3773>
512. Ford TJ, Berry C. Angina: contemporary diagnosis and management. *Heart* 2020;**106**:387–98. <https://doi.org/10.1136/heartjnl-2018-314661>

513. Ferrari R, Camici PG, Crea F, Danchin N, Fox K, Maggioni AP, et al. Expert consensus document: a 'diamond' approach to personalized treatment of angina. *Nat Rev Cardiol* 2018;**15**:120–32. <https://doi.org/10.1038/nrcardio.2017.131>
514. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012;**60**:e44–164. <https://doi.org/10.1016/j.jacc.2012.07.013>
515. Manolis AJ, Boden WE, Collins P, Dechend R, Kallistratos MS, Lopez Sendon J, et al. State of the art approach to managing angina and ischemia: tailoring treatment to the evidence. *Eur J Intern Med* 2021;**92**:40–7. <https://doi.org/10.1016/j.ejim.2021.08.003>
516. Bertero E, Heusch G, Munzel T, Maack C. A pathophysiological compass to personalize antianginal drug treatment. *Nat Rev Cardiol* 2021;**18**:838–52. <https://doi.org/10.1038/s41569-021-00573-w>
517. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetière P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005;**352**:1951–8. <https://doi.org/10.1056/NEJMoa043012>
518. Shu DF, Dong BR, Lin XF, Wu TX, Liu GJ. Long-term beta blockers for stable angina: systematic review and meta-analysis. *Eur J Prev Cardiol* 2012;**19**:330–41. <https://doi.org/10.1177/1741826711409325>
519. Freemantle N, Cleland J, Young P, Mason J, Harrison J. β Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999;**318**:1730–7. <https://doi.org/10.1136/bmj.318.7200.1730>
520. Martínez-Milla J, Raposeiras-Roubin S, Pascual-Figal DA, Ibáñez B. Role of beta-blockers in cardiovascular disease in 2019. *Rev Esp Cardiol (Engl Ed)* 2019;**72**:844–52. <https://doi.org/10.1016/j.rec.2019.04.014>
521. Dahl Aarvik M, Sandven I, Dondo TB, Gale CP, Ruddox V, Munkhaugen J, et al. Effect of oral beta-blocker treatment on mortality in contemporary post-myocardial infarction patients: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother* 2019;**5**:12–20. <https://doi.org/10.1093/ehjcvp/pvy034>
522. Rossello X, Raposeiras-Roubin S, Latini R, Dominguez-Rodriguez A, Barrabés JA, Sánchez PL, et al. Rationale and design of the pragmatic clinical trial tREatment with Beta-blockers after myOcardial infarction withOut reduced ejection fraction (REBOOT). *Eur Heart J Cardiovasc Pharmacother* 2022;**8**:291–301. <https://doi.org/10.1093/ehjcvp/pvab060>
523. Raposeiras-Roubin S, Abu-Assi E, Redondo-Diéguez A, González-Ferreiro R, López-López A, Bouzas-Cruz N, et al. Prognostic benefit of beta-blockers after acute coronary syndrome with preserved systolic function. Still relevant today? *Rev Esp Cardiol (Engl Ed)* 2015;**68**:585–91. <https://doi.org/10.1016/j.rec.2014.07.028>
524. Dondo TB, Hall M, West RM, Jernberg T, Lindahl B, Bueno H, et al. β -Blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. *J Am Coll Cardiol* 2017;**69**:2710–20. <https://doi.org/10.1016/j.jacc.2017.03.578>
525. Kim J, Kang D, Park H, Kang M, Park TK, Lee JM, et al. Long-term β -blocker therapy and clinical outcomes after acute myocardial infarction in patients without heart failure: nationwide cohort study. *Eur Heart J* 2020;**41**:3521–9. <https://doi.org/10.1093/eurheartj/ehaa376>
526. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2021;**42**:3599–726. <https://doi.org/10.1093/eurheartj/ehab368>
527. Watanabe H, Ozasa N, Morimoto T, Shiomi H, Binyuan B, Suwa S, et al. Long-term use of carvedilol in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *PLoS One* 2018;**13**:e0199347. <https://doi.org/10.1371/journal.pone.0199347>
528. Munkhaugen J, Ruddox V, Halvorsen S, Dammen T, Fagerland MW, Hernæs KH, et al. BETAblocker Treatment After acute Myocardial Infarction in revascularized patients without reduced left ventricular ejection fraction (BETAMI): rationale and design of a prospective, randomized, open, blinded end point study. *Am Heart J* 2019;**208**:37–46. <https://doi.org/10.1016/j.ahj.2018.10.005>
529. Kristensen AMD, Bovin A, Zwisler AD, Cerqueira C, Torp-Pedersen C, Bøtker HE, et al. Design and rationale of the Danish trial of beta-blocker treatment after myocardial infarction without reduced ejection fraction: study protocol for a randomized controlled trial. *Trials* 2020;**21**:415. <https://doi.org/10.1186/s13063-020-4214-6>
530. Yndigegn T, Lindahl B, Alfredsson J, Benatar J, Brandin L, Erlinge D, et al. Design and rationale of randomized evaluation of decreased usage of beta-blockers after acute myocardial infarction (REDUCE-AMI). *Eur Heart J Cardiovasc Pharmacother* 2023;**9**:192–7. <https://doi.org/10.1093/ehjcvp/pvac070>
531. Rossello X, Pocock SJ, Julian DG. Long-term use of cardiovascular drugs: challenges for research and for patient care. *J Am Coll Cardiol* 2015;**66**:1273–85. <https://doi.org/10.1016/j.jacc.2015.07.018>
532. Puymirat E, Riant E, Aissaoui N, Soria A, Ducrocq G, Coste P, et al. β Blockers and mortality after myocardial infarction in patients without heart failure: multicentre prospective cohort study. *BMJ* 2016;**354**:i4801. <https://doi.org/10.1136/bmj.i4801>
533. Ishak D, Aktaa S, Lindhagen L, Alfredsson J, Dondo TB, Held C, et al. Association of beta-blockers beyond 1 year after myocardial infarction and cardiovascular outcomes. *Heart* 2023;**109**:1159–65. <https://doi.org/10.1136/heartjnl-2022-322115>
534. Neumann A, Maura G, Weill A, Alla F, Danchin N. Clinical events after discontinuation of beta-blockers in patients without heart failure optimally treated after acute myocardial infarction: a cohort study on the French healthcare databases. *Circ Cardiovasc Qual Outcomes* 2018;**11**:e004356. <https://doi.org/10.1161/CIRCOUTCOMES.117.004356>
535. Zeitouni M, Kerneis M, Lattuca B, Guedeny P, Cayla G, Collet J-P, et al. Do patients need lifelong β -blockers after an uncomplicated myocardial infarction? *Am J Cardiovasc Drugs* 2019;**19**:431–8. <https://doi.org/10.1007/s40256-019-00338-4>
536. van de Ven LL, Vermeulen A, Tans JG, Tans AC, Liem KL, Lageweg NC, et al. Which drug to choose for stable angina pectoris: a comparative study between bisoprolol and nitrates. *Int J Cardiol* 1995;**47**:217–23. [https://doi.org/10.1016/0167-5273\(94\)02194-n](https://doi.org/10.1016/0167-5273(94)02194-n)
537. Ueberbacher HJ, Patyna WD, Krepp P, Puespoek J, Neuhaus R, Hilbich K, et al. [Randomized, double-blind comparison of isorbide-5-mononitrate and delayed-action nifedipine in patients with stable exertional angina. Multicenter Study Group]. *Schweiz Med Wochenschr* 1991;**121**:1836–40.
538. Davies RF, Habibi H, Kline WP, Dessain P, Nadeau C, Phaneuf DC, et al. Effect of amlodipine, atenolol and their combination on myocardial ischemia during treadmill exercise and ambulatory monitoring. Canadian Amlodipine/Atenolol in Silent Ischemia Study (CASIS) Investigators. *J Am Coll Cardiol* 1995;**25**:619–25. [https://doi.org/10.1016/0735-1097\(94\)00436-t](https://doi.org/10.1016/0735-1097(94)00436-t)
539. Klein WW, Jackson G, Tavazzi L. Efficacy of monotherapy compared with combined antianginal drugs in the treatment of chronic stable angina pectoris: a meta-analysis. *Coron Artery Dis* 2002;**13**:427–36. <https://doi.org/10.1097/00019501-200212000-00008>
540. Wei J, Wu T, Yang Q, Chen M, Ni J, Huang D. Nitrates for stable angina: a systematic review and meta-analysis of randomized clinical trials. *Int J Cardiol* 2011;**146**:4–12. <https://doi.org/10.1016/j.ijcard.2010.05.019>
541. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R, et al. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet* 2008;**372**:817–21. [https://doi.org/10.1016/s0140-6736\(08\)61171-x](https://doi.org/10.1016/s0140-6736(08)61171-x)
542. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R, et al. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. *Eur Heart J* 2009;**30**:2337–45. <https://doi.org/10.1093/eurheartj/ehp358>
543. Jiang J, Li Y, Zhou Y, Li X, Li H, Tang B, et al. Oral nicorandil reduces ischemic attacks in patients with stable angina: a prospective, multicenter, open-label, randomized, controlled study. *Int J Cardiol* 2016;**224**:183–7. <https://doi.org/10.1016/j.ijcard.2016.08.305>
544. Horinaka S, Yabe A, Yagi H, Ishimitsu T, Yamazaki T, Suzuki S, et al. Effects of nicorandil on cardiovascular events in patients with coronary artery disease in the Japanese Coronary Artery Disease (JCAD) study. *Circ J* 2010;**74**:503–9. <https://doi.org/10.1253/circj.cj-09-0649>
545. Zhu WL, Shan YD, Guo JX, Wei J-P, Yang X-C, Li T-D, et al. Double-blind, multicenter, active-controlled, randomized clinical trial to assess the safety and efficacy of orally administered nicorandil in patients with stable angina pectoris in China. *Circ J* 2007;**71**:826–33. <https://doi.org/10.1253/circj.71.826>
546. IONA study group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet* 2002;**359**:1269–75. [https://doi.org/10.1016/s0140-6736\(02\)08265-x](https://doi.org/10.1016/s0140-6736(02)08265-x)
547. Di Somma S, Liguori V, Pettito M, Carotenuto A, Bokor D, de Divitiis O, et al. A double-blind comparison of nicorandil and metoprolol in stable effort angina pectoris. *Cardiovasc Drugs Ther* 1993;**7**:119–23. <https://doi.org/10.1007/BF00878320>
548. Döring G. Antianginal and anti-ischemic efficacy of nicorandil in comparison with isorbide-5-mononitrate and isorbide dinitrate: results from two multicenter, double-blind, randomized studies with stable coronary heart disease patients. *J Cardiovasc Pharmacol* 1992;**20** Suppl 3:S74–81. <https://doi.org/10.1097/00005344-199206203-00013>
549. Zhao Y, Peng L, Luo Y, Li S, Zheng Z, Dong R, et al. Trimetazidine improves exercise tolerance in patients with ischemic heart disease: a meta-analysis. *Herz* 2016;**41**:514–22. <https://doi.org/10.1007/s00059-015-4392-2>
550. Peng S, Zhao M, Wan J, Fang Q, Fang D, Li K. The efficacy of trimetazidine on stable angina pectoris: a meta-analysis of randomized clinical trials. *Int J Cardiol* 2014;**177**:780–5. <https://doi.org/10.1016/j.ijcard.2014.10.149>
551. Beltrame JF. Ivabradine and the SIGNIFY conundrum. *Eur Heart J* 2015;**36**:3297–9. <https://doi.org/10.1093/eurheartj/ehv368>
552. Dittrich H, Henneke KH, Pohlmann M, Pongratz G, Bachmann K. Provocation of left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy.

- Comparison of orthostasis testing and nitrate application. *Int J Card Imaging* 1996;**12**: 249–55. <https://doi.org/10.1007/BF01797738>
553. Stauffer JC, Ruiz V, Morard JD. Subaortic obstruction after sildenafil in a patient with hypertrophic cardiomyopathy. *N Engl J Med* 1999;**341**:700–1. <https://doi.org/10.1056/NEJM199908263410916>
554. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2021;**42**:3427–520. <https://doi.org/10.1093/eurheartj/ehab364>
555. Davies A, Fox K, Galassi AR, Banai S, Ylä-Herttuala S, Lüscher TF. Management of refractory angina: an update. *Eur Heart J* 2021;**42**:269–83. <https://doi.org/10.1093/eurheartj/ehaa820>
556. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;**39**:213–60. <https://doi.org/10.1093/eurheartj/ehx419>
557. Juul-Møller S, Edvardsson N, Jahnmatz B, Rosén A, Sørensen S, Omblus R. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. *Lancet* 1992;**340**:1421–5. [https://doi.org/10.1016/0140-6736\(92\)92619-q](https://doi.org/10.1016/0140-6736(92)92619-q)
558. Antithrombotic Trialists' (ATT) Collaboration; Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;**373**:1849–60. [https://doi.org/10.1016/S0140-6736\(09\)60503-1](https://doi.org/10.1016/S0140-6736(09)60503-1)
559. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86. <https://doi.org/10.1136/bmj.324.7329.71>
560. Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 2005;**353**:2373–83. <https://doi.org/10.1056/NEJMra052717>
561. Jones WS, Mulder H, Wruck LM, Pencina MJ, Kripalani S, Muñoz D, et al. Comparative effectiveness of aspirin dosing in cardiovascular disease. *N Engl J Med* 2021;**384**: 1981–90. <https://doi.org/10.1056/NEJMoa2102137>
562. Gragnano F, Cao D, Pirondini L, Franzone A, Kim H-S, von Scheidt M, et al. P2Y₁₂ inhibitor or aspirin monotherapy for secondary prevention of coronary events. *J Am Coll Cardiol* 2023;**82**:89–105. <https://doi.org/10.1016/j.jacc.2023.04.051>
563. Chiarito M, Sanz-Sanchez J, Cannata F, Cao D, Sturla M, Panico C, et al. Monotherapy with a P2Y₁₂ inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. *Lancet* 2020;**395**:1487–95. [https://doi.org/10.1016/S0140-6736\(20\)30315-9](https://doi.org/10.1016/S0140-6736(20)30315-9)
564. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329–39. [https://doi.org/10.1016/S0140-6736\(96\)09457-3](https://doi.org/10.1016/S0140-6736(96)09457-3)
565. Koo BK, Kang J, Park KW, Rhee T-M, Yang H-M, Won K-B, et al. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. *Lancet* 2021;**397**:2487–96. [https://doi.org/10.1016/S0140-6736\(21\)01063-1](https://doi.org/10.1016/S0140-6736(21)01063-1)
566. Kang J, Park KW, Lee H, Hwang D, Yang H-M, Rha S-W, et al. Aspirin versus clopidogrel for long-term maintenance monotherapy after percutaneous coronary intervention: the HOST-EXAM Extended study. *Circulation* 2023;**147**:108–17. <https://doi.org/10.1161/circulationaha.122.062770>
567. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 2009;**120**:2577–85. <https://doi.org/10.1161/CIRCULATIONAHA.109.912550>
568. Storey RF, Angiolillo DJ, Patil SB, Desai B, Ecob R, Husted S, et al. Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary syndromes: the PLATO (PLATElet inhibition and patient Outcomes) PLATELET substudy. *J Am Coll Cardiol* 2010;**56**:1456–62. <https://doi.org/10.1016/j.jacc.2010.03.100>
569. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**: 1045–57. <https://doi.org/10.1056/NEJMoa0904327>
570. Vranckx P, Valgimigli M, Juni P, Hamm C, Steg PG, Heg D, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet* 2018;**392**:940–9. [https://doi.org/10.1016/S0140-6736\(18\)31858-0](https://doi.org/10.1016/S0140-6736(18)31858-0)
571. Franzone A, McFadden E, Leonardi S, Piccolo R, Vranckx P, Serruys PW, et al. Ticagrelor alone versus dual antiplatelet therapy from 1 month after drug-eluting coronary stenting. *J Am Coll Cardiol* 2019;**74**:2223–34. <https://doi.org/10.1016/j.jacc.2019.08.1038>
572. Ono M, Hara H, Kawashima H, Gao C, Wang R, Wykrzykowska JJ, et al. Ticagrelor monotherapy versus aspirin monotherapy at 12 months after percutaneous coronary intervention: a landmark analysis of the GLOBAL LEADERS trial. *EuroIntervention* 2022;**18**:e377–88. <https://doi.org/10.4244/EIJ-D-21-00870>
573. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med* 2019;**381**: 2032–42. <https://doi.org/10.1056/NEJMoa1908419>
574. O'Donoghue ML, Murphy SA, Sabatine MS. The safety and efficacy of aspirin discontinuation on a background of a P2Y₁₂ inhibitor in patients after percutaneous coronary intervention: a systematic review and meta-analysis. *Circulation* 2020;**142**:538–45. <https://doi.org/10.1161/CIRCULATIONAHA.120.046251>
575. Vranckx P, Valgimigli M, Windecker S, Steg P, Hamm C, Juni P, et al. Long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing biolimus-eluting stent implantation: rationale and design of the GLOBAL LEADERS trial. *EuroIntervention* 2016;**12**:1239–45. https://doi.org/10.4244/EIJY15M11_07
576. Kogame N, Guimaraes PO, Modolo R, De Martino F, Tinoco J, Ribeiro EE, et al. Aspirin-free prasugrel monotherapy following coronary artery stenting in patients with stable CAD: the ASET Pilot study. *JACC Cardiovasc Interv* 2020;**13**:2251–62. <https://doi.org/10.1016/j.jcin.2020.06.023>
577. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. *Circulation* 2009;**119**:2553–60. <https://doi.org/10.1161/circulationaha.109.851949>
578. O'Donoghue ML, Braunwald E, Antman EM, Murphy SA, Bates ER, Rozenman Y, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet* 2009;**374**: 989–97. [https://doi.org/10.1016/S0140-6736\(09\)61525-7](https://doi.org/10.1016/S0140-6736(09)61525-7)
579. Teng R, Oliver S, Hayes MA, Butler K. Absorption, distribution, metabolism, and excretion of ticagrelor in healthy subjects. *Drug Metab Dispos* 2010;**38**:1514–21. <https://doi.org/10.1124/dmd.110.032250>
580. Giorgi MA, Cohen Arazi H, Gonzalez CD, Di Girolamo G. Beyond efficacy: pharmacokinetic differences between clopidogrel, prasugrel and ticagrelor. *Expert Opin Pharmacother* 2011;**12**:1285–95. <https://doi.org/10.1517/14656566.2011.550573>
581. Tantry US, Bonello L, Aradi D, Price MJ, Jeong Y-H, Angiolillo DJ, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *J Am Coll Cardiol* 2013;**62**:2261–73. <https://doi.org/10.1016/j.jacc.2013.07.101>
582. Parker WA, Storey RF. Antithrombotic therapy for patients with chronic coronary syndromes. *Heart* 2021;**107**:925–33. <https://doi.org/10.1136/heartjnl-2020-316914>
583. Silvain J, Lattuca B, Beygui F, Rangé G, Motovska Z, Dillinger J-G, et al. Ticagrelor versus clopidogrel in elective percutaneous coronary intervention (ALPHEUS): a randomised, open-label, phase 3b trial. *Lancet* 2020;**396**:1737–44. [https://doi.org/10.1016/S0140-6736\(20\)32236-4](https://doi.org/10.1016/S0140-6736(20)32236-4)
584. Steg PG, Bhatt DL, Simon T, Fox K, Mehta SR, Harrington RA, et al. Ticagrelor in patients with stable coronary disease and diabetes. *N Engl J Med* 2019;**381**:1309–20. <https://doi.org/10.1056/NEJMoa1908077>
585. Hahn JY, Song YB, Oh JH, Chun WJ, Park YH, Jang WJ, et al. Effect of P2Y₁₂ inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA* 2019;**321**:2428–37. <https://doi.org/10.1001/jama.2019.8146>
586. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiohira H, Toyota T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA* 2019;**321**:2414–27. <https://doi.org/10.1001/jama.2019.8145>
587. Valgimigli M, Frigoli E, Heg D, Tijssen J, Juni P, Vranckx P, et al. Dual antiplatelet therapy after PCI in patients at high bleeding risk. *N Engl J Med* 2021;**385**:1643–55. <https://doi.org/10.1056/NEJMoa2108749>
588. Hong SJ, Kim JS, Hong SJ, Lim D-S, Lee S-Y, Yun KH, et al. 1-Month dual-antiplatelet therapy followed by aspirin monotherapy after polymer-free drug-coated stent implantation: one-month DAPT trial. *JACC Cardiovasc Interv* 2021;**14**:1801–11. <https://doi.org/10.1016/j.jcin.2021.06.003>
589. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017;**389**:1025–34. [https://doi.org/10.1016/S0140-6736\(17\)30397-5](https://doi.org/10.1016/S0140-6736(17)30397-5)
590. Urban P, Mehran R, Collieran R, Angiolillo DJ, Byrne RA, Capodanno D, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Eur Heart J* 2019;**40**:2632–53. <https://doi.org/10.1093/eurheartj/ehz372>
591. Costa F, Montalto C, Branca M, Hong S-J, Watanabe H, Franzone A, et al. Dual antiplatelet therapy duration after percutaneous coronary intervention in high bleeding

- risk: a meta-analysis of randomized trials. *Eur Heart J* 2023;**44**:954–68. <https://doi.org/10.1093/eurheartj/ehac706>
592. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;**371**:2155–66. <https://doi.org/10.1056/NEJMoa1409312>
 593. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;**372**:1791–800. <https://doi.org/10.1056/NEJMoa1500857>
 594. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;**377**:1319–30. <https://doi.org/10.1056/NEJMoa1709118>
 595. Bhatt DL, Bonaca MP, Bansilal S, Angiolillo DJ, Cohen M, Storey RF, et al. Reduction in ischemic events with ticagrelor in diabetic patients with prior myocardial infarction in PEGASUS-TIMI 54. *J Am Coll Cardiol* 2016;**67**:2732–40. <https://doi.org/10.1016/j.jacc.2016.03.529>
 596. Bonaca MP, Bhatt DL, Storey RF, Steg PG, Cohen M, Kuder J, et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. *J Am Coll Cardiol* 2016;**67**:2719–28. <https://doi.org/10.1016/j.jacc.2016.03.524>
 597. Bansilal S, Bonaca MP, Corneli JH, Storey RF, Bhatt DL, Steg PG, et al. Ticagrelor for secondary prevention of atherothrombotic events in patients with multivessel coronary disease. *J Am Coll Cardiol* 2018;**71**:489–96. <https://doi.org/10.1016/j.jacc.2017.11.050>
 598. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2018;**391**:219–29. [https://doi.org/10.1016/S0140-6736\(17\)32409-1](https://doi.org/10.1016/S0140-6736(17)32409-1)
 599. Mega JL, Simon T, Collet JP, Anderson JL, Antman EM, Bliden K, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA* 2010;**304**:1821–30. <https://doi.org/10.1001/jama.2010.1543>
 600. Pereira NL, Rihal C, Lennon R, Marcus G, Shrivastava S, Bell MR, et al. Effect of CYP2C19 genotype on ischemic outcomes during oral P2Y₁₂ inhibitor therapy: a meta-analysis. *JACC Cardiovasc Interv* 2021;**14**:739–50. <https://doi.org/10.1016/j.jcin.2021.01.024>
 601. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *Lancet* 2017;**390**:1747–57. [https://doi.org/10.1016/S0140-6736\(17\)32155-4](https://doi.org/10.1016/S0140-6736(17)32155-4)
 602. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof AWJ, van der Harst P, et al. A genotype-guided strategy for oral P2Y₁₂ inhibitors in primary PCI. *N Engl J Med* 2019;**381**:1621–31. <https://doi.org/10.1056/NEJMoa1907096>
 603. Price MJ, Angiolillo DJ, Teirstein PS, Lillie E, Manoukian SV, Berger PB, et al. Platelet reactivity and cardiovascular outcomes after percutaneous coronary intervention: a time-dependent analysis of the Gauging Responsiveness with A VerifyNow P2Y₁₂ assay: Impact on Thrombosis and Safety (GRAVITAS) trial. *Circulation* 2011;**124**:1132–7. <https://doi.org/10.1161/circulationaha.111.029165>
 604. Collet JP, Silvain J, Barthélémy O, Rangé G, Cayla G, Van Belle E, et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. *Lancet* 2014;**384**:1577–85. [https://doi.org/10.1016/S0140-6736\(14\)60612-7](https://doi.org/10.1016/S0140-6736(14)60612-7)
 605. Cayla G, Cuisset T, Silvain J, Leclercq F, Manzo-Silberman S, Saint-Etienne C, et al. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. *Lancet* 2016;**388**:2015–22. [https://doi.org/10.1016/S0140-6736\(16\)31323-X](https://doi.org/10.1016/S0140-6736(16)31323-X)
 606. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, et al. A randomised trial on platelet function-guided de-escalation of antiplatelet treatment in ACS patients undergoing PCI. Rationale and design of the Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes (TROPICAL-ACS) Trial. *Thromb Haemost* 2017;**117**:188–95. <https://doi.org/10.1160/th16-07-0557>
 607. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V, et al. Effect of genotype-guided oral P2Y₁₂ inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. *JAMA* 2020;**324**:761–71. <https://doi.org/10.1001/jama.2020.12443>
 608. Ingraham BS, Farkouh ME, Lennon RJ, So D, Goodman SG, Geller N, et al. Genetic-guided oral P2Y₁₂ inhibitor selection and cumulative ischemic events after percutaneous coronary intervention. *JACC Cardiovasc Interv* 2023;**16**:816–25. <https://doi.org/10.1016/j.jcin.2023.01.356>
 609. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H, Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002;**347**:969–74. <https://doi.org/10.1056/NEJMoa020496>
 610. van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE; Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) Research Group. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet* 2002;**360**:109–13. [https://doi.org/10.1016/S0140-6736\(02\)09409-6](https://doi.org/10.1016/S0140-6736(02)09409-6)
 611. Sixty Plus Reinfarction Study Research Group. A double-blind trial to assess long-term oral anticoagulant therapy in elderly patients after myocardial infarction. Report of the Sixty Plus Reinfarction Study Research Group. *Lancet* 1980;**2**:989–94. [https://doi.org/10.1016/S0140-6736\(80\)92154-6](https://doi.org/10.1016/S0140-6736(80)92154-6)
 612. Sorensen R, Hansen ML, Abildstrom SZ, Hvelplund A, Andersson C, Jørgensen C, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet* 2009;**374**:1967–74. [https://doi.org/10.1016/S0140-6736\(09\)61751-7](https://doi.org/10.1016/S0140-6736(09)61751-7)
 613. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373–498. <https://doi.org/10.1093/eurheartj/ehaa612>
 614. Valgimigli M, Costa F, Lokhnygina Y, Clare RM, Wallentin L, Moliterno DJ, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. *Eur Heart J* 2017;**38**:804–10. <https://doi.org/10.1093/eurheartj/ehw525>
 615. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJGL, Herrman J-P, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;**381**:1107–15. [https://doi.org/10.1016/S0140-6736\(12\)62177-1](https://doi.org/10.1016/S0140-6736(12)62177-1)
 616. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;**375**:2423–34. <https://doi.org/10.1056/NEJMoa1611594>
 617. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017;**377**:1513–24. <https://doi.org/10.1056/NEJMoa1708454>
 618. Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T, Gargiulo G, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet* 2019;**394**:1335–43. [https://doi.org/10.1016/S0140-6736\(19\)31872-0](https://doi.org/10.1016/S0140-6736(19)31872-0)
 619. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med* 2019;**380**:1509–24. <https://doi.org/10.1056/NEJMoa1817083>
 620. Galli M, Andreotti F, Porto I, Crea F. Intracranial haemorrhages vs. stent thromboses with direct oral anticoagulant plus single antiplatelet agent or triple antithrombotic therapy: a meta-analysis of randomized trials in atrial fibrillation and percutaneous coronary intervention/acute coronary syndrome patients. *Europace* 2020;**22**:538–46. <https://doi.org/10.1093/europace/euz345>
 621. Gargiulo G, Goette A, Tijssen J, Eckardt L, Lewalter T, Vranckx P, et al. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J* 2019;**40**:3757–67. <https://doi.org/10.1093/eurheartj/ehz732>
 622. Alexander JH, Wojdyla D, Vora AN, Thomas L, Granger CB, Goodman SG, et al. Risk/benefit tradeoff of antithrombotic therapy in patients with atrial fibrillation early and late after an acute coronary syndrome or percutaneous coronary intervention: insights from AUGUSTUS. *Circulation* 2020;**141**:1618–27. <https://doi.org/10.1161/CIRCULATIONAHA.120.046534>
 623. Lip GYH, Collet JP, Haude M, Byrne R, Chung EH, Fauchier L, et al. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). *Europace* 2019;**21**:192–3. <https://doi.org/10.1093/europace/euy174>
 624. Oldgren J, Steg PG, Hohnloser SH, Lip GYH, Kimura T, Nordaby M, et al. Dabigatran dual therapy with ticagrelor or clopidogrel after percutaneous coronary intervention in atrial fibrillation patients with or without acute coronary syndrome: a subgroup analysis from the RE-DUAL PCI trial. *Eur Heart J* 2019;**40**:1553–62. <https://doi.org/10.1093/eurheartj/ehz059>

625. Rubboli A. Oral anticoagulation alone for concomitant stable coronary artery disease and atrial fibrillation: a definitive strategy? *Int J Cardiol* 2018;**264**:95–6. <https://doi.org/10.1016/j.ijcard.2018.04.023>
626. Patti G, Pecun L, Lucerna M, Huber K, Rohla M, Renda G, et al. Outcomes of anticoagulated patients with atrial fibrillation treated with or without antiplatelet therapy—a pooled analysis from the PREFER in AF and PREFER in AF PROLONGATION registries. *Int J Cardiol* 2018;**270**:160–6. <https://doi.org/10.1016/j.ijcard.2018.06.098>
627. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. *N Engl J Med* 2019;**381**:1103–13. <https://doi.org/10.1056/NEJMoa1904143>
628. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing G-J, Harjola V-P, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020;**41**:543–603. <https://doi.org/10.1093/eurheartj/ehz405>
629. Björklund E, Nielsen SJ, Hansson EC, Karlsson M, Wallinder A, Martinsson A, et al. Secondary prevention medications after coronary artery bypass grafting and long-term survival: a population-based longitudinal study from the SWEDEHEART registry. *Eur Heart J* 2020;**41**:1653–61. <https://doi.org/10.1093/eurheartj/ehz714>
630. Mangano DT. Multicenter Study of Perioperative Ischemia Research Group. Aspirin and mortality from coronary bypass surgery. *N Engl J Med* 2002;**347**:1309–17. <https://doi.org/10.1056/NEJMoa020798>
631. Sousa-Uva M, Storey R, Huber K, Falk V, Leite-Moreira AF, Amour J, et al. Expert position paper on the management of antiplatelet therapy in patients undergoing coronary artery bypass graft surgery. *Eur Heart J* 2014;**35**:1510–4. <https://doi.org/10.1093/eurheartj/ehu158>
632. Sousa-Uva M, Head SJ, Milojevic M, Collet J-P, Landoni G, Castella M, et al. 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. *Eur J Cardiothorac Surg* 2018;**53**:5–33. <https://doi.org/10.1093/ejcts/ezx314>
633. Shaw JR, Li N, Vanassche T, Coppens M, Spyropoulos AC, Syed S, et al. Predictors of preprocedural direct oral anticoagulant levels in patients having an elective surgery or procedure. *Blood Adv* 2020;**4**:3520–7. <https://doi.org/10.1182/bloodadvances.2020002335>
634. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haesler KG, et al. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Europace* 2021;**23**:1612–76. <https://doi.org/10.1093/europace/euab065>
635. Sandner S, Redfors B, Angiolillo DJ, Audisio K, Fremes SE, Janssen PWA, et al. Association of dual antiplatelet therapy with ticagrelor with vein graft failure after coronary artery bypass graft surgery: a systematic review and meta-analysis. *JAMA* 2022;**328**:554–62. <https://doi.org/10.1001/jama.2022.11966>
636. Kulik A, Le May MR, Voisine P, Tardif J-C, DeLarochelliere R, Naidoo S, et al. Aspirin plus clopidogrel versus aspirin alone after coronary artery bypass grafting: the clopidogrel after surgery for coronary artery disease (CASCADE) trial. *Circulation* 2010;**122**:2680–7. <https://doi.org/10.1161/CIRCULATIONAHA.110.978007>
637. Zhao Q, Zhu Y, Xu Z, Cheng Z, Mei J, Chen X, et al. Effect of ticagrelor plus aspirin, ticagrelor alone, or aspirin alone on saphenous vein graft patency 1 year after coronary artery bypass grafting: a randomized clinical trial. *JAMA* 2018;**319**:1677–86. <https://doi.org/10.1001/jama.2018.3197>
638. Filardo G, Damiano RJ Jr, Ailawadi G, Thourani VH, Pollock BD, Sass DM, et al. Epidemiology of new-onset atrial fibrillation following coronary artery bypass graft surgery. *Heart* 2018;**104**:985–92. <https://doi.org/10.1136/heartjnl-2017-312150>
639. Benedetto U, Gaudino MF, Dimagli A, Gerry S, Gray A, Lees B, et al. Postoperative atrial fibrillation and long-term risk of stroke after isolated coronary artery bypass graft surgery. *Circulation* 2020;**142**:1320–9. <https://doi.org/10.1161/CIRCULATIONAHA.120.046940>
640. Taha A, Nielsen SJ, Franzen S, Rezk M, Ahlsson A, Friberg L, et al. Stroke risk stratification in patients with postoperative atrial fibrillation after coronary artery bypass grafting. *J Am Heart Assoc* 2022;**11**:e024703. <https://doi.org/10.1161/JAHA.121.024703>
641. Butt JH, Xian Y, Peterson ED, Olsen PS, Rørth R, Gundlund A, et al. Long-term thromboembolic risk in patients with postoperative atrial fibrillation after coronary artery bypass graft surgery and patients with nonvalvular atrial fibrillation. *JAMA Cardiol* 2018;**3**:417–24. <https://doi.org/10.1001/jamacardio.2018.0405>
642. Taha A, Nielsen SJ, Bergfeldt L, Ahlsson A, Friberg L, Björck S, et al. New-onset atrial fibrillation after coronary artery bypass grafting and long-term outcome: a population-based nationwide study from the SWEDEHEART registry. *J Am Heart Assoc* 2021;**10**:e017966. <https://doi.org/10.1161/JAHA.120.017966>
643. Abraham NS, Hlatky MA, Antman EM, Bhatt DL, Björkman DJ, Clark CB, et al. ACCF/ACG/AHA 2010 Expert Consensus Document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation* 2010;**122**:2619–33. <https://doi.org/10.1161/CIR.0b013e318202f701>
644. Abraham NS, Noseworthy PA, Inselman J, Herrin J, Yao X, Sangaralingham LR, et al. Risk of gastrointestinal bleeding increases with combinations of antithrombotic agents and patient age. *Clin Gastroenterol Hepatol* 2020;**18**:337–46.e19. <https://doi.org/10.1016/j.cgh.2019.05.017>
645. Li L, Geraghty OC, Mehta Z, Rothwell PM, on behalf of the Oxford Vascular Study. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. *Lancet* 2017;**390**:490–9. [https://doi.org/10.1016/S0140-6736\(17\)30770-5](https://doi.org/10.1016/S0140-6736(17)30770-5)
646. Moayeddi P, Eikelboom JW, Bosch J, Connolly SJ, Dyal L, Shestakovska O, et al. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. *Gastroenterology* 2019;**157**:682–91.e2. <https://doi.org/10.1053/j.gastro.2019.05.056>
647. Ahn HJ, Lee SR, Choi EK, Rhee TM, Kwon S, Oh S, et al. Protective effect of proton-pump inhibitor against gastrointestinal bleeding in patients receiving oral anticoagulants: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2022;**88**:4676–87. <https://doi.org/10.1111/bcp.15478>
648. Shang YS, Zhong PY, Ma Y, Bai N, Niu Y, Wang Z-L. Efficacy and safety of proton pump inhibitors in patients with coronary artery diseases receiving oral antiplatelet agents and/or anticoagulants: a systematic review and meta-analysis. *J Cardiovasc Pharmacol* 2022;**80**:1–12. <https://doi.org/10.1097/fjc.0000000000001284>
649. Lin Y, Cai Z, Dong S, Liu H, Pang X, Chen Q, et al. Comparative efficacy and safety of antiplatelet or anticoagulant therapy in patients with chronic coronary syndromes after percutaneous coronary intervention: a network meta-analysis of randomized controlled trials. *Front Pharmacol* 2022;**13**:992376. <https://doi.org/10.3389/fphar.2022.992376>
650. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, et al. Short-versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation* 2012;**125**:2015–26. <https://doi.org/10.1161/CIRCULATIONAHA.111.071589>
651. Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation* 2012;**125**:505–13. <https://doi.org/10.1161/CIRCULATIONAHA.111.059022>
652. Schulz-Schupke S, Byrne RA, Ten Berg JM, Neumann FJ, Han Y, Adriaenssens T, et al. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J* 2015;**36**:1252–63. <https://doi.org/10.1093/eurheartj/ehu523>
653. Han Y, Xu B, Xu K, Guan C, Jing Q, Zheng Q, et al. Six versus 12 months of dual antiplatelet therapy after implantation of biodegradable polymer sirolimus-eluting stent: randomized substudy of the I-LOVE-IT 2 trial. *Circ Cardiovasc Interv* 2016;**9**:e003145. <https://doi.org/10.1161/CIRCINTERVENTIONS.115.003145>
654. Hong SJ, Shin DH, Kim JS, Kim BK, Ko YG, Choi D, et al. 6-Month versus 12-month dual-antiplatelet therapy following long everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. *JACC Cardiovasc Interv* 2016;**9**:1438–46. <https://doi.org/10.1016/j.jcin.2016.04.036>
655. Kim BK, Hong MK, Shin DH, Nam CM, Kim JS, Ko YG, et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol* 2012;**60**:1340–8. <https://doi.org/10.1016/j.jacc.2012.06.043>
656. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA* 2013;**310**:2510–22. <https://doi.org/10.1001/jama.2013.282183>
657. Valgimigli M, Gragnano F, Branca M, Franzona A, Baber U, Jang Y, et al. P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials. *BMJ* 2021;**373**:n1332. <https://doi.org/10.1136/bmj.n1332>
658. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;**383**:955–62. [https://doi.org/10.1016/S0140-6736\(13\)62343-0](https://doi.org/10.1016/S0140-6736(13)62343-0)
659. Potpara TS, Mujovic N, Proietti M, Dagnes N, Hindricks G, Collet JP, et al. Revisiting the effects of omitting aspirin in combined antithrombotic therapies for atrial fibrillation and acute coronary syndromes or percutaneous coronary interventions: meta-analysis of pooled data from the PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS trials. *Europace* 2020;**22**:33–46. <https://doi.org/10.1093/europace/euz259>
660. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 2010;**376**:975–83. [https://doi.org/10.1016/S0140-6736\(10\)61194-4](https://doi.org/10.1016/S0140-6736(10)61194-4)
661. Fiedler KA, Maeng M, Mehilli J, Schulz-Schüpke S, Byrne RA, Sibbing D, et al. Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation: the ISAR-TRIPLE trial. *J Am Coll Cardiol* 2015;**65**:1619–29. <https://doi.org/10.1016/j.jacc.2015.02.050>

662. Proietti M, Airaksinen KEJ, Rubboli A, Schlitt A, Kiviniemi T, Karjalainen PP, et al. Time in therapeutic range and major adverse outcomes in atrial fibrillation patients undergoing percutaneous coronary intervention: the Atrial Fibrillation Undergoing Coronary Artery Stenting (AFCAS) registry. *Am Heart J* 2017;**190**:86–93. <https://doi.org/10.1016/j.ahj.2017.05.016>
663. McDowell TY, Lawrence J, Florian J, Southworth MR, Grant S, Stockbridge N. Relationship between international normalized ratio and outcomes in modern trials with warfarin controls. *Pharmacotherapy* 2018;**38**:899–906. <https://doi.org/10.1002/phar.2161>
664. Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanan A, Schnitzer TJ, et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 2010;**363**:1909–17. <https://doi.org/10.1056/NEJMoa1007964>
665. Lanan A, Garcia-Rodriguez LA, Arroyo MT, Gomollon F, Feu F, Gonzalez-Perez A, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. *Gut* 2006;**55**:1731–8. <https://doi.org/10.1136/gut.2005.080754>
666. Scally B, Emberson JR, Spata E, Reith C, Davies K, Halls H, et al. Effects of gastroprotection by the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomised trials. *Lancet Gastroenterol Hepatol* 2018;**3**:231–41. [https://doi.org/10.1016/S2468-1253\(18\)30037-2](https://doi.org/10.1016/S2468-1253(18)30037-2)
667. Cea Soriano L, Fowkes FGR, Allum AM, Johansson S, Garcia Rodriguez LA. Predictors of bleeding in patients with symptomatic peripheral artery disease: a cohort study using the health improvement network in the United Kingdom. *Thromb Haemost* 2018;**118**:1101–12. <https://doi.org/10.1055/s-0038-1646923>
668. Han Y, Liao Z, Li Y, Zhao X, Ma S, Bao D, et al. Magnetically controlled capsule endoscopy for assessment of antiplatelet therapy-induced gastrointestinal injury. *J Am Coll Cardiol* 2022;**79**:116–28. <https://doi.org/10.1016/j.jacc.2021.10.028>
669. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017;**38**:2459–72. <https://doi.org/10.1093/eurheartj/ehx144>
670. Cholesterol Treatment Trialists' (CTT) Collaboration; Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 2010;**376**:1670–81. [https://doi.org/10.1016/S0140-6736\(10\)61350-5](https://doi.org/10.1016/S0140-6736(10)61350-5)
671. Cholesterol Treatment Trialists' (CTT) Collaboration; Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174 000 participants in 27 randomised trials. *Lancet* 2015;**385**:1397–405. [https://doi.org/10.1016/S0140-6736\(14\)61368-4](https://doi.org/10.1016/S0140-6736(14)61368-4)
672. Ridker PM, Mora S, Rose L; Jupiter Trial Study Group. Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents. *Eur Heart J* 2016;**37**:1373–9. <https://doi.org/10.1093/eurheartj/ehw046>
673. Ray KK, Molemans B, Schoonen WM, Giovos P, Bray S, Kiru G, et al. EU-wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care: the DA VINCI study. *Eur J Prev Cardiol* 2021;**28**:1279–89. <https://doi.org/10.1093/eurjpc/zwaa047>
674. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;**372**:2387–97. <https://doi.org/10.1056/NEJMoa1410489>
675. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;**376**:1713–22. <https://doi.org/10.1056/NEJMoa1615664>
676. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;**379**:2097–107. <https://doi.org/10.1056/NEJMoa1801174>
677. O'Donoghue ML, Giugliano RP, Wiviott SD, Atar D, Keech A, Kuder JF, et al. Long-term evolocumab in patients with established atherosclerotic cardiovascular disease. *Circulation* 2022;**146**:1109–19. <https://doi.org/10.1161/CIRCULATIONAHA.122.061620>
678. Ballantyne CM, Laufs U, Ray KK, Leiter LA, Bays HE, Goldberg AC, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *Eur J Prev Cardiol* 2020;**27**:593–603. <https://doi.org/10.1177/2047487319864671>
679. Ray KK, Bays HE, Catapano AL, Lalwani ND, Bloedon LT, Sterling LR, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *N Engl J Med* 2019;**380**:1022–32. <https://doi.org/10.1056/NEJMoa1803917>
680. Nissen SE, Lincoff AM, Brennan D, Ray KK, Mason D, Kastelein JJP, et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. *New Engl J Med* 2023;**388**:1353–64. <https://doi.org/10.1056/NEJMoa2215024>
681. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med* 2020;**382**:1507–19. <https://doi.org/10.1056/NEJMoa1912387>
682. Patti G, Cannon CP, Murphy SA, Mega S, Pasceri V, Briguori C, et al. Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: a collaborative patient-level meta-analysis of 13 randomized studies. *Circulation* 2011;**123**:1622–32. <https://doi.org/10.1161/CIRCULATIONAHA.110.002451>
683. SOLVD Investigators; Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302. <https://doi.org/10.1056/NEJM199108013250501>
684. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction — results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;**327**:669–77. <https://doi.org/10.1056/NEJM199209033271001>
685. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000;**355**:1575–81. [https://doi.org/10.1016/S0140-6736\(00\)02212-1](https://doi.org/10.1016/S0140-6736(00)02212-1)
686. Heart Outcomes Prevention Evaluation Study Investigators; Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145–53. <https://doi.org/10.1056/NEJM200001203420301>
687. Fox KM; EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;**362**:782–8. [https://doi.org/10.1016/S0140-6736\(03\)14286-9](https://doi.org/10.1016/S0140-6736(03)14286-9)
688. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**:347–57. <https://doi.org/10.1056/NEJMoa1812389>
689. Patel A; ADVANCE Collaborative Group; MacMahon S, Chalmers J, Neal B, Woodward M, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;**370**:829–40. [https://doi.org/10.1016/S0140-6736\(07\)61303-8](https://doi.org/10.1016/S0140-6736(07)61303-8)
690. Braunwald E, Domanski MJ, Fowler SE, Geller NL, Gersh BJ, Hsia J, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;**351**:2058–68. <https://doi.org/10.1056/NEJMoa042739>
691. Bangalore S, Fakhri R, Wandel S, Toklu B, Wandel J, Messerli FH. Renin angiotensin system inhibitors for patients with stable coronary artery disease without heart failure: systematic review and meta-analysis of randomized trials. *BMJ* 2017;**356**:j4. <https://doi.org/10.1136/bmj.j4>
692. Prosser HC, Peck KY, Dinh D, Roberts L, Chandrasekhar J, Brennan A, et al. Role of renin-angiotensin system antagonists on long-term mortality post-percutaneous coronary intervention in reduced and preserved ejection fraction. *Clin Res Cardiol* 2022;**111**:776–86. <https://doi.org/10.1007/s00392-021-01985-x>
693. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004. <https://doi.org/10.1056/NEJMoa1409077>
694. Mogensen UM, Kober L, Kristensen SL, Jhund PS, Gong J, Lefkowitz MP, et al. The effects of sacubitril/valsartan on coronary outcomes in PARADIGM-HF. *Am Heart J* 2017;**188**:35–41. <https://doi.org/10.1016/j.ahj.2017.02.034>
695. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–28. <https://doi.org/10.1056/NEJMoa1504720>
696. Neal B, Perkovic V, Matthews DR, Mahaffey KW, Fulcher G, Meininger G, et al. Rationale, design and baseline characteristics of the CANagliflozin cardiovascular Assessment Study—Renal (CANVAS-R): a randomized, placebo-controlled trial. *Diabetes Obes Metab* 2017;**19**:387–93. <https://doi.org/10.1111/dom.12829>
697. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med* 2020;**383**:1425–35. <https://doi.org/10.1056/NEJMoa2004967>
698. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol* 2021;**6**:148–58. <https://doi.org/10.1001/jamacardio.2020.4511>
699. Mudaliar S, Alloju S, Henry RR. Can a shift in fuel energetics explain the beneficial cardi-renal outcomes in the EMPA-REG OUTCOME study? A unifying hypothesis. *Diabetes Care* 2016;**39**:1115–22. <https://doi.org/10.2337/dc16-0542>
700. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644–57. <https://doi.org/10.1056/NEJMoa1611925>
701. Uthman L, Baartscheer A, Bleijlevens B, Schumacher CA, Fiolet JWT, Koeman A, et al. Class effects of SGLT2 inhibitors in mouse cardiomyocytes and hearts: inhibition of Na⁺/H⁺ exchanger, lowering of cytosolic Na⁺ and vasodilation. *Diabetologia* 2018;**61**:722–6. <https://doi.org/10.1007/s00125-017-4509-7>

702. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose cotransporter 2 (SGLT2) inhibitors: a state-of-the-art review. *JACC Basic Transl Sci* 2020; **5**:632–44. <https://doi.org/10.1016/j.jacbs.2020.02.004>
703. Kristensen SL, Rorth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2019; **7**:776–85. [https://doi.org/10.1016/S2213-8587\(19\)30249-9](https://doi.org/10.1016/S2213-8587(19)30249-9)
704. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; **381**:1995–2008. <https://doi.org/10.1056/NEJMoa1911303>
705. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; **383**:1413–24. <https://doi.org/10.1056/NEJMoa2022190>
706. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; **385**:1451–61. <https://doi.org/10.1056/NEJMoa2107038>
707. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022; **387**:1089–98. <https://doi.org/10.1056/NEJMoa2206286>
708. Razuk V, Chiarito M, Cao D, Nicolas J, Pivato CA, Camaj A, et al. SGLT-2 inhibitors and cardiovascular outcomes in patients with and without a history of heart failure: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother* 2022; **8**:557–67. <https://doi.org/10.1093/ehjcvp/pvaca001>
709. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2023 Focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2023; **44**:3627–39. <https://doi.org/10.1093/eurheartj/ehad195>
710. Gerstein HC, Sattar N, Rosenstock J, Ramasundarahettige C, Praty R, Lopes RD, et al. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. *N Engl J Med* 2021; **385**:896–907. <https://doi.org/10.1056/NEJMoa2108269>
711. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol* 2021; **9**:653–62. [https://doi.org/10.1016/S2213-8587\(21\)00203-5](https://doi.org/10.1016/S2213-8587(21)00203-5)
712. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017; **377**:1119–31. <https://doi.org/10.1056/NEJMoa1707914>
713. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, et al. Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med* 2019; **380**:752–62. <https://doi.org/10.1056/NEJMoa1809798>
714. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019; **381**:2497–505. <https://doi.org/10.1056/NEJMoa1912388>
715. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020; **383**:1838–47. <https://doi.org/10.1056/NEJMoa2021372>
716. Andreis A, Imazio M, Pirolì F, Avondo S, Casula M, Paneva E, et al. Efficacy and safety of colchicine for the prevention of major cardiovascular and cerebrovascular events in patients with coronary artery disease: a systematic review and meta-analysis on 12 869 patients. *Eur J Prev Cardiol* 2022; **28**:1916–25. <https://doi.org/10.1093/eurjpc/zwab045>
717. Abdallah MS, Wang K, Magnuson EA, Osnabrugge RL, Kappetein AP, Morice MC, et al. Quality of life after surgery or DES in patients with 3-vessel or left main disease. *J Am Coll Cardiol* 2017; **69**:2039–50. <https://doi.org/10.1016/j.jacc.2017.02.031>
718. Bittl JA, He Y, Jacobs AK, Yancy CW, Normand SLT; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Bayesian methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. *Circulation* 2013; **127**:2177–85. <https://doi.org/10.1161/CIRCULATIONAHA.112.000646>
719. Yusuf S, Zucker D, Passamani E, Peduzzi P, Takaro T, Fisher LD, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994; **344**:563–70. [https://doi.org/10.1016/s0140-6736\(94\)91963-1](https://doi.org/10.1016/s0140-6736(94)91963-1)
720. Takaro T, Peduzzi P, Detre KM, Hultgren HN, Murphy ML, van der Bel-Kahn J, et al. Survival in subgroups of patients with left main coronary artery disease. Veterans Administration Cooperative Study of surgery for coronary arterial occlusive disease. *Circulation* 1982; **66**:14–22. <https://doi.org/10.1161/01.cir.66.1.14>
721. Talano JV, Scanlon PJ, Meadows WVR, Kahn M, Pifarre R, Gunnar RM. Influence of surgery on survival in 145 patients with left main coronary artery disease. *Circulation* 1975; **52**:1105–111.
722. European Coronary Surgery Study Group. Long-term results of prospective randomised study of coronary artery bypass surgery in stable angina pectoris. European Coronary Surgery Study Group. *Lancet* 1982; **320**:1173–80. [https://doi.org/10.1016/S0140-6736\(82\)91200-4](https://doi.org/10.1016/S0140-6736(82)91200-4)
723. Coronary artery surgery study (CASS). A randomized trial of coronary artery bypass surgery. Survival data. *Circulation* 1983; **68**:939–50. <https://doi.org/10.1161/01.CIR.68.5.939>
724. Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group. Eleven-year survival in the Veterans Administration randomized trial of coronary bypass surgery for stable angina. *New Engl J Med* 1984; **311**:1333–9. <https://doi.org/10.1056/nejm198411223112102>
725. Windecker S, Stortecky S, Stefanini GG, daCosta BR, Rutjes AW, Di Nisio M, et al. Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. *BMJ* 2014; **348**:g3859. <https://doi.org/10.1136/bmj.g3859>
726. Miller RJH, Bonow RO, Gransar H, Park R, Slomka PJ, Friedman JD, et al. Percutaneous or surgical revascularization is associated with survival benefit in stable coronary artery disease. *Eur Heart J Cardiovasc Imaging* 2020; **21**:961–70. <https://doi.org/10.1093/ehjci/jeaa083>
727. Doenst T, Bonow RO, Bhatt DL, Falk V, Gaudino M. Improving terminology to describe coronary artery procedures: JACC review topic of the week. *J Am Coll Cardiol* 2021; **78**:180–8. <https://doi.org/10.1016/j.jacc.2021.05.010>
728. Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet* 2018; **391**:939–48. [https://doi.org/10.1016/s0140-6736\(18\)30423-9](https://doi.org/10.1016/s0140-6736(18)30423-9)
729. Perera D, Clayton T, O’Kane PD, Greenwood JP, Weerackody R, Ryan M, et al. Percutaneous revascularization for ischemic left ventricular dysfunction. *N Engl J Med* 2022; **387**:1351–60. <https://doi.org/10.1056/NEJMoa2206606>
730. Sabatine MS, Bergmark BA, Murphy SA, O’Gara PT, Smith PK, Serruys PW, et al. Percutaneous coronary intervention with drug-eluting stents versus coronary artery bypass grafting in left main coronary artery disease: an individual patient data meta-analysis. *Lancet* 2021; **398**:2247–57. [https://doi.org/10.1016/s0140-6736\(21\)02334-5](https://doi.org/10.1016/s0140-6736(21)02334-5)
731. Serruys PW, Ono M, Garg S, Hara H, Kawashima H, Pompilio G, et al. Percutaneous coronary revascularization: JACC historical breakthroughs in perspective. *J Am Coll Cardiol* 2021; **78**:384–407. <https://doi.org/10.1016/j.jacc.2021.05.024>
732. Bangalore S, Maron David J, Stone Gregg W, Hochman Judith S. Routine revascularization versus initial medical therapy for stable ischemic heart disease. *Circulation* 2020; **142**:841–57. <https://doi.org/10.1161/CIRCULATIONAHA.120.048194>
733. Soares A, Boden WE, Hueb W, Brooks MM, Vlachos HEA, O’Fee K, et al. Death and myocardial infarction following initial revascularization versus optimal medical therapy in chronic coronary syndromes with myocardial ischemia: a systematic review and meta-analysis of contemporary randomized controlled trials. *J Am Heart Assoc* 2021; **10**:e019114. <https://doi.org/10.1161/JAHA.120.019114>
734. Kumar A, Doshi R, Khan SU, Shariff M, Baby J, Majmundar M, et al. Revascularization or optimal medical therapy for stable ischemic heart disease: a Bayesian meta-analysis of contemporary trials. *Cardiovasc Revasc Med* 2022; **40**:42–7. <https://doi.org/10.1016/j.carrev.2021.12.005>
735. Wang HY, Xu B, Dou K, Guan C, Song L, Huang Y, et al. Implications of periprocedural myocardial biomarker elevations and commonly used MI definitions after left main PCI. *JACC Cardiovasc Interv* 2021; **14**:1623–34. <https://doi.org/10.1016/j.jcin.2021.05.006>
736. Bulluck H, Paradies V, Barbato E, Baumbach A, Botker HE, Capodanno D, et al. Prognostically relevant periprocedural myocardial injury and infarction associated with percutaneous coronary interventions: a Consensus Document of the ESC Working Group on Cellular Biology of the Heart and European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2021; **42**:2630–42. <https://doi.org/10.1093/eurheartj/ehab271>
737. Chaitman BR, Alexander KP, Cyr DD, Berger JS, Reynolds HR, Bangalore S, et al. Myocardial infarction in the ISCHEMIA Trial: impact of different definitions on incidence, prognosis, and treatment comparisons. *Circulation* 2021; **143**:790–804. <https://doi.org/10.1161/circulationaha.120.047987>
738. Redfors B, Stone GW, Alexander JH, Bates ER, Bhatt DL, Biondi-Zoccai G, et al. Outcomes according to coronary revascularization modality in the ISCHEMIA trial. *J Am Coll Cardiol* 2024; **83**:549–58. <https://doi.org/10.1016/j.jacc.2023.11.002>
739. Navarese EP, Lansky AJ, Farkouh ME, Grzelakowska K, Bonaca MP, Gorog DA, et al. Effects of elective coronary revascularization vs medical therapy alone on noncardiac mortality: a meta-analysis. *JACC Cardiovasc Interv* 2023; **16**:1144–56. <https://doi.org/10.1016/j.jcin.2023.02.030>
740. Vedin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT, et al. Significance of ischemic heart disease in patients with heart failure and preserved, midrange, and reduced ejection fraction: a nationwide cohort study. *Circ Heart Fail* 2017; **10**:e003875. <https://doi.org/10.1161/circheartfailure.117.003875>
741. Panza JA, Chrzanoski L, Bonow RO. Myocardial viability assessment before surgical revascularization in ischemic cardiomyopathy: JACC review topic of the week. *J Am Coll Cardiol* 2021; **78**:1068–77. <https://doi.org/10.1016/j.jacc.2021.07.004>
742. Rahimtoola SH, Dilsizian V, Kramer CM, Marwick TH, Vanoverschelde JL. Chronic ischemic left ventricular dysfunction: from pathophysiology to imaging and its

- integration into clinical practice. *JACC Cardiovasc Imaging* 2008;**1**:536–55. <https://doi.org/10.1016/j.jcmg.2008.05.009>
743. Kunadian V, Zaman A, Qiu W. Revascularization among patients with severe left ventricular dysfunction: a meta-analysis of observational studies. *Eur J Heart Fail* 2011;**13**: 773–84. <https://doi.org/10.1093/eurjhf/hfr037>
744. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *J Am Coll Cardiol* 2002;**39**:1151–8. [https://doi.org/10.1016/s0735-1097\(02\)01726-6](https://doi.org/10.1016/s0735-1097(02)01726-6)
745. Beanlands RS, Nichol G, Huszti E, Humen D, Racine N, Freeman M, et al. F-18-fluorodeoxyglucose positron emission tomography imaging-assisted management of patients with severe left ventricular dysfunction and suspected coronary disease: a randomized, controlled trial (PARR-2). *J Am Coll Cardiol* 2007;**50**:2002–12. <https://doi.org/10.1016/j.jacc.2007.09.006>
746. Mc Ardle B, Shukla T, Nichol G, deKemp RA, Bernick J, Guo A, et al. Long-term follow-up of outcomes with F-18-fluorodeoxyglucose positron emission tomography imaging-assisted management of patients with severe left ventricular dysfunction secondary to coronary disease. *Circ Cardiovasc Imaging* 2016;**9**:e004331. <https://doi.org/10.1161/circimaging.115.004331>
747. D'Egidio G, Nichol G, Williams KA, Guo A, Garrard L, deKemp R, et al. Increasing benefit from revascularization is associated with increasing amounts of myocardial hibernation: a substudy of the PARR-2 trial. *JACC Cardiovasc Imaging* 2009;**2**:1060–8. <https://doi.org/10.1016/j.jcmg.2009.02.017>
748. Ling LF, Marwick TH, Flores DR, Jaber WA, Brunken RC, Cerqueira MD, et al. Identification of therapeutic benefit from revascularization in patients with left ventricular systolic dysfunction: inducible ischemia versus hibernating myocardium. *Circ Cardiovasc Imaging* 2013;**6**:363–72. <https://doi.org/10.1161/circimaging.112.000138>
749. Petrie MC, Jhund PS, She L, Adlbrecht C, Doenst T, Panza JA, et al. Ten-year outcomes after coronary artery bypass grafting according to age in patients with heart failure and left ventricular systolic dysfunction: an analysis of the extended follow-up of the STICH Trial (Surgical Treatment for Ischemic Heart Failure). *Circulation* 2016;**134**:1314–24. <https://doi.org/10.1161/CIRCULATIONAHA.116.024800>
750. Panza JA, Ellis AM, Al-Khalidi HR, Holly TA, Berman DS, Oh JK, et al. Myocardial viability and long-term outcomes in ischemic cardiomyopathy. *N Engl J Med* 2019;**381**: 739–48. <https://doi.org/10.1056/NEJMoa1807365>
751. Wolff G, Dimitroulis D, Andreotti F, Kołodziejczak M, Jung C, Scicchitano P, et al. Survival benefits of invasive versus conservative strategies in heart failure in patients with reduced ejection fraction and coronary artery disease: a meta-analysis. *Circ Heart Fail* 2017;**10**:e003255. <https://doi.org/10.1161/circheartfailure.116.003255>
752. Sun LY, Gaudino M, Chen RJ, Bader Eddeen A, Ruel M. Long-term outcomes in patients with severely reduced left ventricular ejection fraction undergoing percutaneous coronary intervention vs coronary artery bypass grafting. *JAMA Cardiol* 2020;**5**:631–41. <https://doi.org/10.1001/jamacardio.2020.0239>
753. Völz S, Redfors B, Angerås O, Ioanes D, Odenstedt J, Koul S, et al. Long-term mortality in patients with ischaemic heart failure revascularized with coronary artery bypass grafting or percutaneous coronary intervention: insights from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *Eur Heart J* 2021;**42**: 2657–64. <https://doi.org/10.1093/eurheartj/ehab273>
754. Ono M, Garg S, Onuma Y, Serruys PW. Coronary artery bypass grafting versus percutaneous coronary intervention in ischaemic heart failure. Can reliable treatment decisions in high-risk patients be based on non-randomized data? *Eur Heart J* 2021;**42**: 2665–9. <https://doi.org/10.1093/eurheartj/ehab349>
755. Perera D, Ryan M, Morgan HP, Greenwood JP, Petrie MC, Dodd M, et al. Viability and outcomes with revascularization or medical therapy in ischemic ventricular dysfunction: a prespecified secondary analysis of the REVIVED-BICIS2 trial. *JAMA Cardiol* 2023;**8**:1154–61. <https://doi.org/10.1001/jamacardio.2023.3803>
756. Ryan M, Morgan H, Chiribiri A, Nagel E, Cleland J, Perera D. Myocardial viability testing: all STICHed up, or about to be REVIVED? *Eur Heart J* 2022;**43**:118–26. <https://doi.org/10.1093/eurheartj/ehab729>
757. Shaw LJ, Berman DS, Maron DJ, Mancini GBJ, Hayes SW, Hartigan PM, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008;**117**:1283–91. <https://doi.org/10.1161/circulationaha.107.743963>
758. Gaudino M, Andreotti F, Kimura T. Current concepts in coronary artery revascularisation. *Lancet* 2023;**401**:1611–28. [https://doi.org/10.1016/S0140-6736\(23\)00459-2](https://doi.org/10.1016/S0140-6736(23)00459-2)
759. Kim T, Kang DY, Kim S, Lee JH, Kim AR, Lee YJ, et al. Impact of complete or incomplete revascularization for left main coronary disease: the extended PRECOMBAT study. *JACC Asia* 2023;**3**:65–74. <https://doi.org/10.1016/j.jacasi.2022.10.007>
760. Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, et al. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation* 2013;**128**:141–51. <https://doi.org/10.1161/CIRCULATIONAHA.113.001803>
761. Gallinoro E, Paolisso P, Di Gioia G, Bermpis K, Fernandez-Peregrina E, Candrea A, et al. Deferral of coronary revascularization in patients with reduced ejection fraction based on physiological assessment: impact on long-term survival. *J Am Heart Assoc* 2022;**11**:e026656. <https://doi.org/10.1161/JAHA.122.026656>
762. Ahn JM, Park DW, Lee CV, Chang M, Cavalcante R, Sotomi Y, et al. Comparison of stenting versus bypass surgery according to the completeness of revascularization in severe coronary artery disease: patient-level pooled analysis of the SYNTAX, PRECOMBAT, and BEST trials. *JACC Cardiovasc Interv* 2017;**10**:1415–24. <https://doi.org/10.1016/j.jcin.2017.04.037>
763. Girerd N, Magne J, Rabilloud M, Charbonneau E, Mohamadi S, Pibarot P, et al. The impact of complete revascularization on long-term survival is strongly dependent on age. *Ann Thorac Surg* 2012;**94**:1166–72. <https://doi.org/10.1016/j.athoracsur.2012.05.023>
764. Werner GS, Martin-Yuste V, Hildick-Smith D, Boudou N, Sianos G, Gelev V, et al. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *Eur Heart J* 2018;**39**: 2484–93. <https://doi.org/10.1093/eurheartj/ehy220>
765. Lee SW, Lee PH, Ahn JM, Park DW, Yun SC, Han S, et al. Randomized trial evaluating percutaneous coronary intervention for the treatment of chronic total occlusion. *Circulation* 2019;**139**:1674–83. <https://doi.org/10.1161/CIRCULATIONAHA.118.031313>
766. Simsek B, Kostantinis S, Karacsonyi J, Alwasd K, Megaly M, Karpaliotis D, et al. A systematic review and meta-analysis of clinical outcomes of patients undergoing chronic total occlusion percutaneous coronary intervention. *J Invasive Cardiol* 2022;**34**:E763–75.
767. Werner GS, Hildick-Smith D, Martin Yuste V, Boudou N, Sianos G, Gelev V, et al. Three-year outcomes of a randomized multicentre trial comparing revascularization and optimal medical therapy for chronic total coronary occlusions (EuroCTO). *EuroIntervention* 2023;**19**:571–9. <https://doi.org/10.4244/eij-d-23-00312>
768. Takahashi K, Serruys PW, Gao C, Ono M, Wang R, Thuji DJFM, et al. Ten-year all-cause death according to completeness of revascularization in patients with three-vessel disease or left main coronary artery disease: insights from the SYNTAX Extended survival study. *Circulation* 2021;**144**:96–109. <https://doi.org/10.1161/CIRCULATIONAHA.120.046289>
769. Leviner DB, Torregrossa G, Puskas JD. Incomplete revascularization: what the surgeon needs to know. *Ann Cardiothorac Surg* 2018;**7**:463–9. <https://doi.org/10.21037/acs.2018.06.07>
770. Gaba P, Gersh BJ, Ali ZA, Moses JW, Stone GW. Complete versus incomplete coronary revascularization: definitions, assessment and outcomes. *Nat Rev Cardiol* 2021;**18**: 155–68. <https://doi.org/10.1038/s41569-020-00457-5>
771. Lamy A, Eikelboom J, Sheth T, Connolly S, Bosch J, Fox KAA, et al. Rivaroxaban, aspirin, or both to prevent early coronary bypass graft occlusion: the COMPASS-CABG study. *J Am Coll Cardiol* 2019;**73**:121–30. <https://doi.org/10.1016/j.jacc.2018.10.048>
772. Xenogiannis I, Zenati M, Bhatt DL, Rao SV, Rodés-Cabau J, Goldman S, et al. Saphenous vein graft failure: from pathophysiology to prevention and treatment strategies. *Circulation* 2021;**144**:728–45. <https://doi.org/10.1161/CIRCULATIONAHA.120.052163>
773. Han Z, Zhang G, Chen Y. Early asymptomatic graft failure in coronary artery bypass grafting: a study based on computed tomography angiography analysis. *J Cardiothorac Surg* 2023;**18**:98. <https://doi.org/10.1186/s13019-023-02199-0>
774. Head SJ, Borgermann J, Osnabrugge RL, Kieser TM, Falk V, Taggart DP, et al. Coronary artery bypass grafting: Part 2—optimizing outcomes and future prospects. *Eur Heart J* 2013;**34**:2873–86. <https://doi.org/10.1093/eurheartj/ehs284>
775. Stone GW. Multivessel PCI on its 40th anniversary: finally a match for CABG? *Eur Heart J* 2017;**38**:3135–8. <https://doi.org/10.1093/eurheartj/ehx528>
776. Osnabrugge RL, Speir AM, Head SJ, Fonner CE, Fonner E, Kappetein AP, et al. Performance of EuroSCORE II in a large US database: implications for transcatheter aortic valve implantation. *Eur J Cardiothorac Surg* 2014;**46**:400–8; discussion 408. <https://doi.org/10.1093/ejcts/ezu033>
777. Thuji D, Habib RH, Head SJ, Puskas JD, Taggart DP, Stone GW, et al. Prognostic performance of the Society of Thoracic Surgeons risk score in patients with left main coronary artery disease undergoing revascularisation: a post hoc analysis of the EXCEL trial. *EuroIntervention* 2020;**16**:36–43. <https://doi.org/10.4244/EIJ-D-19-00417>
778. Reichart D, Rosato S, Nammias W, Onorati F, Dalén M, Castro L, et al. Clinical frailty scale and outcome after coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2018;**54**:1102–9. <https://doi.org/10.1093/ejcts/ezy222>
779. Zhang YJ, Iqbal J, Campos CM, Klaveren DV, Bourantas CV, Dawkins KD, et al. Prognostic value of site SYNTAX score and rationale for combining anatomic and clinical factors in decision making: insights from the SYNTAX trial. *J Am Coll Cardiol* 2014;**64**:423–32. <https://doi.org/10.1016/j.jacc.2014.05.022>
780. Bonaros N, Van Craenenbroeck E. A good operation is not enough, when it comes to frail patients. *Eur J Cardiothorac Surg* 2023;**64**:ezad205. <https://doi.org/10.1093/ejcts/ezad205>
781. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 2005;**1**:219–27.
782. Byrne RA, Frenes S, Capodanno D, Czerny M, Doenst T, Emberson JR, et al. 2022 Joint ESC/EACTS review of the 2018 guideline recommendations on the revascularization of left main coronary artery disease in patients at low surgical risk and anatomy

- suitable for PCI or CABG. *Eur Heart J* 2023;**44**:4310–20. <https://doi.org/10.1093/eurheartj/ehad476>
783. Calborean PA, Grebenisan P, Nistor IA, Pal K, Vacariu V, Drincal RK, et al. Prediction of 3-year all-cause and cardiovascular cause mortality in a prospective percutaneous coronary intervention registry: machine learning model outperforms conventional clinical risk scores. *Atherosclerosis* 2022;**350**:33–40. <https://doi.org/10.1016/j.atherosclerosis.2022.03.028>
784. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 2013;**381**:639–50. [https://doi.org/10.1016/s0140-6736\(13\)60108-7](https://doi.org/10.1016/s0140-6736(13)60108-7)
785. Escaned J, Collet C, Ryan N, Luigi De Maria G, Walsh S, Sabate M, et al. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. *Eur Heart J* 2017;**38**:3124–34. <https://doi.org/10.1093/eurheartj/ehx512>
786. Cavalcante R, Sotomi Y, Mancone M, Whan Lee C, Ahn JM, Onuma Y, et al. Impact of the SYNTAX scores I and II in patients with diabetes and multivessel coronary disease: a pooled analysis of patient level data from the SYNTAX, PRECOMBAT, and BEST trials. *Eur Heart J* 2017;**38**:1969–77. <https://doi.org/10.1093/eurheartj/ehx138>
787. Hara H, Shiomi H, van Klaveren D, Kent DM, Steyerberg EW, Garg S, et al. External validation of the SYNTAX score II 2020. *J Am Coll Cardiol* 2021;**78**:1227–38. <https://doi.org/10.1016/j.jacc.2021.07.027>
788. Modolo R, Chichareon P, van Klaveren D, Dressler O, Zhang Y, Sabik JF, et al. Impact of non-respect of SYNTAX score II recommendation for surgery in patients with left main coronary artery disease treated by percutaneous coronary intervention: an EXCEL substudy. *Eur J Cardiothorac Surg* 2020;**57**:676–83. <https://doi.org/10.1093/ejcts/ezz274>
789. Takahashi K, Serruys PW, Fuster V, Farkouh ME, Spertus JA, Cohen DJ, et al. Redevelopment and validation of the SYNTAX score II to individualise decision making between percutaneous and surgical revascularisation in patients with complex coronary artery disease: secondary analysis of the multicentre randomised controlled SYNTAXES trial with external cohort validation. *Lancet* 2020;**396**:1399–412. [https://doi.org/10.1016/S0140-6736\(20\)32114-0](https://doi.org/10.1016/S0140-6736(20)32114-0)
790. De Silva K, Morton G, Sicard P, Chong E, Indermuehle A, Clapp B, et al. Prognostic utility of BCIS myocardial jeopardy score for classification of coronary disease burden and completeness of revascularization. *Am J Cardiol* 2013;**111**:172–7. <https://doi.org/10.1016/j.amjcard.2012.09.012>
791. Kapoor JR, Gienger AL, Ardehali R, Varghese R, Perez MV, Sundaram V, et al. Isolated disease of the proximal left anterior descending artery comparing the effectiveness of percutaneous coronary interventions and coronary artery bypass surgery. *JACC Cardiovasc Interv* 2008;**1**:483–91. <https://doi.org/10.1016/j.jcin.2008.07.001>
792. Thiele H, Neumann-Schiederwind P, Jacobs S, Boudriot E, Walther T, Mohr FW, et al. Randomized comparison of minimally invasive direct coronary artery bypass surgery versus sirolimus-eluting stenting in isolated proximal left anterior descending coronary artery stenosis. *J Am Coll Cardiol* 2009;**53**:2324–31. <https://doi.org/10.1016/j.jacc.2009.03.032>
793. Blazek S, Holzhey D, Jungert C, Borger MA, Fuernau G, Desch S, et al. Comparison of bare-metal stenting with minimally invasive bypass surgery for stenosis of the left anterior descending coronary artery: 10-year follow-up of a randomized trial. *JACC Cardiovasc Interv* 2013;**6**:20–6. <https://doi.org/10.1016/j.jcin.2012.09.008>
794. Blazek S, Rossbach C, Borger MA, Fuernau G, Desch S, Eitel I, et al. Comparison of sirolimus-eluting stenting with minimally invasive bypass surgery for stenosis of the left anterior descending coronary artery: 7-year follow-up of a randomized trial. *JACC Cardiovasc Interv* 2015;**8**:30–8. <https://doi.org/10.1016/j.jcin.2014.08.006>
795. Thuijs D, Kappetein AP, Serruys PW, Mohr FW, Morice MC, Mack MJ, et al. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. *Lancet* 2019;**394**:1325–34. [https://doi.org/10.1016/s0140-6736\(19\)31997-x](https://doi.org/10.1016/s0140-6736(19)31997-x)
796. Gianoli M, de Jong AR, Jacob KA, Namba HF, van der Kaaij NP, van der Harst P, et al. Minimally invasive surgery or stenting for left anterior descending artery disease—meta-analysis. *Int J Cardiol Heart Vasc* 2022;**40**:101046. <https://doi.org/10.1016/j.ijcha.2022.101046>
797. Patel NC, Hemli JM, Seetharam K, Singh VP, Scheinerman SJ, Pirelli L, et al. Minimally invasive coronary bypass versus percutaneous coronary intervention for isolated complex stenosis of the left anterior descending coronary artery. *J Thorac Cardiovasc Surg* 2022;**163**:1839–46.e1. <https://doi.org/10.1016/j.jtcvs.2020.04.171>
798. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;**360**:961–72. <https://doi.org/10.1056/NEJMoa0804626>
799. Giacoppo D, Colleran R, Cassese S, Frangieh AH, Wiebe J, Joner M, et al. Percutaneous coronary intervention vs coronary artery bypass grafting in patients with left main coronary artery stenosis: a systematic review and meta-analysis. *JAMA Cardiol* 2017;**2**:1079–88. <https://doi.org/10.1001/jamacardio.2017.2895>
800. Palmerini T, Serruys P, Kappetein AP, Genereux P, Riva DD, Reggiani LB, et al. Clinical outcomes with percutaneous coronary revascularization vs coronary artery bypass grafting surgery in patients with unprotected left main coronary artery disease: a meta-analysis of 6 randomized trials and 4,686 patients. *Am Heart J* 2017;**190**:54–63. <https://doi.org/10.1016/j.ahj.2017.05.005>
801. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, et al. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012;**367**:2375–84. <https://doi.org/10.1056/NEJMoa1211585>
802. Ahmad Y, Howard JP, Arnold AD, Cook CM, Prasad M, Ali ZA, et al. Mortality after drug-eluting stents vs. coronary artery bypass grafting for left main coronary artery disease: a meta-analysis of randomized controlled trials. *Eur Heart J* 2020;**41**:3228–35. <https://doi.org/10.1093/eurheartj/ehaa135>
803. Kuno T, Ueyama H, Rao SV, Cohen MG, Tamis-Holland JE, Thompson C, et al. Percutaneous coronary intervention or coronary artery bypass graft surgery for left main coronary artery disease: a meta-analysis of randomized trials. *Am Heart J* 2020;**227**:9–10. <https://doi.org/10.1016/j.ahj.2020.06.001>
804. D'Ascenzo F, De Filippo O, Elia E, Doronzo MP, Omedè P, Montefusco A, et al. Percutaneous vs. surgical revascularization for patients with unprotected left main stenosis: a meta-analysis of 5-year follow-up randomized controlled trials. *Eur Heart J Qual Care Clin Outcomes* 2021;**7**:476–85. <https://doi.org/10.1093/ehjqcc/qcaa041>
805. Hildick-Smith D, Eged M, Banning A, Brunel P, Ferenc M, Hovasse T, et al. The European bifurcation club Left Main Coronary Stent study: a randomized comparison of stepwise provisional vs. systematic dual stenting strategies (EBC MAIN). *Eur Heart J* 2021;**42**:3829–39. <https://doi.org/10.1093/eurheartj/ehab283>
806. Kandzari DE, Gershlick AH, Serruys PW, Leon MB, Morice MC, Simonton CA, et al. Outcomes among patients undergoing distal left main percutaneous coronary intervention. *Circ Cardiovasc Interv* 2018;**11**:e007007. <https://doi.org/10.1161/CIRCINTERVENTIONS.118.007007>
807. Choi KH, Song YB, Lee JM, Park TK, Yang JH, Hahn JY, et al. Prognostic effects of treatment strategies for left main versus non-left main bifurcation percutaneous coronary intervention with current-generation drug-eluting stent. *Circ Cardiovasc Interv* 2020;**13**:e008543. <https://doi.org/10.1161/CIRCINTERVENTIONS.119.008543>
808. Ninomiya K, Serruys PW, Garg S, Gao C, Masuda S, Lunardi M, et al. Predicted and observed mortality at 10 years in patients with bifurcation lesions in the SYNTAX trial. *JACC Cardiovasc Interv* 2022;**15**:1231–42. <https://doi.org/10.1016/j.jcin.2022.04.025>
809. Wang HY, Zhang R, Dou K, Huang Y, Xie L, Qiao Z, et al. Left main bifurcation stenting: impact of residual ischaemia on cardiovascular mortality. *Eur Heart J* 2023;**44**:4324–36. <https://doi.org/10.1093/eurheartj/ehad318>
810. Holm NR, Andreasen LN, Neghabat O, Laanmets P, Kumsars I, Bennett J, et al. OCT or angiography guidance for PCI in complex bifurcation lesions. *N Engl J Med* 2023;**389**:1477–87. <https://doi.org/10.1056/NEJMoa2307770>
811. Xu B, Redfors B, Yang Y, Qiao S, Wu Y, Chen J, et al. Impact of operator experience and volume on outcomes after left main coronary artery percutaneous coronary intervention. *JACC Cardiovasc Interv* 2016;**9**:2086–93. <https://doi.org/10.1016/j.jcin.2016.08.011>
812. Kinnaird T, Gallagher S, Anderson R, Sharp A, Farooq V, Ludman P, et al. Are higher operator volumes for unprotected left main stem percutaneous coronary intervention associated with improved patient outcomes? A survival analysis of 6724 procedures from the British Cardiovascular Intervention Society National Database. *Circ Cardiovasc Interv* 2020;**13**:e008782. <https://doi.org/10.1161/CIRCINTERVENTIONS.119.008782>
813. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stähle E, Colombo A, et al. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery Trial. *Circulation* 2014;**129**:2388–94. <https://doi.org/10.1161/CIRCULATIONAHA.113.006689>
814. Park SJ, Kim YH, Park DW, Yun SC, Ahn JM, Song HG, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med* 2011;**364**:1718–27. <https://doi.org/10.1056/NEJMoa1100452>
815. Ahn JM, Roh JH, Kim YH, Park DW, Yun SC, Lee PH, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease: 5-year outcomes of the PRECOMBAT study. *J Am Coll Cardiol* 2015;**65**:2198–206. <https://doi.org/10.1016/j.jacc.2015.03.033>
816. Park DW, Ahn JM, Park H, Yun SC, Kang DY, Lee PH, et al. Ten-year outcomes after drug-eluting stents versus coronary artery bypass grafting for left main coronary disease: extended follow-up of the PRECOMBAT trial. *Circulation* 2020;**141**:1437–46. <https://doi.org/10.1161/CIRCULATIONAHA.120.046039>
817. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stähle E, Colombo A, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation* 2010;**121**:2645–53. <https://doi.org/10.1161/circulationaha.109.899211>
818. Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Stähle E, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment

- of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J* 2011;**32**:2125–34. <https://doi.org/10.1093/eurheartj/ehr213>
819. Makikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IBA, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet* 2016;**388**:2743–52. [https://doi.org/10.1016/S0140-6736\(16\)32052-9](https://doi.org/10.1016/S0140-6736(16)32052-9)
 820. Holm NR, Makikallio T, Lindsay MM, Spence MS, Erglis A, Menown IBA, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: updated 5-year outcomes from the randomised, non-inferiority NOBLE trial. *Lancet* 2020;**395**:191–9. [https://doi.org/10.1016/S0140-6736\(19\)32972-1](https://doi.org/10.1016/S0140-6736(19)32972-1)
 821. Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med* 2016;**375**:2223–35. <https://doi.org/10.1056/NEJMoa1610227>
 822. Stone GW, Kappetein AP, Sabik JF, Pocock SJ, Morice MC, Puskas J, et al. Five-year outcomes after PCI or CABG for left main coronary disease. *N Engl J Med* 2019;**381**:1820–30. <https://doi.org/10.1056/NEJMoa1909406>
 823. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stähle E, Colombo A, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013;**381**:629–38. [https://doi.org/10.1016/S0140-6736\(13\)60141-5](https://doi.org/10.1016/S0140-6736(13)60141-5)
 824. Farkouh ME, Domanski M, Dangas GD, Godoy LC, Mack MJ, Siami FS, et al. Long-term survival following multivessel revascularization in patients with diabetes: the FREEDOM follow-on study. *J Am Coll Cardiol* 2019;**73**:629–38. <https://doi.org/10.1016/j.jacc.2018.11.001>
 825. Parasca CA, Head SJ, Milojevic M, Mack MJ, Serruys PW, Morice MC, et al. Incidence, characteristics, predictors, and outcomes of repeat revascularization after percutaneous coronary intervention and coronary artery bypass grafting: the SYNTAX trial at 5 years. *JACC Cardiovasc Interv* 2016;**9**:2493–507. <https://doi.org/10.1016/j.jcin.2016.09.044>
 826. van Nunen LX, Zimmermann FM, Tonino PA, Barbato E, Baumbach A, Engström T, et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. *Lancet* 2015;**386**:1853–60. [https://doi.org/10.1016/S0140-6736\(15\)00057-4](https://doi.org/10.1016/S0140-6736(15)00057-4)
 827. Zimmermann FM, Ding VY, Pijls NHJ, Piroth Z, van Straten AHM, Szekely L, et al. Fractional flow reserve-guided pci or coronary bypass surgery for 3-vessel coronary artery disease: 3-year follow-up of the FAME 3 trial. *Circulation* 2023;**148**:950–8. <https://doi.org/10.1161/CIRCULATIONAHA.123.065770>
 828. Piroth Z, Otsuki H, Zimmermann FM, Ferenci T, Keulards DCJ, Yeung AC, et al. Prognostic value of measuring fractional flow reserve after percutaneous coronary intervention in patients with complex coronary artery disease: insights from the FAME 3 trial. *Circ Cardiovasc Interv* 2022;**15**:884–91. <https://doi.org/10.1161/CIRCINTERVENTIONS.122.012542>
 829. Collison D, Didagelos M, Aetesam-Ur-Rahman M, Copt S, McDade R, McCartney P, et al. Post-stenting fractional flow reserve vs coronary angiography for optimization of percutaneous coronary intervention (TARGET-FFR). *Eur Heart J* 2021;**42**:4656–68. <https://doi.org/10.1093/eurheartj/ehab449>
 830. Patel MR, Jeremias A, Maehara A, Matsumura M, Zhang Z, Schneider J, et al. 1-Year outcomes of blinded physiological assessment of residual ischemia after successful PCI: DEFINE PCI trial. *JACC Cardiovasc Interv* 2022;**15**:52–61. <https://doi.org/10.1016/j.jcin.2021.09.042>
 831. Hwang D, Koo BK, Zhang J, Park J, Yang S, Kim M, et al. Prognostic implications of fractional flow reserve after coronary stenting: a systematic review and meta-analysis. *JAMA Netw Open* 2022;**5**:e2232842. <https://doi.org/10.1001/jamanetworkopen.2022.32842>
 832. Collet C, Johnson Nils P, Mizukami T, Fearon WF, Berry C, Sonck J, et al. Impact of post-PCI FFR stratified by coronary artery. *JACC Cardiovasc Interv* 2023;**16**:2396–408. <https://doi.org/10.1016/j.jcin.2023.08.018>
 833. Dai N, Yuan S, Dou K, Zhang R, Hu N, He J, et al. Prognostic implications of pre-stent pullback pressure gradient and poststent quantitative flow ratio in patients undergoing percutaneous coronary intervention. *J Am Heart Assoc* 2022;**11**:e024903. <https://doi.org/10.1161/JAHA.121.024903>
 834. Dai N, Tang X, Chen Z, Huang D, Duan S, Qian J, et al. Pre-stenting angiography-FFR based physiological map provides virtual intervention and predicts physiological and clinical outcomes. *Catheter Cardiovasc Interv* 2023;**101**:1053–61. <https://doi.org/10.1002/ccd.30635>
 835. Kikuta Y, Cook CM, Sharp ASP, Salinas P, Kawase Y, Shiono Y, et al. Pre-angioplasty instantaneous wave-free ratio pullback predicts hemodynamic outcome in humans with coronary artery disease: primary results of the international multicenter iFR GRADIENT registry. *JACC Cardiovasc Interv* 2018;**11**:757–67. <https://doi.org/10.1016/j.jcin.2018.03.005>
 836. Biscaglia S, Verardi FM, Tebaldi M, Guiducci V, Cagliani S, Campana R, et al. QFR-based virtual PCI or conventional angiography to guide PCI: the AQVA trial. *JACC Cardiovasc Interv* 2023;**16**:783–94. <https://doi.org/10.1016/j.jcin.2022.10.054>
 837. Bouisset F, Ohashi H, Andreini D, Collet C. (September 19, 2023) Role of coronary computed tomography angiography to optimise percutaneous coronary intervention outcomes. *Heart* 2024;**110**:1056–1062
 838. Sonck J, Nagumo S, Norgaard BL, Otake H, Ko B, Zhang J, et al. Clinical validation of a virtual planner for coronary interventions based on coronary CT angiography. *JACC Cardiovasc Imaging* 2022;**15**:1242–55. doi: [10.1016/j.jcmg.2022.02.003](https://doi.org/10.1016/j.jcmg.2022.02.003)
 839. Van Belle E, Raposo L, Bravo Baptista S, Vincent F, Porouchani S, Cosenza A, et al. Impact of an interactive CT/FFR(CT) interventional planner on coronary artery disease management decision making. *JACC Cardiovasc Imaging* 2021;**14**:1068–70. <https://doi.org/10.1016/j.jcmg.2020.09.040>
 840. Lee JM, Choi KH, Song YB, Lee JY, Lee SJ, Lee SY, et al. Intravascular imaging-guided or angiography-guided complex PCI. *N Engl J Med* 2023;**388**:1668–79. <https://doi.org/10.1056/NEJMoa2216607>
 841. Ali ZA, Landmesser U, Maehara A, Matsumura M, Shlofmitz RA, Guagliumi G, et al. Optical coherence tomography-guided versus angiography-guided PCI. *N Engl J Med* 2023;**389**:1466–76. <https://doi.org/10.1056/NEJMoa2305861>
 842. Sabik JF III, Blackstone EH, Gillinov AM, Banbury MK, Smedira NG, Lytle BW. Influence of patient characteristics and arterial grafts on freedom from coronary reoperation. *J Thorac Cardiovasc Surg* 2006;**131**:90–8. <https://doi.org/10.1016/j.jtcvs.2005.05.024>
 843. Locker C, Schaff HV, Dearani JA, Joyce LD, Park SJ, Burkhardt HM, et al. Multiple arterial grafts improve late survival of patients undergoing coronary artery bypass graft surgery: analysis of 8622 patients with multivessel disease. *Circulation* 2012;**126**:1023–30. <https://doi.org/10.1161/CIRCULATIONAHA.111.084624>
 844. Lowenstern A, Wu J, Bradley SM, Fanaroff AC, Tcheng JE, Wang TY. Current landscape of hybrid revascularization: a report from the NCDR CathPCI Registry. *Am Heart J* 2019;**215**:167–77. <https://doi.org/10.1016/j.ahj.2019.06.014>
 845. Ganyukov VI, Kochergin NA, Shilov AA, Tarasov RS, Skupien J, Kozyrin KA, et al. Randomized clinical trial of surgical versus percutaneous versus hybrid multivessel coronary revascularization: 3 years' follow-up. *JACC Cardiovasc Interv* 2021;**14**:1163–5. <https://doi.org/10.1016/j.jcin.2021.02.037>
 846. Makoul G, Clayman ML. An integrative model of shared decision making in medical encounters. *Patient Educ Couns* 2006;**60**:301–12. <https://doi.org/10.1016/j.pec.2005.06.010>
 847. Mulley AG, Trimble C, Elwyn G. Stop the silent misdiagnosis: patients' preferences matter. *BMJ* 2012;**345**:e6572. <https://doi.org/10.1136/bmj.e6572>
 848. Hughes TM, Merath K, Chen Q, Sun S, Palmer E, Idrees JJ, et al. Association of shared decision-making on patient-reported health outcomes and healthcare utilization. *Am J Surg* 2018;**216**:7–12. <https://doi.org/10.1016/j.amjsurg.2018.01.011>
 849. Nuis RJ, Jadoon A, van Dalen BM, Dulfer K, Snelder SM, Yazdi MT, et al. Patient perspectives on left main stem revascularization strategies, the OPINION-2 study. *J Cardiol* 2021;**77**:271–8. <https://doi.org/10.1016/j.jcc.2020.09.009>
 850. Oudkerk Pool MD, Hooglugt JQ, Schijven MP, Mulder BJM, Bouma BJ, de Winter RJ, et al. Review of digitalized patient education in cardiology: a future ahead? *Cardiology* 2021;**146**:263–71. <https://doi.org/10.1159/000512778>
 851. Lincoln TE, Buddadhumaruk P, Arnold RM, Scheunemann LP, Ernecoff NC, Chang CCH, et al. Association between shared decision-making during family meetings and surrogates' trust in their ICU physician. *Chest* 2023;**163**:1214–24. <https://doi.org/10.1016/j.chest.2022.10.028>
 852. Ayton DR, Barker AL, Peeters G, Berkovic DE, Lefkowitz J, Brennan A, et al. Exploring patient-reported outcomes following percutaneous coronary intervention: a qualitative study. *Health Expect* 2018;**21**:457–65. <https://doi.org/10.1111/hex.12636>
 853. Kipp R, Lehman J, Israel J, Edwards N, Becker T, Raval AN. Patient preferences for coronary artery bypass graft surgery or percutaneous intervention in multivessel coronary artery disease. *Catheter Cardiovasc Interv* 2013;**82**:212–8. <https://doi.org/10.1002/ccd.24399>
 854. Wittberg G, Segev A, Barac YD, Raanani E, Assali A, Finkelstein A, et al. Heart team/guidelines discordance is associated with increased mortality: data from a national survey of revascularization in patients with complex coronary artery disease. *Circ Cardiovasc Interv* 2021;**14**:e009686. <https://doi.org/10.1161/circinterventions.120.009686>
 855. Patterson T, McConkey HZR, Ahmed-Jushuf F, Moschonas K, Nguyen H, Karamasis GV, et al. Long-term outcomes following heart team revascularization recommendations in complex coronary artery disease. *J Am Heart Assoc* 2019;**8**:e011279. <https://doi.org/10.1161/JAHA.118.011279>
 856. Jonik S, Marchel M, Huczek Z, Kochman J, Wilimski R, Kuśmierczyk M, et al. An individualized approach of multidisciplinary heart team for myocardial revascularization and valvular heart disease—state of art. *J Pers Med* 2022;**12**:705. <https://doi.org/10.3390/jpm12050705>
 857. McKeown L, Hong YA, Kreps GL, Xue H. Trends and differences in perceptions of patient-centered communication among adults in the US. *Patient Educ Couns* 2023;**106**:128–34. <https://doi.org/10.1016/j.pec.2022.10.010>
 858. Tsang MB, Schwalm JD, Gandhi S, Sibbald MG, Gafni A, Mercuri M, et al. Comparison of heart team vs interventional cardiologist recommendations for the treatment of

- patients with multivessel coronary artery disease. *JAMA Netw Open* 2020;**3**:e2012749. <https://doi.org/10.1001/jamanetworkopen.2020.12749>
859. Dzavik V, Ghali WA, Norris C, Mitchell LB, Koshal A, Saunders LD, et al. Long-term survival in 11,661 patients with multivessel coronary artery disease in the era of stenting: a report from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) investigators. *Am Heart J* 2001;**142**:119–26. <https://doi.org/10.1067/mhj.2001.116072>
860. Lee PH, Ahn JM, Chang M, Baek S, Yoon SH, Kang SJ, et al. Left main coronary artery disease: secular trends in patient characteristics, treatments, and outcomes. *J Am Coll Cardiol* 2016;**68**:1233–46. <https://doi.org/10.1016/j.jacc.2016.05.089>
861. Panza JA, Velazquez EJ, She L, Smith PK, Nicolau JC, Favalaro RR, et al. Extent of coronary and myocardial disease and benefit from surgical revascularization in ischemic LV dysfunction [Corrected]. *J Am Coll Cardiol* 2014;**64**:553–61. <https://doi.org/10.1016/j.jacc.2014.04.064>
862. Sullivan PG, Wallach JD, Ioannidis JP. Meta-analysis comparing established risk prediction models (EuroSCORE II, STS Score, and ACEF Score) for perioperative mortality during cardiac surgery. *Am J Cardiol* 2016;**118**:1574–82. <https://doi.org/10.1016/j.amjcard.2016.08.024>
863. Ad N, Holmes SD, Patel J, Pritchard G, Shuman DJ, Halpin L. Comparison of EuroSCORE II, original EuroSCORE, and the Society of Thoracic Surgeons Risk Score in cardiac surgery patients. *Ann Thorac Surg* 2016;**102**:573–9. <https://doi.org/10.1016/j.athoracsur.2016.01.105>
864. Sinha S, Dimagli A, Dixon L, Gaudino M, Caputo M, Vohra HA, et al. Systematic review and meta-analysis of mortality risk prediction models in adult cardiac surgery. *Interact Cardiovasc Thorac Surg* 2021;**33**:673–86. <https://doi.org/10.1093/icvts/ivab151>
865. Scudeler TL, Farkouh ME, Hueb W, Rezende PC, Campolina AG, Martins EB, et al. Coronary atherosclerotic burden assessed by SYNTAX scores and outcomes in surgical, percutaneous or medical strategies: a retrospective cohort study. *BMJ Open* 2022;**12**:e062378. <https://doi.org/10.1136/bmjopen-2022-062378>
866. Kuno T, Kiyohara Y, Maehara A, Ueyama HA, Kampaktsis PN, Takagi H, et al. Comparison of intravascular imaging, functional, or angiographically guided coronary intervention. *J Am Coll Cardiol* 2023;**82**:2167–76. <https://doi.org/10.1016/j.jacc.2023.09.823>
867. Chen H, Hong L, Xi G, Wang H, Hu J, Liu Q, et al. Prognostic value of quantitative flow ratio in patients with coronary heart disease after percutaneous coronary intervention therapy: a meta-analysis. *Front Cardiovasc Med* 2023;**10**:1164290. <https://doi.org/10.3389/fcvm.2023.1164290>
868. Agarwal SK, Kasula S, Hacıoğlu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing post-intervention fractional flow reserve to optimize acute results and the relationship to long-term outcomes. *JACC Cardiovasc Interv* 2016;**9**:1022–31. <https://doi.org/10.1016/j.jcin.2016.01.046>
869. Mилоjević M, Serruys PW, Sabik JF, Kandzari DE, Schampaert E, van Boven AJ, et al. Bypass surgery or stenting for left main coronary artery disease in patients with diabetes. *J Am Coll Cardiol* 2019;**73**:1616–28. <https://doi.org/10.1016/j.jacc.2019.01.037>
870. Gaudino M, Audisio K, Hueb WA, Stone GW, Farkouh ME, Di Franco A, et al. Coronary artery bypass grafting versus medical therapy in patients with stable coronary artery disease: an individual patient data pooled meta-analysis of randomized trials. *J Thorac Cardiovasc Surg* 2024;**167**:1022–32.e14. <https://doi.org/10.1016/j.jtcvs.2022.06.003>
871. Bari 2D Study Group; Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;**360**:2503–15. <https://doi.org/10.1056/NEJMoa0805796>
872. Park DW, Kim YH, Song HG, Ahn JM, Kim WJ, Lee JY, et al. Long-term outcome of stents versus bypass surgery in diabetic and nondiabetic patients with multivessel or left main coronary artery disease: a pooled analysis of 5775 individual patient data. *Circ Cardiovasc Interv* 2012;**5**:467–75. <https://doi.org/10.1161/circinterventions.112.969915>
873. Kamalesh M, Sharp TG, Tang XC, Shunk K, Ward HB, Walsh J, et al. Percutaneous coronary intervention versus coronary bypass surgery in United States veterans with diabetes. *J Am Coll Cardiol* 2013;**61**:808–16. <https://doi.org/10.1016/j.jacc.2012.11.044>
874. Kappetein AP, Head SJ, Morice MC, Banning AP, Serruys PW, Mohr FW, et al. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *Eur J Cardiothorac Surg* 2013;**43**:1006–13. <https://doi.org/10.1093/ejcts/ezt017>
875. Booth J, Clayton T, Pepper J, Nugara F, Flather M, Sigwart U, et al. Randomized, controlled trial of coronary artery bypass surgery versus percutaneous coronary intervention in patients with multivessel coronary artery disease: six-year follow-up from the Stent or Surgery Trial (SoS). *Circulation* 2008;**118**:381–8. <https://doi.org/10.1161/circulationaha.107.739144>
876. Park SJ, Ahn JM, Kim YH, Park DW, Yun SC, Lee JY, et al. Trial of everolimus-eluting stents or bypass surgery for coronary disease. *N Engl J Med* 2015;**372**:1204–12. <https://doi.org/10.1056/NEJMoa1415447>
877. Hueb WA, Bellotti G, de Oliveira SA, Arie S, de Albuquerque CP, Jatene AD, et al. Medicine, Angioplasty or Surgery Study (MASS): a prospective, randomized trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending artery stenoses. *J Am Coll Cardiol* 1995;**26**:1600–5. [https://doi.org/10.1016/0735-1097\(95\)00384-3](https://doi.org/10.1016/0735-1097(95)00384-3)
878. Aziz O, Rao C, Panesar SS, Jones C, Morris S, Darzi A, et al. Meta-analysis of minimally invasive internal thoracic artery bypass versus percutaneous revascularisation for isolated lesions of the left anterior descending artery. *BMJ* 2007;**334**:617. <https://doi.org/10.1136/bmj.39106.476215.BE>
879. Deppe A-C, Liakopoulos OJ, Kuhn EW, Slottosch I, Scherner M, Choi YH, et al. Minimally invasive direct coronary bypass grafting versus percutaneous coronary intervention for single-vessel disease: a meta-analysis of 2885 patients. *Eur J Cardiothorac Surg* 2015;**47**:397–406. <https://doi.org/10.1093/ejcts/ezu285>
880. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, et al. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 2016;**18**:613–25. <https://doi.org/10.1002/ehf.566>
881. Fox KF, Cowie MR, Wood DA, Coats AJ, Gibbs JS, Underwood SR, et al. Coronary artery disease as the cause of incident heart failure in the population. *Eur Heart J* 2001;**22**:228–36. <https://doi.org/10.1053/ehj.2000.2289>
882. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail* 2020;**22**:1342–56. <https://doi.org/10.1002/ehf.1858>
883. Shah SJ, Lam CSP, Svedlund S, Saraste A, Hage C, Tan RS, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. *Eur Heart J* 2018;**39**:3439–50. <https://doi.org/10.1093/eurheartj/ehy531>
884. Yang JH, Obokata M, Reddy YNV, Redfield MM, Lerman A, Borlaug BA. Endothelium-dependent and independent coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;**22**:432–41. <https://doi.org/10.1002/ehf.1671>
885. Sinha A, Rahman H, Webb A, Shah AM, Perera D. Untangling the pathophysiologic link between coronary microvascular dysfunction and heart failure with preserved ejection fraction. *Eur Heart J* 2021;**42**:4431–41. <https://doi.org/10.1093/eurheartj/ehab653>
886. Crea F, Bairey Merz CN, Beltrame JF, Kaski JC, Ogawa H, Ong P, et al. The parallel tales of microvascular angina and heart failure with preserved ejection fraction: a paradigm shift. *Eur Heart J* 2017;**38**:473–7. <https://doi.org/10.1093/eurheartj/ehw461>
887. Rush CJ, Berry C, Oldroyd KG, Rocchiccioli JP, Lindsay MM, Touyz RM, et al. Prevalence of coronary artery disease and coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction. *JAMA Cardiol* 2021;**6**:1130–43. <https://doi.org/10.1001/jamacardio.2021.1825>
888. Arnold JR, Kanagala P, Budgeon CA, Jerosch-Herold M, Gulsin G, Singh A, et al. Prevalence and prognostic significance of microvascular dysfunction in heart failure with preserved ejection fraction. *JACC Cardiovasc Imaging* 2022;**15**:1001–11. <https://doi.org/10.1016/j.jcmg.2021.11.022>
889. Lin X, Wu G, Wang S, Huang J. The prevalence of coronary microvascular dysfunction (CMD) in heart failure with preserved ejection fraction (HFpEF): a systematic review and meta-analysis. *Heart Fail Rev* 2024;**29**:405–16. <https://doi.org/10.1007/s10741-023-10362-x>
890. Paolisso P, Gallinoro E, Belmonte M, Bertolone DT, Bermpeis K, De Colle C, et al. Coronary microvascular dysfunction in patients with heart failure: characterization of patterns in HFref versus HFpEF. *Circ Heart Fail* 2023;**17**:e010805. <https://doi.org/10.1161/circheartfailure.123.010805>
891. Taqueti VR, Solomon SD, Shah AM, Desai AS, Groarke JD, Osborne MT, et al. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. *Eur Heart J* 2018;**39**:840–9. <https://doi.org/10.1093/eurheartj/ehx721>
892. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013;**62**:263–71. <https://doi.org/10.1016/j.jacc.2013.02.092>
893. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, et al. Stress echocardiography expert consensus statement—executive summary: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur Heart J* 2009;**30**:278–89. <https://doi.org/10.1093/eurheartj/ehn492>
894. Garbi M, McDonagh T, Cosyns B, Bucciarelli-Ducci C, Edvardsen T, Kitsiou A, et al. Appropriateness criteria for cardiovascular imaging use in heart failure: report of literature review. *Eur Heart J Cardiovasc Imaging* 2015;**16**:147–53. <https://doi.org/10.1093/ehjci/jeu299>
895. Ghostine S, Caussin C, Habis M, Habib Y, Clement C, Sigal-Cinqualbre A, et al. Non-invasive diagnosis of ischaemic heart failure using 64-slice computed tomography. *Eur Heart J* 2008;**29**:2133–40. <https://doi.org/10.1093/eurheartj/ehn072>
896. Andreini D, Pontone G, Bartorelli AL, Agostoni P, Mushtaq S, Bertella E, et al. Sixty-four-slice multidetector computed tomography: an accurate imaging modality for the evaluation of coronary arteries in dilated cardiomyopathy of unknown etiology. *Circ Cardiovasc Imaging* 2009;**2**:199–205. <https://doi.org/10.1161/circimaging.108.822809>
897. van den Boogert TPW, Claessen B, van Randen A, van Schuppen J, Boekholdt SM, Beijk MAM, et al. Implementation of CT coronary angiography as an alternative to invasive coronary angiography in the diagnostic work-up of non-coronary cardiac surgery,

- cardiomyopathy, heart failure and ventricular arrhythmias. *J Clin Med* 2021;**10**:2374. <https://doi.org/10.3390/jcm10112374>
898. Chow BJW, Coyle D, Hossain A, Laine M, Hanninen H, Ukkonen H, et al. Computed tomography coronary angiography for patients with heart failure (CTA-HF): a randomized controlled trial (IMAGE-HF 1C). *Eur Heart J Cardiovasc Imaging* 2021;**22**:1083–90. <https://doi.org/10.1093/ehjci/jeaa109>
899. Fox K, Ford I, Steg PG, Tendera M, Ferrari R; BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**372**:807–16. [https://doi.org/10.1016/S0140-6736\(08\)61170-8](https://doi.org/10.1016/S0140-6736(08)61170-8)
900. Vitale C, Wajngaten M, Sposato B, Gebara O, Rossini P, Fini M, et al. Trimetazidine improves left ventricular function and quality of life in elderly patients with coronary artery disease. *Eur Heart J* 2004;**25**:1814–21. <https://doi.org/10.1016/j.ehj.2004.06.034>
901. Wilson SR, Scirica BM, Braunwald E, Murphy SA, Karwowska-Prokopczuk E, Buros JL, et al. Efficacy of ranolazine in patients with chronic angina observations from the randomized, double-blind, placebo-controlled MERLIN-TIMI (metabolic efficiency with ranolazine for less ischemia in non-ST-segment elevation acute coronary syndromes) 36 trial. *J Am Coll Cardiol* 2009;**53**:1510–6. <https://doi.org/10.1016/j.jacc.2009.01.037>
902. Cohn JN, Ziesche S, Smith R, Anand I, Dunkan VVB, Loeb H, et al. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril. *Circulation* 1997;**96**:856–63. <https://doi.org/10.1161/01.CIR.96.3.856>
903. Branch KR, Probstfield JL, Eikelboom JW, Bosch J, Maggioni AP, Cheng RK, et al. Rivaroxaban with or without aspirin in patients with heart failure and chronic coronary or peripheral artery disease. *Circulation* 2019;**140**:529–37. <https://doi.org/10.1161/circulationaha.119.039609>
904. Mehra MR, Vaduganathan M, Fu M, Ferreira JP, Anker SD, Cleland JGF, et al. A comprehensive analysis of the effects of rivaroxaban on stroke or transient ischaemic attack in patients with heart failure, coronary artery disease, and sinus rhythm: the COMMANDER HF trial. *Eur Heart J* 2019;**40**:3593–602. <https://doi.org/10.1093/eurheartj/ehz427>
905. Chieffo A, Dudek D, Hassager C, Combes A, Gramegna M, Halvorsen S, et al. Joint EAPCI/ACVC expert consensus document on percutaneous ventricular assist devices. *Eur Heart J Acute Cardiovasc Care* 2021;**10**:570–83. <https://doi.org/10.1093/ehjacc/zuab015>
906. O'Neill WW, Kleiman NS, Moses J, Henriques JPS, Dixon S, Massaro J, et al. A prospective, randomized clinical trial of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention: the PROTECT II study. *Circulation* 2012;**126**:1717–27. <https://doi.org/10.1161/CIRCULATIONAHA.112.098194>
907. O'Neill WW, Anderson M, Burkhoff D, Grines CL, Kapur NK, Lansky AJ, et al. Improved outcomes in patients with severely depressed LVEF undergoing percutaneous coronary intervention with contemporary practices. *Am Heart J* 2022;**248**:139–49. <https://doi.org/10.1016/j.ahj.2022.02.006>
908. Morgan H, Ryan M, Briceno N, Modi B, Rahman H, Arnold S, et al. Coronary jeopardy score predicts ischemic etiology in patients with left ventricular systolic dysfunction. *J Invasive Cardiol* 2022;**34**:E683–5.
909. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, et al. Impact of exercise rehabilitation on exercise capacity and quality-of-life in heart failure: individual participant meta-analysis. *J Am Coll Cardiol* 2019;**73**:1430–43. <https://doi.org/10.1016/j.jacc.2018.12.072>
910. Kitzman DW, Brubaker PH, Herrington DM, Morgan TM, Stewart KP, Hundley WG, et al. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *J Am Coll Cardiol* 2013;**62**:584–92. <https://doi.org/10.1016/j.jacc.2013.04.033>
911. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2016;**315**:36–46. <https://doi.org/10.1001/jama.2015.17346>
912. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;**362**:759–66. [https://doi.org/10.1016/S0140-6736\(03\)14282-1](https://doi.org/10.1016/S0140-6736(03)14282-1)
913. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Køber L, Maggioni AP, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;**349**:1893–906. <https://doi.org/10.1056/NEJMoa032292>
914. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;**362**:772–6. [https://doi.org/10.1016/S0140-6736\(03\)14284-5](https://doi.org/10.1016/S0140-6736(03)14284-5)
915. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int J Cardiol* 2002;**82**:149–58. [https://doi.org/10.1016/S0167-5273\(01\)00600-3](https://doi.org/10.1016/S0167-5273(01)00600-3)
916. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**:877–83. <https://doi.org/10.1056/NEJMoa013474>
917. Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;**337**:1576–84. <https://doi.org/10.1056/NEJM199711273372202>
918. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. *Eur Heart J* 2000;**21**:2071–8. <https://doi.org/10.1053/ehj.2000.2476>
919. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000;**102**:748–54. <https://doi.org/10.1161/01.cir.102.7.748>
920. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–37. <https://doi.org/10.1056/NEJMoa043399>
921. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–38. <https://doi.org/10.1056/NEJMoa0906431>
922. Cleland JG, Abraham WT, Linde C, Gold MR, Young JB, Claude Daubert J, et al. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. *Eur Heart J* 2013;**34**:3547–56. <https://doi.org/10.1093/eurheartj/ehz290>
923. Brignole M, Botto G, Mont L, Iacopino S, De Marchi G, Oddone D, et al. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. *Eur Heart J* 2011;**32**:2420–9. <https://doi.org/10.1093/eurheartj/ehr162>
924. Stavrakis S, Garabelli P, Reynolds DW. Cardiac resynchronization therapy after atrioventricular junction ablation for symptomatic atrial fibrillation: a meta-analysis. *Europace* 2012;**14**:1490–7. <https://doi.org/10.1093/eurpace/eus193>
925. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfese L, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med* 2013;**368**:1585–93. <https://doi.org/10.1056/NEJMoa1210356>
926. Rahman H, Ryan M, Lumley M, Modi B, McConkey H, Ellis H, et al. Coronary microvascular dysfunction is associated with myocardial ischemia and abnormal coronary perfusion during exercise. *Circulation* 2019;**140**:1805–16. <https://doi.org/10.1161/circulationaha.119.041595>
927. Lee SH, Shin D, Lee JM, van de Hoef TP, Hong D, Choi KH, et al. Clinical relevance of ischemia with nonobstructive coronary arteries according to coronary microvascular dysfunction. *J Am Heart Assoc* 2022;**11**:e025171. <https://doi.org/10.1161/JAHA.121.025171>
928. Reynolds HR, Diaz A, Cyr DD, Shaw LJ, Mancini GB, Leipsic J, et al. Ischemia with non-obstructive coronary arteries: insights from the ISCHEMIA trial. *JACC Cardiovasc Imaging* 2023;**16**:63–74. <https://doi.org/10.1016/j.jccmg.2022.06.015>
929. Jespersen L, Hvelplund A, Abildstrom SZ, Pedersen S, Galatius S, Madsen JK, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J* 2012;**33**:734–44. <https://doi.org/10.1093/eurheartj/ehz331>
930. Aziz A, Hansen HS, Sechtem U, Prescott E, Ong P. Sex-related differences in vasomotor function in patients with angina and unobstructed coronary arteries. *J Am Coll Cardiol* 2017;**70**:2349–58. <https://doi.org/10.1016/j.jacc.2017.09.016>
931. Boerhout CKM, de Waard GA, Lee JM, Mejia-Renteria H, Lee SH, Jung JH, et al. Prognostic value of structural and functional coronary microvascular dysfunction in patients with non-obstructive coronary artery disease; from the multicentre international ILLIAS registry. *EuroIntervention* 2022;**18**:719–28. <https://doi.org/10.4244/eij-d-22-00043>
932. Ong P, Camici PG, Beltrame JF, Crea F, Shimokawa H, Sechtem U, et al. International standardization of diagnostic criteria for microvascular angina. *Int J Cardiol* 2018;**250**:16–20. <https://doi.org/10.1016/j.ijcard.2017.08.068>
933. Mejia-Renteria H, van der Hoeven N, van de Hoef TP, Heemelaar J, Ryan N, Lerman A, et al. Targeting the dominant mechanism of coronary microvascular dysfunction with intracoronary physiology tests. *Int J Cardiovasc Imaging* 2017;**33**:1041–59. <https://doi.org/10.1007/s10554-017-1136-9>
934. Mygind ND, Michelsen MM, Pena A, Frestad D, Dose N, Aziz A, et al. Coronary microvascular function and cardiovascular risk factors in women with angina pectoris and no obstructive coronary artery disease: the iPOWER study. *J Am Heart Assoc* 2016;**5**:e003064. <https://doi.org/10.1161/JAHA.115.003064>
935. Pepine CJ, Anderson RD, Sharaf BL, Reis SE, Smith KM, Handberg EM, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated

- for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. *J Am Coll Cardiol* 2010;**55**:2825–32. <https://doi.org/10.1016/j.jacc.2010.01.054>
936. Murthy VL, Naya M, Taqueti VR, Foster CR, Gaber M, Hainer J, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation* 2014;**129**:2518–27. <https://doi.org/10.1161/CIRCULATIONAHA.113.008507>
937. Demir OM, Boerhout CKM, de Waard GA, van de Hoef TP, Patel N, Beijik MAM, et al. Comparison of doppler flow velocity and thermodilution derived indexes of coronary physiology. *JACC Cardiovasc Interv* 2022;**15**:1060–70. <https://doi.org/10.1016/j.jcin.2022.03.015>
938. Zeiher AM, Schächinger V, Minners J. Long-term cigarette smoking impairs endothelium-dependent coronary arterial vasodilator function. *Circulation* 1995;**92**:1094–100. <https://doi.org/10.1161/01.CIR.92.5.1094>
939. Sara JD, Widmer RJ, Matsuzawa Y, Lennon RJ, Lerman LO, Lerman A. Prevalence of coronary microvascular dysfunction among patients with chest pain and nonobstructive coronary artery disease. *JACC Cardiovasc Interv* 2015;**8**:1445–53. <https://doi.org/10.1016/j.jcin.2015.06.017>
940. Chhabra L, Kowligi NG. Low incidence of diabetes mellitus in coronary microvascular dysfunction: an intriguing association. *JACC Cardiovasc Interv* 2016;**9**:395–6. <https://doi.org/10.1016/j.jcin.2015.11.017>
941. Ishimori ML, Martin R, Berman DS, Goykhan P, Shaw LJ, Shufelt C, et al. Myocardial ischemia in the absence of obstructive coronary artery disease in systemic lupus erythematosus. *JACC Cardiovasc Imaging* 2011;**4**:27–33. <https://doi.org/10.1016/j.jcmg.2010.09.019>
942. Recio-Mayoral A, Rimoldi OE, Camici PG, Kaski JC. Inflammation and microvascular dysfunction in cardiac syndrome X patients without conventional risk factors for coronary artery disease. *JACC Cardiovasc Imaging* 2013;**6**:660–7. <https://doi.org/10.1016/j.jcmg.2012.12.011>
943. Fairweather D. Sex differences in inflammation during atherosclerosis. *Clin Med Insights Cardiol* 2014;**8**:49–59. <https://doi.org/10.4137/CMC.S17068>
944. Recio-Mayoral A, Mason JC, Kaski JC, Rubens MB, Harari OA, Camici PG. Chronic inflammation and coronary microvascular dysfunction in patients without risk factors for coronary artery disease. *Eur Heart J* 2009;**30**:1837–43. <https://doi.org/10.1093/eurheartj/ehp205>
945. Konst RE, Elias-Smale SE, Lier A, Bode C, Maas AH. Different cardiovascular risk factors and psychosocial burden in symptomatic women with and without obstructive coronary artery disease. *Eur J Prev Cardiol* 2019;**26**:657–9. <https://doi.org/10.1177/2047487318814298>
946. van der Meer RE, Maas AH. The role of mental stress in ischaemia with no obstructive coronary artery disease and coronary vasomotor disorders. *Eur Cardiol* 2021;**16**:e37. <https://doi.org/10.15420/ecr.2021.20>
947. Suda A, Takahashi J, Hao K, Kikuchi Y, Shindo T, Ikeda S, et al. Coronary functional abnormalities in patients with angina and nonobstructive coronary artery disease. *J Am Coll Cardiol* 2019;**74**:2350–60. <https://doi.org/10.1016/j.jacc.2019.08.1056>
948. Vrints CJ, Bult H, Hitter E, Herman AG, Snoeck JP. Impaired endothelium-dependent cholinergic coronary vasodilation in patients with angina and normal coronary arteriograms. *J Am Coll Cardiol* 1992;**19**:21–31. [https://doi.org/10.1016/0735-1097\(92\)90046-p](https://doi.org/10.1016/0735-1097(92)90046-p)
949. Beltrame JF, Sasayama S, Maseri A. Racial heterogeneity in coronary artery vasomotor reactivity: differences between Japanese and Caucasian patients. *J Am Coll Cardiol* 1999;**33**:1442–52. [https://doi.org/10.1016/s0735-1097\(99\)00073-x](https://doi.org/10.1016/s0735-1097(99)00073-x)
950. Sueda S, Kohno H, Fukuda H, Ochi N, Kawada H, Hayashi Y, et al. Frequency of provoked coronary spasms in patients undergoing coronary arteriography using a spasm provocation test via intracoronary administration of ergonovine. *Angiology* 2004;**55**:403–11. <https://doi.org/10.1177/000331970405500407>
951. Hung MY, Hsu KH, Hung MJ, Cheng CW, Cherng VJ. Interactions among gender, age, hypertension and C-reactive protein in coronary vasospasm. *Eur J Clin Invest* 2010;**40**:1094–103. <https://doi.org/10.1111/j.1365-2362.2010.02360.x>
952. Gulati M, Khan N, George M, Berry C, Chieffo A, Camici PG, et al. Ischemia with no obstructive coronary artery disease (INOCA): a patient self-report quality of life survey from INOCA international. *Int J Cardiol* 2023;**371**:28–39. <https://doi.org/10.1016/j.ijcard.2022.09.047>
953. Shaw LJ, Merz CN, Pepine CJ, Reis SE, Bittner V, Kip KE, et al. The economic burden of angina in women with suspected ischemic heart disease: results from the National Institutes of Health–National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation. *Circulation* 2006;**114**:894–904. <https://doi.org/10.1161/circulationaha.105.609990>
954. Shaw LJ, Shaw RE, Merz CN, Brindis RG, Klein LW, Nallamothu B, et al. Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence and in-hospital mortality in the American College of Cardiology–National Cardiovascular Data Registry. *Circulation* 2008;**117**:1787–801. <https://doi.org/10.1161/CIRCULATIONAHA.107.726562>
955. Gulati M, Cooper-DeHoff RM, McClure C, Johnson BD, Shaw LJ, Handberg EM, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med* 2009;**169**:843–50. <https://doi.org/10.1001/archinternmed.2009.50>
956. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol* 2011;**58**:849–60. <https://doi.org/10.1016/j.jacc.2011.02.074>
957. Jespersen L, Abildstrom SZ, Hvelplund A, Madsen JK, Galatius S, Pedersen F, et al. Burden of hospital admission and repeat angiography in angina pectoris patients with and without coronary artery disease: a registry-based cohort study. *PLoS One* 2014;**9**:e93170. <https://doi.org/10.1371/journal.pone.0093170>
958. Radico F, Zimarino M, Fulgenzi F, Ricci F, Di Nicola M, Jespersen L, et al. Determinants of long-term clinical outcomes in patients with angina but without obstructive coronary artery disease: a systematic review and meta-analysis. *Eur Heart J* 2018;**39**:2135–46. <https://doi.org/10.1093/eurheartj/ehy185>
959. Maddox TM, Stanislawski MA, Grunwald GK, Bradley SM, Ho PM, Tsai TT, et al. Nonobstructive coronary artery disease and risk of myocardial infarction. *JAMA* 2014;**312**:1754–63. <https://doi.org/10.1001/jama.2014.14681>
960. Kelshiker MA, Seligman H, Howard JP, Rahman H, Foley M, Nowbar AN, et al. Coronary flow reserve and cardiovascular outcomes: a systematic review and meta-analysis. *Eur Heart J* 2022;**43**:1582–93. <https://doi.org/10.1093/eurheartj/ehab775>
961. Boerhout CKM, Lee JM, de Waard GA, Mejia-Renteria H, Lee SH, Jung JH, et al. Microvascular resistance reserve: diagnostic and prognostic performance in the ILIAS registry. *Eur Heart J* 2023;**44**:2862–9. <https://doi.org/10.1093/eurheartj/ehad378>
962. Zhou W, Lee Jonan Chun Y, Leung Siu T, Lai A, Lee TF, Chiang JB, et al. Long-term prognosis of patients with coronary microvascular disease using stress perfusion cardiac magnetic resonance. *JACC Cardiovasc Imaging* 2021;**14**:602–11. <https://doi.org/10.1016/j.jcmg.2020.09.034>
963. Lanza GA, Sestito A, Sgueglia GA, Infusino F, Manolfi M, Crea F, et al. Current clinical features, diagnostic assessment and prognostic determinants of patients with variant angina. *Int J Cardiol* 2007;**118**:41–7. <https://doi.org/10.1016/j.ijcard.2006.06.016>
964. Taqueti VR, Di Carli MF. Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC state-of-the-art review. *J Am Coll Cardiol* 2018;**72**:2625–41. <https://doi.org/10.1016/j.jacc.2018.09.042>
965. Sidik NP, Stanley B, Sykes R, Morrow AJ, Bradley CP, McDermott M, et al. Invasive endotyping in patients with angina and no obstructive coronary artery disease: a randomized controlled trial. *Circulation* 2024;**149**:7–23. <https://doi.org/10.1161/CIRCULATIONAHA.123.064751>
966. Rahman H, Demir OM, Khan F, Ryan M, Ellis H, Mills MT, et al. Physiological stratification of patients with angina due to coronary microvascular dysfunction. *J Am Coll Cardiol* 2020;**75**:2538–49. <https://doi.org/10.1016/j.jacc.2020.03.051>
967. Belmonte M, Pijls NHJ, Bertolone DT, Bertolone DT, Keulards DCJ, Viscusi MM, et al. Measuring absolute coronary flow and microvascular resistance by thermodilution. *J Am Coll Cardiol* 2024;**83**:699–709. <https://doi.org/10.1016/j.jacc.2023.12.014>
968. Feenstra RGT, Woudstra J, Bijloo I, Vink CEM, Boerhout CKM, de Waard GA, et al. Post-spastic flow recovery time to document vasospasm induced ischemia during acetylcholine provocation testing. *Int J Cardiol Heart Vasc* 2023;**47**:101220. <https://doi.org/10.1016/j.ijcha.2023.101220>
969. Sueda S, Kohno H, Fukuda H, Ochi N, Kawada H, Hayashi Y, et al. Induction of coronary artery spasm by two pharmacological agents: comparison between intracoronary injection of acetylcholine and ergonovine. *Coron Artery Dis* 2003;**14**:451–7. <https://doi.org/10.1097/00019501-200309000-00006>
970. Montone RA, Rinaldi R, Del Buono MG, Gurgoglione F, La Vecchia G, Russo M, et al. Safety and prognostic relevance of acetylcholine testing in patients with stable myocardial ischaemia or myocardial infarction and non-obstructive coronary arteries. *EuroIntervention* 2022;**18**:e666–76. <https://doi.org/10.4244/eij-d-21-00971>
971. Takahashi T, Samuels BA, Li W, Parikh MA, Wei J, Moses JW, et al. Safety of provocative testing with intracoronary acetylcholine and implications for standard protocols. *J Am Coll Cardiol* 2022;**79**:2367–78. <https://doi.org/10.1016/j.jacc.2022.03.385>
972. Montone RA, Niccoli G, Fracassi F, Russo M, Gurgoglione F, Cammà G, et al. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. *Eur Heart J* 2018;**39**:91–8. <https://doi.org/10.1093/eurheartj/ehx667>
973. Layland J, Carrick D, Lee M, Oldroyd K, Berry C. Adenosine: physiology, pharmacology, and clinical applications. *JACC Cardiovasc Interv* 2014;**7**:581–91. <https://doi.org/10.1016/j.jcin.2014.02.009>
974. Mizukami T, Sonck J, Gallinoro E, Kodeboina M, Canvedra A, Nagumo S, et al. Duration of hyperemia with intracoronary administration of papaverine. *J Am Heart Assoc* 2021;**10**:e018562. <https://doi.org/10.1161/JAHA.120.018562>
975. Kern MJ, Deligonul U, Serota H, Gudipati C, Buckingham T. Ventricular arrhythmia due to intracoronary papaverine: analysis of QT intervals and coronary vasodilatory reserve. *Cathet Cardiovasc Diagn* 1990;**19**:229–36. <https://doi.org/10.1002/ccd.1810190402>

976. Nakayama M, Tanaka N, Sakoda K, Hokama Y, Hoshino K, Kimura Y, et al. Papaverine-induced polymorphic ventricular tachycardia during coronary flow reserve study of patients with moderate coronary artery disease—analysis of ECG data. *Circ J* 2015;**79**:530–6. <https://doi.org/10.1253/circj.CJ-14-1118>
977. Beltrame JF, Tavella R, Jones D, Zeitz C. Management of ischaemia with non-obstructive coronary arteries (INOCA). *BMJ* 2021;**375**:e060602. <https://doi.org/10.1136/bmj-2021-060602>
978. Ford TJ, Stanley B, Sidik N, Good R, Rocchiccioli P, McEntegart M, et al. 1-Year outcomes of angina management guided by invasive coronary function testing (CorMicA). *JACC Cardiovasc Interv* 2020;**13**:33–45. <https://doi.org/10.1016/j.jcin.2019.11.001>
979. Kaski JC, Crea F, Gersh BJ, Camici PG. Reappraisal of ischemic heart disease. *Circulation* 2018;**138**:1463–80. <https://doi.org/10.1161/CIRCULATIONAHA.118.031373>
980. Sinha A, Rahman H, Douiri A, Demir OM, De Silva K, Clapp B, et al. ChaMP-CMD: a phenotype-blinded, randomized controlled, cross-over trial. *Circulation* 2024;**149**:36–47. <https://doi.org/10.1161/CIRCULATIONAHA.123.066680>
981. Jansen TPJ, Konst RE, de Vos A, Paradies V, Teerenstra S, van den Oord SCH, et al. Efficacy of diltiazem to improve coronary vasomotor dysfunction in ANOCA: the EDIT-CMD randomized clinical trial. *JACC Cardiovasc Imaging* 2022;**15**:1473–84. <https://doi.org/10.1016/j.jcmg.2022.03.012>
982. Guarini G, Huqi A, Morrone D, Capozza P, Todiere G, Marzilli M. Pharmacological approaches to coronary microvascular dysfunction. *Pharmacol Ther* 2014;**144**:283–302. <https://doi.org/10.1016/j.pharmthera.2014.06.008>
983. Cattaneo M, Porretta AP, Gallino A. Ranolazine: drug overview and possible role in primary microvascular angina management. *Int J Cardiol* 2015;**181**:376–81. <https://doi.org/10.1016/j.ijcard.2014.12.055>
984. Imran TF, Malapero R, Qavi AH, Hasan Z, de la Torre B, Patel YR, et al. Efficacy of spinal cord stimulation as an adjunct therapy for chronic refractory angina pectoris. *Int J Cardiol* 2017;**227**:535–42. <https://doi.org/10.1016/j.ijcard.2016.10.105>
985. Lee BK, Lim HS, Fearon WF, Yong AS, Yamada R, Tanaka S, et al. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. *Circulation* 2015;**131**:1054–60. <https://doi.org/10.1161/CIRCULATIONAHA.114.012636>
986. Shufelt CL, Thomson LE, Goykhman P, Agarwal M, Mehta PK, Sedlak T, et al. Cardiac magnetic resonance imaging myocardial perfusion reserve index assessment in women with microvascular coronary dysfunction and reference controls. *Cardiovasc Diagn Ther* 2013;**3**:153–60. <https://doi.org/10.3978/j.issn.2223-3652.2013.08.02>
987. Echavarría-Pinto M, Escaned J, Macías E, Medina M, Gonzalo N, Petraco R, et al. Disturbed coronary hemodynamics in vessels with intermediate stenoses evaluated with fractional flow reserve: a combined analysis of epicardial and microcirculatory involvement in ischemic heart disease. *Circulation* 2013;**128**:2557–66. <https://doi.org/10.1161/CIRCULATIONAHA.112.001345>
988. Kaski JC, Rosano G, Gavrielides S, Chen L. Effects of angiotensin-converting enzyme inhibition on exercise-induced angina and ST segment depression in patients with microvascular angina. *J Am Coll Cardiol* 1994;**23**:652–7. [https://doi.org/10.1016/0735-1097\(94\)90750-1](https://doi.org/10.1016/0735-1097(94)90750-1)
989. Erdamar H, Sen N, Tavil Y, Yazc HU, Turfan M, Poyraz F, et al. The effect of nebivolol treatment on oxidative stress and antioxidant status in patients with cardiac syndrome-X. *Coron Artery Dis* 2009;**20**:238–44. <https://doi.org/10.1097/mca.0b013e32830936bb>
990. Kayaalti F, Kalay N, Basar E, Mavili E, Duran M, Ozdogru I, et al. Effects of nebivolol therapy on endothelial functions in cardiac syndrome X. *Heart Vessels* 2010;**25**:92–6. <https://doi.org/10.1007/s00380-009-1170-1>
991. Antman E, Muller J, Goldberg S, MacAlpin R, Rubenfire M, Tabatznik B, et al. Nifedipine therapy for coronary-artery spasm. Experience in 127 patients. *N Engl J Med* 1980;**302**:1269–73. <https://doi.org/10.1056/nejm198006053022301>
992. Johnson SM, Mauritson DR, Willerson JT, Hillis LD. A controlled trial of verapamil for Prinzmetal's variant angina. *N Engl J Med* 1981;**304**:862–6. <https://doi.org/10.1056/nejm198104093041502>
993. Ginsburg R, Lamb IH, Schroeder JS, Hu M, Harrison DC. Randomized double-blind comparison of nifedipine and isosorbide dinitrate in variant angina pectoris due to coronary artery spasm. *Am Heart J* 1982;**103**:44–8. [https://doi.org/10.1016/0002-8703\(82\)90527-0](https://doi.org/10.1016/0002-8703(82)90527-0)
994. Pesola A, Lauro A, Gallo R, Madeo A, Cosentino G. Efficacy of diltiazem in variant angina. Results of a double-blind crossover study in CCU by Holter monitoring. The possible occurrence of a withdrawal syndrome. *G Ital Cardiol* 1987;**17**:329–39.
995. Chahine RA, Feldman RL, Giles TD, Nicod P, Raizner AE, Weiss RJ, et al. Randomized placebo-controlled trial of amlodipine in vasospastic angina. Amlodipine Study 160 Group. *J Am Coll Cardiol* 1993;**21**:1365–70. [https://doi.org/10.1016/0735-1097\(93\)90310-w](https://doi.org/10.1016/0735-1097(93)90310-w)
996. Oikawa Y, Matsuno S, Yajima J, Nakamura M, Ono T, Ishiwata S, et al. Effects of treatment with once-daily nifedipine CR and twice-daily benidipine on prevention of symptomatic attacks in patients with coronary spastic angina pectoris—Adalat Trial vs Coniel in Tokyo against Coronary Spastic Angina (ATTACK CSA). *J Cardiol* 2010;**55**:238–47. <https://doi.org/10.1016/j.jicc.2009.11.005>
997. Aschermann M, Bultas J, Karetová D, Köbel F, Kozáková M, Simper D. Randomized double-blind comparison of isosorbide dinitrate and nifedipine in variant angina pectoris. *Am J Cardiol* 1990;**65**:J46–9. [https://doi.org/10.1016/0002-9149\(90\)91312-t](https://doi.org/10.1016/0002-9149(90)91312-t)
998. Seitz A, Feenstra R, Konst RE, Martínez Pereyra V, Beck S, Beijl MAM, et al. Acetylcholine rechallenge: a first step toward tailored treatment in patients with coronary artery spasm. *JACC Cardiovasc Interv* 2022;**15**:65–75. <https://doi.org/10.1016/j.jcin.2021.10.003>
999. Nishigaki K, Inoue Y, Yamanouchi Y, Fukumoto Y, Yasuda S, Sueda S, et al. Prognostic effects of calcium channel blockers in patients with vasospastic angina—a meta-analysis. *Circ J* 2010;**74**:1943–50. <https://doi.org/10.1253/circj.cj-10-0292>
1000. Winniford MD, Gabliani G, Johnson SM, Mauritson DR, Fulton KL, Hillis LD. Concomitant calcium antagonist plus isosorbide dinitrate therapy for markedly active variant angina. *Am Heart J* 1984;**108**:1269–73. [https://doi.org/10.1016/0002-8703\(84\)90752-x](https://doi.org/10.1016/0002-8703(84)90752-x)
1001. Gu SZ, Beska B, Chan D, Neely D, Batty JA, Adams-Hall J, et al. Cognitive decline in older patients with non-ST elevation acute coronary syndrome. *J Am Heart Assoc* 2019;**8**:e011218. <https://doi.org/10.1161/jaha.118.011218>
1002. Beska B, Coakley D, MacGowan G, Adams-Hall J, Wilkinson C, Kunadian V. Frailty and quality of life after invasive management for non-ST elevation acute coronary syndrome. *Heart* 2022;**108**:203–11. <https://doi.org/10.1136/heartjnl-2021-319064>
1003. Beska B, Mills GB, Ratcovich H, Wilkinson C, Damluji AA, Kunadian V. Impact of multimorbidity on long-term outcomes in older adults with non-ST elevation acute coronary syndrome in the North East of England: a multi-centre cohort study of patients undergoing invasive care. *BMJ Open* 2022;**12**:e061830. <https://doi.org/10.1136/bmjopen-2022-061830>
1004. Mills GB, Ratcovich H, Adams-Hall J, Beska B, Kirkup E, Raharjo DE, et al. Is the contemporary care of the older persons with acute coronary syndrome evidence-based? *Eur Heart J Open* 2022;**2**:oeab044. <https://doi.org/10.1093/ehjopen/oeab044>
1005. Ratcovich H, Beska B, Mills G, Holmvang L, Adams-Hall J, Stevenson H, et al. Five-year clinical outcomes in patients with frailty aged ≥ 75 years with non-ST elevation acute coronary syndrome undergoing invasive management. *Eur Heart J Open* 2022;**2**:oeac035. <https://doi.org/10.1093/ehjopen/oeac035>
1006. Sinclair H, Batty JA, Qiu W, Kunadian V. Engaging older patients in cardiovascular research: observational analysis of the ICON-1 study. *Open Heart* 2016;**3**:e000436. <https://doi.org/10.1136/openhrt-2016-000436>
1007. Mas-Llado C, Gonzalez-Del-Hoyo M, Siquier-Padilla J, Blaya-Peña L, Coughlan JJ, García de la Villa B, et al. Representativeness in randomised clinical trials supporting acute coronary syndrome guidelines. *Eur Heart J Qual Care Clin Outcomes* 2023;**9**:796–805. <https://doi.org/10.1093/ehjqco/qcad007>
1008. Rossello X, Ferreira JP, Caimari F, Lamiral Z, Sharma A, Mehta C, et al. Influence of sex, age and race on coronary and heart failure events in patients with diabetes and post-acute coronary syndrome. *Clin Res Cardiol* 2021;**110**:1612–24. <https://doi.org/10.1007/s00392-021-01859-2>
1009. Varenne O, Cook S, Sideris G, Kedev S, Cuisset T, Carrié D, et al. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. *Lancet* 2018;**391**:41–50. [https://doi.org/10.1016/S0140-6736\(17\)32713-7](https://doi.org/10.1016/S0140-6736(17)32713-7)
1010. Chung K, Wilkinson C, Veerasamy M, Kunadian V. Frailty scores and their utility in older patients with cardiovascular disease. *Interv Cardiol* 2021;**16**:e05. <https://doi.org/10.15420/icr.2020.18>
1011. Vogel B, Acevedo M, Appelman Y, Bairey Merz CN, Chieffo A, Figtree GA, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. *Lancet* 2021;**397**:2385–438. [https://doi.org/10.1016/S0140-6736\(21\)00684-x](https://doi.org/10.1016/S0140-6736(21)00684-x)
1012. Gaudino M, Di Franco A, Cao D, Giustino G, Bairey Merz CN, Fremes SE, et al. Sex-related outcomes of medical, percutaneous, and surgical interventions for coronary artery disease: JACC focus seminar 3/7. *J Am Coll Cardiol* 2022;**79**:1407–25. <https://doi.org/10.1016/j.jacc.2021.07.066>
1013. Jackson J, Alkhalil M, Ratcovich H, Wilkinson C, Mehran R, Kunadian V. Evidence base for the management of women with non-ST elevation acute coronary syndrome. *Heart* 2022;**108**:1682–9. <https://doi.org/10.1136/heartjnl-2021-320533>
1014. Ahmed R, Dunford J, Mehran R, Robson S, Kunadian V. Pre-eclampsia and future cardiovascular risk among women: a review. *J Am Coll Cardiol* 2014;**63**:1815–22. <https://doi.org/10.1016/j.jacc.2014.02.529>
1015. Maas A, Rosano G, Cifkova R, Chieffo A, van Dijken D, Hamoda H, et al. Cardiovascular health after menopause transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynaecologists, and endocrinologists. *Eur Heart J* 2021;**42**:967–84. <https://doi.org/10.1093/eurheartj/ehaa1044>
1016. Zhu D, Chung HF, Dobson AJ, Pandeya N, Giles GG, Bruisma F, et al. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. *Lancet Public Health* 2019;**4**:e553–64. [https://doi.org/10.1016/S2468-2667\(19\)30155-0](https://doi.org/10.1016/S2468-2667(19)30155-0)
1017. Parikh NI, Gonzalez JM, Anderson CAM, Judd SE, Rexrode KM, Hlatky MA, et al. Adverse pregnancy outcomes and cardiovascular disease risk: unique opportunities for cardiovascular disease prevention in women: a scientific statement from the American Heart Association. *Circulation* 2021;**143**:e902–16. <https://doi.org/10.1161/cir.0000000000000961>

1018. Rossello X, Mas-Lladó C, Pocock S, Vicent L, van de Werf F, Chin CT, et al. Sex differences in mortality after an acute coronary syndrome increase with lower country wealth and higher income inequality. *Rev Esp Cardiol (Engl Ed)* 2022;**75**:392–400. <https://doi.org/10.1016/j.rec.2021.05.006>
1019. Sims M, Kershaw KN, Breathett K, Jackson EA, Lewis LM, Mujahid MS, et al. Importance of housing and cardiovascular health and well-being: a scientific statement from the American Heart Association. *Circ Cardiovasc Qual Outcomes* 2020;**13**:e000089. <https://doi.org/10.1161/hcq.0000000000000089>
1020. Wilkinson C, Bebb O, Dondo TB, Munyombwe T, Casadei B, Clarke S, et al. Sex differences in quality indicator attainment for myocardial infarction: a nationwide cohort study. *Heart* 2019;**105**:516–23. <https://doi.org/10.1136/heartjnl-2018-313959>
1021. Kosmidou I, Leon MB, Zhang Y, Serruys PW, von Birgelen C, Smits PC, et al. Long-term outcomes in women and men following percutaneous coronary intervention. *J Am Coll Cardiol* 2020;**75**:1631–40. <https://doi.org/10.1016/j.jacc.2020.01.056>
1022. Angraal S, Khera R, Wang Y, Lu Y, Jean R, Dreyer RP, et al. Sex and race differences in the utilization and outcomes of coronary artery bypass grafting among medicare beneficiaries, 1999–2014. *J Am Heart Assoc* 2018;**7**:e009014. <https://doi.org/10.1161/JAHA.118.009014>
1023. Sarma AA, Braunwald E, Cannon CP, Guo J, Im KA, Antman EM, et al. Outcomes of women compared with men after non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol* 2019;**74**:3013–22. <https://doi.org/10.1016/j.jacc.2019.09.065>
1024. Chichareon P, Modolo R, Kerkmeijer L, Tomaniak M, Kogame N, Takahashi K, et al. Association of sex with outcomes in patients undergoing percutaneous coronary intervention: a subgroup analysis of the GLOBAL LEADERS randomized clinical trial. *JAMA Cardiol* 2020;**5**:21–9. <https://doi.org/10.1001/jamacardio.2019.4296>
1025. Ratcovich H, Alkhalil M, Beska B, Holmvang L, Lawless M, Gede Dennis Sukadana I, et al. Sex differences in long-term outcomes in older adults undergoing invasive treatment for non-ST elevation acute coronary syndrome: an ICON-1 sub-study. *Int J Cardiol Heart Vasc* 2022;**42**:101118. <https://doi.org/10.1016/j.ijcha.2022.101118>
1026. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;**288**:321–33. <https://doi.org/10.1001/jama.288.3.321>
1027. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrié D, Naber C, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med* 2015;**373**:2038–47. <https://doi.org/10.1056/NEJMoa1503943>
1028. Windecker S, Latib A, Kedhi E, Kirtane AJ, Kandzari DE, Mehran R, et al. Polymer-based or polymer-free stents in patients at high bleeding risk. *N Engl J Med* 2020;**382**:1208–18. <https://doi.org/10.1056/NEJMoa1910021>
1029. Angiolillo DJ, Cao D, Baber U, Sartori S, Zhang Z, Dangas G, et al. Impact of age on the safety and efficacy of ticagrelor monotherapy in patients undergoing PCI. *JACC Cardiovasc Interv* 2021;**14**:1434–46. <https://doi.org/10.1016/j.jcin.2021.04.043>
1030. Escaned J, Cao D, Baber U, Nicolas J, Sartori S, Zhang Z, et al. Ticagrelor monotherapy in patients at high bleeding risk undergoing percutaneous coronary intervention: TWILIGHT-HBR. *Eur Heart J* 2021;**42**:4624–34. <https://doi.org/10.1093/eurheartj/ehab702>
1031. Mehran R, Cao D, Angiolillo DJ, Bangalore S, Bhatt DL, Ge J, et al. 3- or 1-Month DAPT in patients at high bleeding risk undergoing everolimus-eluting stent implantation. *JACC Cardiovasc Interv* 2021;**14**:1870–83. <https://doi.org/10.1016/j.jcin.2021.07.016>
1032. Valgimigli M, Cao D, Angiolillo DJ, Bangalore S, Bhatt DL, Ge J, et al. Duration of dual antiplatelet therapy for patients at high bleeding risk undergoing PCI. *J Am Coll Cardiol* 2021;**78**:2060–72. <https://doi.org/10.1016/j.jacc.2021.08.074>
1033. Restivo V, Candiloro S, Daidone M, Norrito R, Cataldi M, Minutolo G, et al. Systematic review and meta-analysis of cardiovascular risk in rheumatological disease: symptomatic and non-symptomatic events in rheumatoid arthritis and systemic lupus erythematosus. *Autoimmun Rev* 2022;**21**:102925. <https://doi.org/10.1016/j.autrev.2021.102925>
1034. Kerola AM, Kazemi A, Rollefstad S, Lillegraven S, Sexton J, Wibetoe G, et al. All-cause and cause-specific mortality in rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis: a nationwide registry study. *Rheumatology (Oxford)* 2022;**61**:4656–66. <https://doi.org/10.1093/rheumatology/keac210>
1035. Zöller B, Li X, Sundquist J, Sundquist K. Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. *BMC Neurol* 2012;**12**:41. <https://doi.org/10.1186/1471-2377-12-41>
1036. Zöller B, Li X, Sundquist J, Sundquist K. Risk of subsequent coronary heart disease in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. *PLoS One* 2012;**7**:e33442. <https://doi.org/10.1371/journal.pone.0033442>
1037. Kuo CF, Yu KH, See LC, Chou IJ, Ko YS, Chang HC, et al. Risk of myocardial infarction among patients with gout: a nationwide population-based study. *Rheumatology (Oxford)* 2013;**52**:111–7. <https://doi.org/10.1093/rheumatology/kes169>
1038. Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, de Ramón E, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. *Ann Rheum Dis* 2015;**74**:1011–8. <https://doi.org/10.1136/annrheumdis-2013-204838>
1039. Alenghat FJ. The prevalence of atherosclerosis in those with inflammatory connective tissue disease by race, age, and traditional risk factors. *Sci Rep* 2016;**6**:20303. <https://doi.org/10.1038/srep20303>
1040. Tektonidou MG, Lewandowski LB, Hu J, Dasgupta A, Ward MM. Survival in adults and children with systemic lupus erythematosus: a systematic review and Bayesian meta-analysis of studies from 1950 to 2016. *Ann Rheum Dis* 2017;**76**:2009–16. <https://doi.org/10.1136/annrheumdis-2017-211663>
1041. Aouba A, Gonzalez Chiappe S, Eb M, Delmas C, de Boysson H, Bienvenu B, et al. Mortality causes and trends associated with giant cell arteritis: analysis of the French national death certificate database (1980–2011). *Rheumatology (Oxford)* 2018;**57**:1047–55. <https://doi.org/10.1093/rheumatology/key028>
1042. Houben E, Penne EL, Voskuyl AE, van der Heijden JW, Otten RHJ, Boers M, et al. Cardiovascular events in anti-neutrophil cytoplasmic antibody-associated vasculitis: a meta-analysis of observational studies. *Rheumatology (Oxford)* 2018;**57**:555–62. <https://doi.org/10.1093/rheumatology/kez338>
1043. Houben E, Mendel A, van der Heijden JW, Simsek S, Bax WA, Carette S, et al. Prevalence and management of cardiovascular risk factors in ANCA-associated vasculitis. *Rheumatology (Oxford)* 2019;**58**:2333–5. <https://doi.org/10.1093/rheumatology/kez229>
1044. Cen X, Feng S, Wei S, Yan L, Sun L. Systemic sclerosis and risk of cardiovascular disease: a PRISMA-compliant systematic review and meta-analysis of cohort studies. *Medicine (Baltimore)* 2020;**99**:e23009. <https://doi.org/10.1097/md.0000000000003009>
1045. Chung CP, Oeser A, Raggi P, Gebretsadik T, Shintani AK, Sokka T, et al. Increased coronary-artery atherosclerosis in rheumatoid arthritis: relationship to disease duration and cardiovascular risk factors. *Arthritis Rheum* 2005;**52**:3045–53. <https://doi.org/10.1002/art.21288>
1046. Roman MJ, Moeller E, Davis A, Paget SA, Crow MK, Lockshin MD, et al. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. *Ann Intern Med* 2006;**144**:249–56. <https://doi.org/10.7326/0003-4819-144-4-200602210-00006>
1047. Kobayashi H, Giles JT, Polak JF, Blumenthal RS, Leffell MS, Szklo M, et al. Increased prevalence of carotid artery atherosclerosis in rheumatoid arthritis is artery-specific. *J Rheumatol* 2010;**37**:730–9. <https://doi.org/10.3899/jrheum.090670>
1048. Giles JT, Post VVS, Blumenthal RS, Polak J, Petri M, Gelber AC, et al. Longitudinal predictors of progression of carotid atherosclerosis in rheumatoid arthritis. *Arthritis Rheum* 2011;**63**:3216–25. <https://doi.org/10.1002/art.30542>
1049. Ajejanova S, de Faire U, Jogestrand T, Frostegård J, Häfström I. Carotid atherosclerosis, disease measures, oxidized low-density lipoproteins, and atheroprotective natural antibodies for cardiovascular disease in early rheumatoid arthritis—an inception cohort study. *J Rheumatol* 2012;**39**:1146–54. <https://doi.org/10.3899/jrheum.111334>
1050. Lucke M, Messner W, Kim ES, Husni ME. The impact of identifying carotid plaque on addressing cardiovascular risk in psoriatic arthritis. *Arthritis Res Ther* 2016;**18**:178. <https://doi.org/10.1186/s13075-016-1074-2>
1051. Fischer K, Przepiera-Będzak H, Brzosko I, Sawicki M, Walecka A, Brzosko M. Anti-phosphatidylethanolamine and anti-phosphatidylserine antibodies—association with renal involvement, atherosclerosis, cardiovascular manifestations, Raynaud phenomenon and disease activity in Polish patients with systemic lupus erythematosus. *Biomolecules* 2022;**12**:1328. <https://doi.org/10.3390/biom12101328>
1052. Gonzalez-Juanatey C, Llorca J, Martin J, Gonzalez-Gay MA. Carotid intima-media thickness predicts the development of cardiovascular events in patients with rheumatoid arthritis. *Semin Arthritis Rheum* 2009;**38**:366–71. <https://doi.org/10.1016/j.semarthrit.2008.01.012>
1053. Evans MR, Escalante A, Batafarano DF, Freeman GL, O'Leary DH, del Rincón I. Carotid atherosclerosis predicts incident acute coronary syndromes in rheumatoid arthritis. *Arthritis Rheum* 2011;**63**:1211–20. <https://doi.org/10.1002/art.30265>
1054. Lam SHM, Cheng IT, Li EK, Wong P, Lee J, Yip RML, et al. DAPSA, carotid plaque and cardiovascular events in psoriatic arthritis: a longitudinal study. *Ann Rheum Dis* 2020;**79**:1320–6. <https://doi.org/10.1136/annrheumdis-2020-217595>
1055. Gupta A, Kesavabhotla K, Baradaran H, Kamel H, Pandya A, Giambone AE, et al. Plaque echolucency and stroke risk in asymptomatic carotid stenosis: a systematic review and meta-analysis. *Stroke* 2015;**46**:91–7. <https://doi.org/10.1161/strokeaha.114.006091>
1056. Semb AG, Ik Dahl E, Hisdal J, Olsen IC, Rollefstad S. Exploring cardiovascular disease risk evaluation in patients with inflammatory joint diseases. *Int J Cardiol* 2016;**223**:331–6. <https://doi.org/10.1016/j.ijcard.2016.08.129>
1057. Galarza-Delgado DA, Azpiri-Lopez JR, Colunga-Pedraza IJ, Guajardo-Jauregui N, Rodriguez-Romero AB, Lugo-Perez S, et al. Cardiovascular risk reclassification according to six cardiovascular risk algorithms and carotid ultrasound in psoriatic arthritis patients. *Clin Rheumatol* 2022;**41**:1413–20. <https://doi.org/10.1007/s10067-021-06002-0>
1058. Semb AG, Kvien TK, DeMicco DA, Fayyad R, Wun CC, LaRosa JC, et al. Effect of intensive lipid-lowering therapy on cardiovascular outcome in patients with and those without inflammatory joint disease. *Arthritis Rheum* 2012;**64**:2836–46. <https://doi.org/10.1002/art.34524>

1059. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJL, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis* 2017;**76**:17–28. <https://doi.org/10.1136/annrheumdis-2016-209775>
1060. Xie W, Huang H, Xiao S, Yang X, Zhang Z. Effect of statin use on cardiovascular events and all-cause mortality in immune-mediated inflammatory diseases: a systematic review and meta-analysis involving 148,722 participants. *Pharmacol Res* 2020;**160**: 105057. <https://doi.org/10.1016/j.phrs.2020.105057>
1061. Drosos GC, Vedder D, Houben E, Boekel L, Atzeni F, Badreh S, et al. EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases, including systemic lupus erythematosus and antiphospholipid syndrome. *Ann Rheum Dis* 2022;**81**:768–79. <https://doi.org/10.1136/annrheumdis-2021-221733>
1062. Rahmadi AR, Pranata R, Raffaello WM, Yonas E, Ramadhian MP, Natadikarta MRR, et al. The effect of statin on major adverse cardiovascular events and mortality in patients with rheumatoid arthritis—a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci* 2022;**26**:3171–8. https://doi.org/10.26355/eurrev_202205_28734
1063. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;**387**:957–67. [https://doi.org/10.1016/S0140-6736\(15\)01225-8](https://doi.org/10.1016/S0140-6736(15)01225-8)
1064. McEvoy JW, Touyz RM, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, et al. ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J* 2024. <https://doi.org/10.1093/eurheartj/ehae178>
1065. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;**39**: 3021–104. <https://doi.org/10.1093/eurheartj/ehy339>
1066. Suwalski P, Kowalewski M, Jasiński M, Staromyński J, Zembala M, Widenka K, et al. Surgical ablation for atrial fibrillation during isolated coronary artery bypass surgery. *Eur J Cardiothorac Surg* 2020;**57**:691–700. <https://doi.org/10.1093/ejcts/ezz298>
1067. Van Gelder IC, Kotecha D, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, et al. 2024 ESC Guidelines for the management of atrial fibrillation. *Eur Heart J* 2024. <https://doi.org/10.1093/eurheartj/ehae176>
1068. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2022;**43**: 561–632. <https://doi.org/10.1093/eurheartj/ehab395>
1069. Thompson S, James M, Wiebe N, Hemmelgarn B, Manns B, Klarenbach S, et al. Cause of death in patients with reduced kidney function. *J Am Soc Nephrol* 2015;**26**:2504–11. <https://doi.org/10.1681/asn.2014070714>
1070. Sarnak MJ, Amann K, Bangalore S, Cavalcanti JL, Charytan DM, Craig JC, et al. Chronic kidney disease and coronary artery disease: JACC state-of-the-art review. *J Am Coll Cardiol* 2019;**74**:1823–38. <https://doi.org/10.1016/j.jacc.2019.08.1017>
1071. Konstantinidis I, Nadkarni GN, Yacoub R, Saha A, Simoes P, Parikh CR, et al. Representation of patients with kidney disease in trials of cardiovascular interventions: an updated systematic review. *JAMA Intern Med* 2016;**176**:121–4. <https://doi.org/10.1001/jamainternmed.2015.6102>
1072. Morales J, Handelsman Y. Cardiovascular outcomes in patients with diabetes and kidney disease: JACC review topic of the week. *J Am Coll Cardiol* 2023;**82**:161–70. <https://doi.org/10.1016/j.jacc.2023.04.052>
1073. Mehran R, Dangas GD, Weisbord SD. Contrast-associated acute kidney injury. *N Engl J Med* 2019;**380**:2146–55. <https://doi.org/10.1056/NEJMra1805256>
1074. Bangalore S, Maron DJ, O'Brien SM, Fleg JL, Kretov EI, Briguori C, et al. Management of coronary disease in patients with advanced kidney disease. *N Engl J Med* 2020;**382**: 1608–18. <https://doi.org/10.1056/NEJMoa1915925>
1075. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J, Hannan EL. Revascularization in patients with multivessel coronary artery disease and chronic kidney disease: everolimus-eluting stents versus coronary artery bypass graft surgery. *J Am Coll Cardiol* 2015;**66**:1209–20. <https://doi.org/10.1016/j.jacc.2015.06.1334>
1076. Wang Y, Zhu S, Gao P, Zhang Q. Comparison of coronary artery bypass grafting and drug-eluting stents in patients with chronic kidney disease and multivessel disease: a meta-analysis. *Eur J Intern Med* 2017;**43**:28–35. <https://doi.org/10.1016/j.ejim.2017.04.002>
1077. Raposeiras-Roubin S, Abu-Assi E, Munoz-Pousa I, Rossello X, Cespón-Fernández M, Melendo Viu M, et al. Usefulness of bleeding after acute coronary syndromes for unmasking silent cancer. *Am J Cardiol* 2020;**125**:1801–8. <https://doi.org/10.1016/j.amjcard.2020.03.023>
1078. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J* 2022;**43**:4229–361. <https://doi.org/10.1093/eurheartj/ehac244>
1079. Falanga A, Leader A, Ambaglio C, Bagoly Z, Castaman G, Elalamy I, et al. EHA guidelines on management of antithrombotic treatments in thrombocytopenic patients with cancer. *Hemasphere* 2022;**6**:e750. <https://doi.org/10.1097/hs9.0000000000000750>
1080. Shah ASV, Stelzle D, Lee KK, Beck EJ, Alam S, Clifford S, et al. Global burden of atherosclerotic cardiovascular disease in people living with HIV: systematic review and meta-analysis. *Circulation* 2018;**138**:1100–12. <https://doi.org/10.1161/circulationaha.117.033369>
1081. Lee D. HIV: how to manage dyslipidaemia in HIV. *Drugs Context* 2022;**11**:2021-8-7. <https://doi.org/10.7573/dic.2021-8-7>
1082. Dekkers CC, Westerink J, Hoepelman AIM, Arends JE. Overcoming obstacles in lipid-lowering therapy in patients with HIV—a systematic review of current evidence. *AIDS Rev* 2018;**20**:205–19. <https://doi.org/10.24875/AIDSRev.18000016>
1083. Feinstein MJ, Hsue PY, Benjamin LA, Bloomfield GS, Currier JS, Freiberg MS, et al. Characteristics, prevention, and management of cardiovascular disease in people living with HIV: a scientific statement from the American Heart Association. *Circulation* 2019;**140**:e98–124. <https://doi.org/10.1161/cir.0000000000000695>
1084. Foster HME, Celis-Morales CA, Nicholl BI, Petermann-Rocha F, Pell JP, Gill JMR, et al. The effect of socioeconomic deprivation on the association between an extended measurement of unhealthy lifestyle factors and health outcomes: a prospective analysis of the UK Biobank cohort. *Lancet Public Health* 2018;**3**:e576–85. [https://doi.org/10.1016/s2468-2667\(18\)30200-7](https://doi.org/10.1016/s2468-2667(18)30200-7)
1085. Floud S, Balkwill A, Moser K, Reeves GK, Green J, Beral V, et al. The role of health-related behavioural factors in accounting for inequalities in coronary heart disease risk by education and area deprivation: prospective study of 1.2 million UK women. *BMC Med* 2016;**14**:145. <https://doi.org/10.1186/s12916-016-0687-2>
1086. Stringhini S, Carmeli C, Jokela M, Avendaño M, Muennig P, Guida F, et al. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1.7 million men and women. *Lancet* 2017;**389**:1229–37. [https://doi.org/10.1016/s0140-6736\(16\)32380-7](https://doi.org/10.1016/s0140-6736(16)32380-7)
1087. Di Girolamo C, Nusselder WJ, Bopp M, Brønnum-Hansen H, Costa G, Kovács K, et al. Progress in reducing inequalities in cardiovascular disease mortality in Europe. *Heart* 2020;**106**:40–9. <https://doi.org/10.1136/heartjnl-2019-315129>
1088. Leyland AH, Dundas R. Declining cardiovascular mortality masks unpalatable inequalities. *Heart* 2020;**106**:6–7. <https://doi.org/10.1136/heartjnl-2019-315708>
1089. Sidhu GS, Ward C, Ferdinand KC. Racial disparity in atherosclerotic cardiovascular disease in hospitalized patients with diabetes 2005–2015: potential warning signs for future U.S. public health. *Am J Prev Cardiol* 2020;**4**:100095. <https://doi.org/10.1016/j.ajpc.2020.100095>
1090. Pursnani S, Merchant M. South Asian ethnicity as a risk factor for coronary heart disease. *Atherosclerosis* 2020;**315**:126–30. <https://doi.org/10.1016/j.atherosclerosis.2020.10.007>
1091. Patel AP, Wang M, Kartoun U, Ng K, Khara AV. Quantifying and understanding the higher risk of atherosclerotic cardiovascular disease among South Asian individuals: results from the UK Biobank Prospective Cohort Study. *Circulation* 2021;**144**: 410–22. <https://doi.org/10.1161/circulationaha.120.052430>
1092. Hosseini F, Malhi N, Sellers SL, Khan N, Li CK, Taylor CM, et al. The morphology of coronary artery disease in South Asians vs white Caucasians and its implications. *Can J Cardiol* 2022;**38**:1570–9. <https://doi.org/10.1016/j.cjca.2022.05.005>
1093. Magavern EF, Jacobs B, Warren H, Finocchiaro G, Finer S, van Heel DA, et al. CYP2C19 genotype prevalence and association with recurrent myocardial infarction in British-South Asians treated with clopidogrel. *JACC Adv* 2023;**2**:100573. <https://doi.org/10.1016/j.jaccadv.2023.100573>
1094. Beral V, Banks E, Reeves G. Evidence from randomised trials on the long-term effects of hormone replacement therapy. *Lancet* 2002;**360**:942–4. [https://doi.org/10.1016/s0140-6736\(02\)11032-4](https://doi.org/10.1016/s0140-6736(02)11032-4)
1095. Boardman HM, Hartley L, Eisinga A, Main C, Roqué i Figuls M, Bonfill Cosp X, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database Syst Rev* 2015;**3**:CD002229. <https://doi.org/10.1002/14651858.CD002229.pub4>
1096. Gili S, Grosso Marra W, D'Ascenzo F, Lonni E, Calcagno A, Cannillo M, et al. Comparative safety and efficacy of statins for primary prevention in human immunodeficiency virus-positive patients: a systematic review and meta-analysis. *Eur Heart J* 2016;**37**:3600–9. <https://doi.org/10.1093/eurheartj/ehv734>
1097. Bergström G, Persson M, Adiels M, Björnsen E, Bonander C, Ahlström H, et al. Prevalence of subclinical coronary artery atherosclerosis in the general population. *Circulation* 2021;**144**:916–29. <https://doi.org/10.1161/circulationaha.121.055340>
1098. Nasir K, Cainzos-Achirica M, Valero-Elizondo J, Ali SS, Havistin R, Lakshman S, et al. Coronary atherosclerosis in an asymptomatic U.S. population: Miami Heart Study at Baptist Health South Florida. *JACC Cardiovasc Imaging* 2022;**15**:1604–18. <https://doi.org/10.1016/j.jcmg.2022.03.010>
1099. Baber U, Mehran R, Sartori S, Schoos MM, Sillesen H, Muntendam P, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the Biomag study. *J Am Coll Cardiol* 2015;**65**:1065–74. <https://doi.org/10.1016/j.jacc.2015.01.017>
1100. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2006;**113**:30–7. <https://doi.org/10.1161/circulationaha.105.580696>

1101. SCORE2 working group, ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J* 2021;**42**:2439–54. <https://doi.org/10.1093/eurheartj/ehab309>
1102. Krogsbøll LT, Jørgensen KJ, Gøtzsche PC. General health checks in adults for reducing morbidity and mortality from disease. *Cochrane Database Syst Rev* 2019;1:CD009009. <https://doi.org/10.1002/14651858.CD009009.pub3>
1103. Si S, Moss JR, Sullivan TR, Newton SS, Stocks NP. Effectiveness of general practice-based health checks: a systematic review and meta-analysis. *Br J Gen Pract* 2014;**64**:e47–53. <https://doi.org/10.3399/bjgp14X676456>
1104. Peters SA, den Ruijter HM, Bots ML, Moons KG. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. *Heart* 2012;**98**:177–184. <https://doi.org/10.1136/heartjnl-2011-300747>
1105. Arad Y, Spadaro LA, Roth M, Newstein D, Guerci AD. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. *J Am Coll Cardiol* 2005;**46**:166–72. <https://doi.org/10.1016/j.jacc.2005.02.089>
1106. Lindholt JS, Sogaard R, Rasmussen LM, Mejldal A, Lambrechtsen J, Steffensen FH, et al. Five-year outcomes of the Danish cardiovascular screening (DANCAVAS) trial. *N Engl J Med* 2022;**387**:1385–94. <https://doi.org/10.1056/NEJMoa2208681>
1107. Ajufo E, Ayers CR, Vigen R, Joshi PH, Rohatgi A, de Lemos JA, et al. Value of coronary artery calcium scanning in association with the net benefit of aspirin in primary prevention of atherosclerotic cardiovascular disease. *JAMA Cardiol* 2021;**6**:179–87. <https://doi.org/10.1001/jamacardio.2020.4939>
1108. Chiles C, Duan F, Gladish GW, Ravenel JG, Baginski SG, Snyder BS, et al. Association of coronary artery calcification and mortality in the National Lung Screening Trial: a comparison of three scoring methods. *Radiology* 2015;**276**:82–90. <https://doi.org/10.1148/radiol.15142062>
1109. Hecht HS, Cronin P, Blaha MJ, Budoff MJ, Kazerooni EA, Narula J, et al. 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: a report of the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology. *J Cardiovasc Comput Tomogr* 2017;**11**:74–84. <https://doi.org/10.1016/j.jcct.2016.11.003>
1110. Williams MC, Abbas A, Tarr E, Alam S, Nicol E, Shambrook J, et al. Reporting incidental coronary, aortic valve and cardiac calcification on non-gated thoracic computed tomography, a consensus statement from the BSCI/BSCCT and BSTI. *Br J Radiol* 2021;**94**:20200894. <https://doi.org/10.1259/bjr.20200894>
1111. Sillesen H, Sartori S, Sandholt B, Baber U, Mehran R, Fuster V. Carotid plaque thickness and carotid plaque burden predict future cardiovascular events in asymptomatic adult Americans. *Eur Heart J Cardiovasc Imaging* 2018;**19**:1042–50. <https://doi.org/10.1093/ehjci/ehx239>
1112. SCORE2-OP working group, ESC Cardiovascular risk collaboration. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. *Eur Heart J* 2021;**42**:2455–67. <https://doi.org/10.1093/eurheartj/ehab312>
1113. Backman W, Levine SA, Wenger NK, Harold JG. Shared decision-making for older adults with cardiovascular disease. *Clin Cardiol* 2020;**43**:196–204. <https://doi.org/10.1002/clc.23267>
1114. Street RL Jr, Makoul G, Arora NK, Epstein RM. How does communication heal? Pathways linking clinician–patient communication to health outcomes. *Patient Educ Couns* 2009;**74**:295–301. <https://doi.org/10.1016/j.pec.2008.11.015>
1115. Zolnierok KB, Dimatteo MR. Physician communication and patient adherence to treatment: a meta-analysis. *Med Care* 2009;**47**:826–34. <https://doi.org/10.1097/MLR.0b013e31819a5acc>
1116. Thomas M, Jones PG, Arnold SV, Spertus JA. Interpretation of the Seattle angina questionnaire as an outcome measure in clinical trials and clinical care: a review. *JAMA Cardiol* 2021;**6**:593–9. <https://doi.org/10.1001/jamacardio.2020.7478>
1117. Saxon JT, Chan PS, Tran AT, Angraal S, Jones PG, Grantham JA, et al. Comparison of patient-reported vs physician-estimated angina in patients undergoing elective and urgent percutaneous coronary intervention. *JAMA Netw Open* 2020;**3**:e207406. <https://doi.org/10.1001/jamanetworkopen.2020.7406>
1118. Moore PM, Rivera Mercado S, Grez Artigues M, Lawrie TA. Communication skills training for healthcare professionals working with people who have cancer. *Cochrane Database Syst Rev* 2013;**3**:CD003751. <https://doi.org/10.1002/14651858.CD003751.pub3>
1119. Yao M, Zhou XY, Xu ZJ, Lehman R, Haroon S, Jackson D, et al. The impact of training healthcare professionals' communication skills on the clinical care of diabetes and hypertension: a systematic review and meta-analysis. *BMC Fam Pract* 2021;**22**:152. <https://doi.org/10.1186/s12875-021-01504-x>
1120. Austin CA, Mohottige D, Sudore RL, Smith AK, Hanson LC. Tools to promote shared decision making in serious illness: a systematic review. *JAMA Intern Med* 2015;**175**:1213–21. <https://doi.org/10.1001/jamainternmed.2015.1679>
1121. Hoffrage U, Lindsey S, Hertwig R, Gigerenzer G. Communicating statistical information. *Science* 2000;**290**:2261–2. <https://doi.org/10.1126/science.290.5500.2261>
1122. Akl EA, Oxman AD, Herrin J, Vist GE, Terrenato I, Sperati F, et al. Using alternative statistical formats for presenting risks and risk reductions. *Cochrane Database Syst Rev* 2011;**3**:CD006776. <https://doi.org/10.1002/14651858.CD006776.pub2>
1123. Navar AM, Stone NJ, Martin SS. What to say and how to say it: effective communication for cardiovascular disease prevention. *Curr Opin Cardiol* 2016;**31**:537–44. <https://doi.org/10.1097/hco.0000000000000322>
1124. French DP, Cameron E, Benton JS, Deaton C, Harvie M. Can communicating personalised disease risk promote healthy behaviour change? A systematic review of systematic reviews. *Ann Behav Med* 2017;**51**:718–29. <https://doi.org/10.1007/s12160-017-9895-z>
1125. Schulberg SD, Ferry AV, Jin K, Marshall L, Neubeck L, Strachan FE, et al. Cardiovascular risk communication strategies in primary prevention. A systematic review with narrative synthesis. *J Adv Nurs* 2022;**78**:3116–40. <https://doi.org/10.1111/jan.15327>
1126. Hedberg B, Malm D, Karlsson JE, Arestedt K, Brostrom A. Factors associated with confidence in decision making and satisfaction with risk communication among patients with atrial fibrillation. *Eur J Cardiovasc Nurs* 2018;**17**:446–55. <https://doi.org/10.1177/1474515117741891>
1127. Frieling T. Non-cardiac chest pain. *Visc Med* 2018;**34**:92–6. <https://doi.org/10.1159/000486440>
1128. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, et al. 2021 AHA/ACC/AASE/CHEST/SAEM/SCCT/SCMR Guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2021;**78**:e187–285. <https://doi.org/10.1016/j.jacc.2021.07.053>
1129. Jha MK, Qamar A, Vaduganathan M, Charney DS, Murrough JW. Screening and management of depression in patients with cardiovascular disease: JACC state-of-the-art review. *J Am Coll Cardiol* 2019;**73**:1827–45. <https://doi.org/10.1016/j.jacc.2019.01.041>
1130. Wen Y, Yang Y, Shen J, Luo S. Anxiety and prognosis of patients with myocardial infarction: a meta-analysis. *Clin Cardiol* 2021;**44**:761–70. <https://doi.org/10.1002/clc.23605>
1131. Peter RS, Meyer ML, Mons U, Schöttker B, Keller F, Schmucker R, et al. Long-term trajectories of anxiety and depression in patients with stable coronary heart disease and risk of subsequent cardiovascular events. *Depress Anxiety* 2020;**37**:784–92. <https://doi.org/10.1002/da.23011>
1132. Fernandes N, Prada L, Rosa MM, Ferreira JJ, Costa J, Pinto FJ, et al. The impact of SSRIs on mortality and cardiovascular events in patients with coronary artery disease and depression: systematic review and meta-analysis. *Clin Res Cardiol* 2021;**110**:183–93. <https://doi.org/10.1007/s00392-020-01697-8>
1133. Parker EL, Banfield M, Fassnacht DB, Hatfield T, Kyrios M. Contemporary treatment of anxiety in primary care: a systematic review and meta-analysis of outcomes in countries with universal healthcare. *BMC Fam Pract* 2021;**22**:92. <https://doi.org/10.1186/s12875-021-01445-5>
1134. Gulliksson M, Burell G, Vessby B, Lundin L, Toss H, Svärdsudd K. Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care project (SUPRIM). *Arch Intern Med* 2011;**171**:134–40. <https://doi.org/10.1001/archinternmed.2010.510>
1135. Doyle F, Freedland KE, Carney RM, de Jonge P, Dickens C, Pedersen SS, et al. Hybrid systematic review and network meta-analysis of randomized controlled trials of interventions for depressive symptoms in patients with coronary artery disease. *Psychosom Med* 2021;**83**:423–31. <https://doi.org/10.1097/psy.0000000000000944>
1136. World Health Organization. Adherence to Long-Term Therapies: Evidence for Action. 2003. <https://iris.who.int/handle/10665/42682>
1137. Foley L, Larkin J, Lombard-Vance R, Murphy AW, Hynes L, Galvin E, et al. Prevalence and predictors of medication non-adherence among people living with multimorbidity: a systematic review and meta-analysis. *BMJ Open* 2021;**11**:e044987. <https://doi.org/10.1136/bmjopen-2020-044987>
1138. Kotseva K, De Backer G, De Bacquer D, Rydén L, Hoes A, Grobbee D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. *Eur J Prev Cardiol* 2019;**26**:824–35. <https://doi.org/10.1177/2047487318825350>
1139. Pedretti RFE, Hansen D, Ambrosetti M, Back M, Berger T, Ferreira MC, et al. How to optimize the adherence to a guideline-directed medical therapy in the secondary prevention of cardiovascular diseases: a clinical consensus statement from the European Association of Preventive Cardiology (EAPC). *Eur J Prev Cardiol* 2023;**30**:149–66. <https://doi.org/10.1093/eurjpc/zwac204>
1140. Gardner B, Lally P, Wardle J. Making health habitual: the psychology of 'habit-formation' and general practice. *Br J Gen Pract* 2012;**62**:e664–6. <https://doi.org/10.3399/bjgp12X659466>
1141. Brørs G, Dalen H, Allore H, Deaton C, Fridlund B, Osborne RH, et al. Health literacy and risk factors for coronary artery disease (from the CONCARD^{PCI} study). *Am J Cardiol* 2022;**179**:22–30. <https://doi.org/10.1016/j.amjcard.2022.06.016>
1142. Jennings CS, Astin F, Prescott E, Hansen T, Gale Chris P, De Bacquer D. Illness perceptions and health literacy are strongly associated with health-related quality of life,

- anxiety and depression in patients with coronary heart disease: results from the EUROASPIRE V cross-sectional survey. *Eur J Cardiovasc Nurs* 2023;**22**:719–29. <https://doi.org/10.1093/eurjcn/zvac105>
1143. Chiang CY, Choi KC, Ho KM, Yu SF. Effectiveness of nurse-led patient-centered care behavioral risk modification on secondary prevention of coronary heart disease: a systematic review. *Int J Nurs Stud* 2018;**84**:28–39. <https://doi.org/10.1016/j.ijnurstu.2018.04.012>
1144. O'Connor EA, Evans CV, Rushkin MC, Redmond N, Lin JS. Behavioral counseling to promote a healthy diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2020;**324**:2076–94. <https://doi.org/10.1001/jama.2020.17108>
1145. Garcia-Lunar I, van der Ploeg HP, Fernandez Alvira JM, van Nassau F, Castellano Vázquez JM, van der Beek AJ, et al. Effects of a comprehensive lifestyle intervention on cardiovascular health: the TANSNIP-PESA trial. *Eur Heart J* 2022;**43**:3732–45. <https://doi.org/10.1093/eurheartj/ehac378>
1146. Gandhi S, Chen S, Hong L, Sun K, Gong E, Li C, et al. Effect of mobile health interventions on the secondary prevention of cardiovascular disease: systematic review and meta-analysis. *Can J Cardiol* 2017;**33**:219–31. <https://doi.org/10.1016/j.cjca.2016.08.017>
1147. Akinosun AS, Polson R, Diaz-Skeete Y, De Kock JH, Carragher L, Leslie S, et al. Digital technology interventions for risk factor modification in patients with cardiovascular disease: systematic review and meta-analysis. *JMIR Mhealth Uhealth* 2021;**9**:e21061. <https://doi.org/10.2196/21061>
1148. Kaihara T, Intan-Goey V, Scherrenberg M, Falter M, Frederix I, Dendale P. Impact of activity trackers on secondary prevention in patients with coronary artery disease: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2022;**29**:1047–56. <https://doi.org/10.1093/eurjpc/zwab146>
1149. Patterson K, Davey R, Keegan R, Freene N. Smartphone applications for physical activity and sedentary behaviour change in people with cardiovascular disease: a systematic review and meta-analysis. *PLoS One* 2021;**16**:e0258460. <https://doi.org/10.1371/journal.pone.0258460>
1150. Du L, Cheng Z, Zhang Y, Li Y, Mei D. The impact of medication adherence on clinical outcomes of coronary artery disease: a meta-analysis. *Eur J Prev Cardiol* 2017;**24**:962–70. <https://doi.org/10.1177/2047487317695628>
1151. Sanfélix-Gimeno G, Peiró S, Ferreros I, Pérez-Vicente R, Librero J, Catalá-López F, et al. Adherence to evidence-based therapies after acute coronary syndrome: a retrospective population-based cohort study linking hospital, outpatient, and pharmacy health information systems in Valencia, Spain. *J Manag Care Pharm* 2013;**19**:247–57. <https://doi.org/10.18553/jmcp.2013.19.3.247>
1152. Garcia RA, Spertus JA, Benton MC, Jones PG, Mark DB, Newman JD, et al. Association of medication adherence with health outcomes in the ISCHEMIA trial. *J Am Coll Cardiol* 2022;**80**:755–65. <https://doi.org/10.1016/j.jacc.2022.05.045>
1153. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2014;**2014**:CD000011. <https://doi.org/10.1002/14651858.CD000011.pub4>
1154. Conn VS, Ruppert TM. Medication adherence outcomes of 771 intervention trials: systematic review and meta-analysis. *Prev Med* 2017;**99**:269–76. <https://doi.org/10.1016/j.ypmed.2017.03.008>
1155. Fuller RH, Perel P, Navarro-Ruan T, Nieuwlaat R, Haynes RB, Huffman MD. Improving medication adherence in patients with cardiovascular disease: a systematic review. *Heart* 2018;**104**:1238–43. <https://doi.org/10.1136/heartjnl-2017-312571>
1156. Cross AJ, Elliott RA, Petrie K, Kuruvilla L, George J. Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications. *Cochrane Database Syst Rev* 2020;**5**:CD012419. <https://doi.org/10.1002/14651858.CD012419.pub2>
1157. Mahtani KR, Heneghan CJ, Glasziou PP, Perera R. Reminder packaging for improving adherence to self-administered long-term medications. *Cochrane Database Syst Rev* 2011;**9**:CD005025. <https://doi.org/10.1002/14651858.CD005025.pub3>
1158. Lapa ME, Swabe GM, Rollman BL, Muldoon MF, Thurston RC, Magnani JW. Assessment of depression and adherence to guideline-directed medical therapies following percutaneous coronary intervention. *JAMA Netw Open* 2022;**5**:e2246317. <https://doi.org/10.1001/jamanetworkopen.2022.46317>
1159. Schmieder RE, Wassmann S, Predel HG, Weisser B, Blettenberg J, Gillessen A, et al. Improved persistence to medication, decreased cardiovascular events and reduced all-cause mortality in hypertensive patients with use of single-pill combinations: results from the START-study. *Hypertension* 2023;**80**:1127–35. <https://doi.org/10.1161/HYPERTENSIONAHA.122.20810>
1160. Simon ST, Kini V, Levy AE, Ho PM. Medication adherence in cardiovascular medicine. *BMJ* 2021;**374**:n1493. <https://doi.org/10.1136/bmj.n1493>
1161. Thom S, Poulter N, Field J, Patel A, Prabhakaran D, Stanton A, et al. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the UMPIRE randomized clinical trial. *JAMA* 2013;**310**:918–29. <https://doi.org/10.1001/jama.2013.277064>
1162. Jeong SM, Kim S, Wook Shin D, Han K, Hyun Park S, Hyuk Kim S, et al. Persistence and adherence to antihypertensive drugs in newly treated hypertensive patients according to initial prescription. *Eur J Prev Cardiol* 2021;**28**:e1–4. <https://doi.org/10.1177/2047487319900326>
1163. Castellano JM, Pocock SJ, Bhatt DL, Quesada AJ, Owen R, Fernandez-Ortiz A, et al. Polypill strategy in secondary cardiovascular prevention. *N Engl J Med* 2022;**387**:967–77. <https://doi.org/10.1056/NEJMoa2208275>
1164. Adler AJ, Martin N, Mariani J, Tajer CD, Owolabi OO, Free C, et al. Mobile phone text messaging to improve medication adherence in secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2017;**4**:CD011851. <https://doi.org/10.1002/14651858.CD011851.pub2>
1165. Kassavou A, Mirzaei V, Brimicombe J, Edwards S, Massou E, Prevost AT, et al. A highly tailored text and voice messaging intervention to improve medication adherence in patients with either or both hypertension and type 2 diabetes in a UK primary care setting: feasibility randomized controlled trial of clinical effectiveness. *J Med Internet Res* 2020;**22**:e16629. <https://doi.org/10.2196/16629>
1166. Castellano JM, Sanz G, Penalvo JL, Bansilal S, Fernández-Ortiz A, Alvarez L, et al. A polypill strategy to improve adherence: results from the FOCUS project. *J Am Coll Cardiol* 2014;**64**:2071–82. <https://doi.org/10.1016/j.jacc.2014.08.021>
1167. Wilson PW, D'Agostino R Sr, Bhatt DL, Eagle K, Pencina MJ, Smith SC, et al. An international model to predict recurrent cardiovascular disease. *Am J Med* 2012;**125**:695–703.e1. <https://doi.org/10.1016/j.amjmed.2012.01.014>
1168. De Bacquer D, Ueda P, Reiner Z, De Sutter J, De Smedt D, Lovic D, et al. Prediction of recurrent event in patients with coronary heart disease: the EUROASPIRE risk model. *Eur J Prev Cardiol* 2022;**29**:328–39. <https://doi.org/10.1093/eurjpc/zwaa128>
1169. De Bacquer D, Ueda P, Reiner Z, De Sutter J, De Smedt D, Lovic D, et al. EUROASPIRE Risk Calculator. <https://www.calconic.com/calculator/widgets/euroaspire-risk-factor-%20calculator/5f6223fab75b14001e1f3c67?layouts=true>
1170. Cho SMJ, Koyama S, Honigberg MC, Sarakka I, Haidermota S, Ganesh S, et al. Genetic, sociodemographic, lifestyle, and clinical risk factors of recurrent coronary artery disease events: a population-based cohort study. *Eur Heart J* 2023;**44**:3456–65. <https://doi.org/10.1093/eurheartj/ehad380>
1171. Iribarren C, Lu M, Jorgenson E, Martínez M, Lluís-Ganella C, Subirana I, et al. Clinical utility of multimarker genetic risk scores for prediction of incident coronary heart disease: a cohort study among over 51 000 individuals of European ancestry. *Circ Cardiovasc Genet* 2016;**9**:531–40. <https://doi.org/10.1161/CIRCGENETICS.116.001522>
1172. Weintraub WS, Boden WE. Can we measurably improve the prediction of recurrent coronary artery disease events? *Eur Heart J* 2023;**44**:3466–8. <https://doi.org/10.1093/eurheartj/ehad464>
1173. Park D-W, Kang D-Y, Ahn J-M, Yun S-C, Yoon Y-H, Hur S-H, et al. Routine functional testing or standard care in high-risk patients after PCI. *New Engl J Med* 2022;**387**:905–15. <https://doi.org/10.1056/NEJMoa2208335>
1174. Chan M, Ridley L, Dunn DJ, Tian DH, Liou K, Ozdirik J, et al. A systematic review and meta-analysis of multidetector computed tomography in the assessment of coronary artery bypass grafts. *Int J Cardiol* 2016;**221**:898–905. <https://doi.org/10.1016/j.ijcard.2016.06.264>
1175. Li Y, Yu M, Li W, Lu Z, Wei M, Zhang J. Third generation dual-source CT enables accurate diagnosis of coronary restenosis in all size stents with low radiation dose and preserved image quality. *Eur Radiol* 2018;**28**:2647–54. <https://doi.org/10.1007/s00330-017-5256-3>
1176. Mansour HH, Alajerami YS, Abushab KM, Quffa KM. The diagnostic accuracy of coronary computed tomography angiography in patients with and without previous coronary interventions. *J Med Imaging Radiat Sci* 2022;**53**:81–6. <https://doi.org/10.1016/j.jmir.2021.10.005>
1177. Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. *J Am Coll Cardiol* 1996;**28**:616–26. [https://doi.org/10.1016/0735-1097\(96\)00206-9](https://doi.org/10.1016/0735-1097(96)00206-9)
1178. Barbero U, Iannaccone M, d'Ascenzo F, Barbero C, Mohamed A, Annone U, et al. 64 Slice-coronary computed tomography sensitivity and specificity in the evaluation of coronary artery bypass graft stenosis: a meta-analysis. *Int J Cardiol* 2016;**216**:52–7. <https://doi.org/10.1016/j.ijcard.2016.04.156>
1179. de Winter RW, Rahman MS, van Diemen PA, Schumacher SP, Jukema RA, Somsen YBO, et al. Diagnostic and management strategies in patients with late recurrent angina after coronary artery bypass grafting. *Curr Cardiol Rep* 2022;**24**:1309–25. <https://doi.org/10.1007/s11886-022-01746-w>
1180. Zellweger MJ, Hachamovitch R, Kang X, Hayes SW, Friedman JD, Germano G, et al. Threshold, incidence, and predictors of prognostically high-risk silent ischemia in asymptomatic patients without prior diagnosis of coronary artery disease. *J Nucl Cardiol* 2009;**16**:193–200. <https://doi.org/10.1007/s12350-008-9016-2>
1181. Al-Lamee RK, Shun-Shin MJ, Howard JP, Nowbar AN, Rajkumar C, Thompson D, et al. Dobutamine stress echocardiography ischemia as a predictor of the placebo-controlled efficacy of percutaneous coronary intervention in stable coronary artery disease: the stress echocardiography-stratified analysis of ORBITA. *Circulation* 2019;**140**:1971–80. <https://doi.org/10.1161/CIRCULATIONAHA.119.042918>
1182. Stefanini GG, Alfonso F, Barbato E, Byrne R, Capodanno D, Colaneri R, et al. Management of myocardial revascularisation failure: an expert consensus document

- of the EAPCI. *EuroIntervention* 2020;**16**:e875–90. <https://doi.org/10.4244/eij-d-20-00487>
1183. Taniwaki M, Windecker S, Zaugg S, Stefanini GG, Baumgartner S, Zanchin T, et al. The association between in-stent neoatherosclerosis and native coronary artery disease progression: a long-term angiographic and optical coherence tomography cohort study. *Eur Heart J* 2015;**36**:2167–76. <https://doi.org/10.1093/eurheartj/ehv227>
 1184. Pereg D, Fefer P, Samuel M, Wolff R, Czarnecki A, Deb S, et al. Native coronary artery patency after coronary artery bypass surgery. *JACC Cardiovasc Interv* 2014;**7**:761–7. <https://doi.org/10.1016/j.jcin.2014.01.164>
 1185. Adriaenssens T, Joner M, Godschalk TC, Malik N, Alfonso F, Xhepa E, et al. Optical coherence tomography findings in patients with coronary stent thrombosis: a report of the PRESTIGE consortium (prevention of late stent thrombosis by an interdisciplinary global European effort). *Circulation* 2017;**136**:1007–21. <https://doi.org/10.1161/circulationaha.117.026788>
 1186. Giacoppo D, Alfonso F, Xu B, Claessen BEPM, Adriaenssens T, Jensen C, et al. Drug-coated balloon angioplasty versus drug-eluting stent implantation in patients with coronary stent restenosis. *J Am Coll Cardiol* 2020;**75**:2664–78. <https://doi.org/10.1016/j.jacc.2020.04.006>
 1187. Giacoppo D, Alvarez-Covarrubias HA, Koch T, Cassese S, Xhepa E, Kessler T, et al. Coronary artery restenosis treatment with plain balloon, drug-coated balloon, or drug-eluting stent: 10-year outcomes of the ISAR-DESIRE 3 trial. *Eur Heart J* 2023;**44**:1343–57. <https://doi.org/10.1093/eurheartj/ehad026>
 1188. Elgendy IY, Mahmoud AN, Elgendy AY, Mojadidi MK, Elbadawi A, Eshtehardi P, et al. Drug-eluting balloons versus everolimus-eluting stents for in-stent restenosis: a meta-analysis of randomized trials. *Cardiovasc Revasc Med* 2019;**20**:612–8. <https://doi.org/10.1016/j.carrev.2018.08.010>
 1189. Doenst T, Sousa-Uva M. How to deal with nonsevere stenoses in coronary artery bypass grafting—a critical perspective on competitive flow and surgical precision. *Curr Opin Cardiol* 2022;**37**:468–73. <https://doi.org/10.1097/hco.0000000000000993>
 1190. Zhao DX, Leacche M, Balaguer JM, Boudoulas KD, Damp JA, Greulich JP, et al. Routine intraoperative completion angiography after coronary artery bypass grafting and 1-stop hybrid revascularization results from a fully integrated hybrid catheterization laboratory/operating room. *J Am Coll Cardiol* 2009;**53**:232–41. <https://doi.org/10.1016/j.jacc.2008.10.011>
 1191. Mehta RH, Ferguson TB, Lopes RD, Hafley GE, Mack MJ, Kouchoukos NT, et al. Saphenous vein grafts with multiple versus single distal targets in patients undergoing coronary artery bypass surgery: one-year graft failure and five-year outcomes from the Project of Ex-Vivo Vein Graft Engineering via Transfection (PREVENT) IV trial. *Circulation* 2011;**124**:280–8. <https://doi.org/10.1161/circulationaha.110.991299>
 1192. Morrison DA, Sethi G, Sacks J, Henderson WG, Grover F, Sedlis S, et al. Percutaneous coronary intervention versus repeat bypass surgery for patients with medically refractory myocardial ischemia: AWESOME randomized trial and registry experience with post-CABG patients. *J Am Coll Cardiol* 2002;**40**:1951–4. [https://doi.org/10.1016/s0735-1097\(02\)02560-3](https://doi.org/10.1016/s0735-1097(02)02560-3)
 1193. Xenogiannis I, Tajti P, Hall AB, Alaswad K, Rinfret S, Nicholson W, et al. Update on cardiac catheterization in patients with prior coronary artery bypass graft surgery. *JACC Cardiovasc Interv* 2019;**12**:1635–49. <https://doi.org/10.1016/j.jcin.2019.04.051>
 1194. Doenst T, Haverich A, Serruys P, Bonow RO, Kappetein P, Falk V, et al. PCI and CABG for treating stable coronary artery disease: JACC review topic of the week. *J Am Coll Cardiol* 2019;**73**:964–76. <https://doi.org/10.1016/j.jacc.2018.11.053>
 1195. Sabik JF 3rd, Raza S, Blackstone EH, Houghtaling PL, Lytle BW. Value of internal thoracic artery grafting to the left anterior descending coronary artery at coronary reoperation. *J Am Coll Cardiol* 2013;**61**:302–10. <https://doi.org/10.1016/j.jacc.2012.09.045>
 1196. Brenner SJ, Lytle BW, Casserly IP, Ellis SG, Topol EJ, Lauer MS. Predictors of revascularization method and long-term outcome of percutaneous coronary intervention or repeat coronary bypass surgery in patients with multivessel coronary disease and previous coronary bypass surgery. *Eur Heart J* 2006;**27**:413–8. <https://doi.org/10.1093/eurheartj/ehi646>
 1197. Brilakis ES, O'Donnell CI, Penny W, Armstrong EJ, Tsai T, Maddox TM, et al. Percutaneous coronary intervention in native coronary arteries versus bypass grafts in patients with prior coronary artery bypass graft surgery: insights from the Veterans Affairs clinical assessment, reporting, and tracking program. *JACC Cardiovasc Interv* 2016;**9**:884–93. <https://doi.org/10.1016/j.jcin.2016.01.034>
 1198. Caceres J, Atal P, Arora R, Yee D. Enhanced external counterpulsation: a unique treatment for the “No-Option” refractory angina patient. *J Clin Pharm Ther* 2021;**46**:295–303. <https://doi.org/10.1111/jcpt.13330>
 1199. Verheye S, Jolicœur EM, Behan MW, Pettersson T, Sainsbury P, Hill J, et al. Efficacy of a device to narrow the coronary sinus in refractory angina. *N Engl J Med* 2015;**372**:519–27. <https://doi.org/10.1056/NEJMoa1402556>
 1200. Hochstadt A, Itach T, Merdler I, Ghantous E, Ziv-Baran T, Leshno M, et al. Effectiveness of coronary sinus reducer for treatment of refractory angina: a meta-analysis. *Can J Cardiol* 2022;**38**:376–83. <https://doi.org/10.1016/j.cjca.2021.12.009>
 1201. Foley MJ, Rajkumar CA, Ahmed-Jushuf F, Simader FA, Chotai S, Pathimagaraj RH, et al. Coronary sinus reducer for the treatment of refractory angina (ORBITA-COSMIC): a randomised, placebo-controlled trial. *Lancet* 2024;**403**:1543–53. [https://doi.org/10.1016/s0140-6736\(24\)00256-3](https://doi.org/10.1016/s0140-6736(24)00256-3)
 1202. Velagapudi P, Turagam M, Kolte D, Khera S, Hyder O, Gordon P, et al. Intramyocardial autologous CD34+ cell therapy for refractory angina: a meta-analysis of randomized controlled trials. *Cardiovasc Revasc Med* 2019;**20**:215–9. <https://doi.org/10.1016/j.carrev.2018.05.018>
 1203. Jones DA, Weeraman D, Colicchia M, Hussain MA, Veerapen D, Andiapien M, et al. The impact of cell therapy on cardiovascular outcomes in patients with refractory angina. *Circ Res* 2019;**124**:1786–95. <https://doi.org/10.1161/circresaha.118.314118>
 1204. Giannini F, Baldetti L, Konigstein M, Rosseel L, Ruparella N, Gallone G, et al. Safety and efficacy of the reducer: a multi-center clinical registry—REDUCE study. *Int J Cardiol* 2018;**269**:40–4. <https://doi.org/10.1016/j.ijcard.2018.06.116>
 1205. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:1505–35. <https://doi.org/10.1002/ejhf.1236>
 1206. Adamo M, Grasso C, Capodanno D, Rubbio AP, Scandura S, Giannini C, et al. Five-year clinical outcomes after percutaneous edge-to-edge mitral valve repair: insights from the multicenter GRASP-IT registry. *Am Heart J* 2019;**217**:32–41. <https://doi.org/10.1016/j.ahj.2019.06.015>
 1207. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022;**43**:3997–4126. <https://doi.org/10.1093/eurheartj/ehac262>
 1208. Praz F, Muraru D, Kreidel F, Lurz P, Hahn RT, Delgado V, et al. Transcatheter treatment for tricuspid valve disease. *EuroIntervention* 2021;**17**:791–808. <https://doi.org/10.4244/eij-d-21-00695>
 1209. Sorajja P, Whisenant B, Hamid N, Naik H, Makkar R, Tadros P, et al. Transcatheter repair for patients with tricuspid regurgitation. *New Engl J Med* 2023;**388**:1833–42. <https://doi.org/10.1056/NEJMoa2300525>
 1210. Sogaard R, Diederichsen ACP, Rasmussen LM, Lambrechtsen J, Steffensen FH, Frost L, et al. Cost effectiveness of population screening vs. no screening for cardiovascular disease: the Danish Cardiovascular Screening trial (DANCAVAS). *Eur Heart J* 2022;**43**:4392–402. <https://doi.org/10.1093/eurheartj/ehac488>
 1211. Schinkel AF, Bax JJ, Poldermans D, Elhendy A, Ferrari R, Rahimtoola SH. Hibernating myocardium: diagnosis and patient outcomes. *Curr Probl Cardiol* 2007;**32**:375–410. <https://doi.org/10.1016/j.cpcardiol.2007.04.001>