ESC European Society of Cardiology

European Heart Journal (2024) **00**, 1–123
https://doi.org/10.1093/eurheartj/ehae177

ESC GUIDELINES

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

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* 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.

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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 McInerny (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.

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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

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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

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ARC-HBR	Academic Research Consortium for High Bleeding Risk
ARNI	Angiotensin receptor neprilysin inhibitor
ART	Antiretroviral therapy
ASCVD	Atherosclerotic cardiovascular disease
ASE	American Society of Echocardiography
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
BARC	Bleeding Academic Research Consortium
b.i.d.	bis in die (twice daily)
BMI	Body mass index
BP	Blood pressure
b.p.m.	Beats per minute
CABG	Coronary artery bypass grafting
CAC	Coronary artery calcification
CACS	Coronary artery calcium score
CACS-CL	CACS + risk-factor-weighted clinical likelihood (RF-CL) model
CAD	Coronary artery disease
CANTOS	Canakinumab Antiinflammatory Thrombosis Outcome Study
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CCB	Calcium channel blocker
CCS	Chronic coronary syndrome(s)
CCTA	Coronary computed tomography angiography
CFC	Coronary flow capacity
CFR	Coronary flow reserve
CFVR	Coronary flow velocity reserve
CHA_2DS_2-VASc	Congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, sex category (female)
CI	Confidence interval
CKD	Chronic kidney disease
CMD	Coronary microvascular dysfunction
CMR	Cardiac magnetic resonance
COLCOT	Colchicine Cardiovascular Outcomes Trial
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
CRT	Cardiac resynchronization therapy
CT	Computed tomography
CVD	Cardiovascular disease
CYP2C19	Cytochrome P450 2C19
CYP3A4	Cytochrome P450 3A4
CZT	Cadmium–zinc–telluride
DAPT	Dual antiplatelet therapy
DEFINE GPS	Distal Evaluation of Functional Performance with Intravascular Sensors to Assess the Narrowing Effect: Guided Physiologic Stenting
DES	Drug-eluting stent
DEFINE-FLAIR	Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation
DHP	Dihydropyridine
DM	Diabetes mellitus
DOAC	Direct oral anticoagulant
dPR	Diastolic pressure ratio
DSE	Dobutamine stress echocardiography
EACTS	European Association for Cardio-Thoracic Surgery
EACVI	European Association of Cardiovascular Imaging
ECG	Electrocardiogram
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESC	European Society of Cardiology
EXCEL	Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization
FAME	Fractional Flow Reserve versus Angiography for Multivessel Evaluation
FFR	Fractional flow reserve
FFR-CT	Coronary computed tomography angiography-derived fractional flow reserve
FREEDOM	Strategies for Multivessel Revascularization in Patients with Diabetes
GDMT	Guideline-directed medical therapy
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GLOBAL 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
GLP-1	Glucagon-like peptide-1
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries
HbA1c	Glycated haemoglobin
HBR	High bleeding risk
HDL-C	High-density lipoprotein cholesterol
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HIV	Human immunodeficiency virus
HMR	Hyperaemic myocardial velocity resistance
HOST-EXAM	Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-EXtended Antiplatelet Monotherapy
HR	Hazard ratio
hs-CRP	High-sensitivity C-reactive protein
HSR	Hyperaemic stenosis resistance
i.c.	Intracoronary
i.v.	Intravenous
ICA	Invasive coronary angiography
ICD	Implantable cardioverter defibrillator
ICFT	Invasive coronary functional testing
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
ILIAS	Inclusive Invasive Physiological Assessment in Angina Syndromes
IMR	Index of microcirculatory resistance
INOCA	Ischaemia with non-obstructive coronary arteries
INR	International normalized ratio
IQR	Interquartile range

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ISCHEMIA	Initial Invasive or Conservative Strategy for Stable Coronary Disease (trial)
ISR	In-stent restenosis
ISTH	International Society on Thrombosis and Haemostasis
IVUS	Intravascular ultrasound
LAD	Left anterior descending
LBBB	Left bundle branch block
LDL-C	Low-density lipoprotein cholesterol
LGE	Late gadolinium enhancement
LIMA	Left internal mammary artery
LITA	Left internal thoracic artery
LMCA	Left main coronary artery
LMCAD	Left main coronary artery disease
LODOCO2	LOw-DOse COlchicine 2
LOE	Level of evidence
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MACCE	Major adverse cardiac or cerebrovascular events
MACE	Major adverse cardiovascular events
MASTER-DAPT	Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen
MBF	Myocardial blood flow
MCE	Myocardial contrast echocardiography
MCS	Mechanical circulatory support
MFR	Myocardial flow reserve
mHealth	Mobile device-based healthcare
MI	Myocardial infarction
MIDCAB	Minimally invasive direct coronary artery bypass
MRA	Mineralocorticoid receptor antagonist
MRI	Magnetic resonance imaging
MRR	Microvascular resistance reserve
MVA	Microvascular angina
MVD	Multivessel disease
NNH	Number needed to harm
NNT	Number needed to treat to prevent an adverse event
NOBLE	Nordic–Baltic–British Left Main Revascularisation Study
NSTEMI	Non-ST-segment elevation myocardial infarction
NTG	Nitroglycerine
NYHA	New York Heart Association
OAC	Oral anticoagulant
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
PDE-5	Phosphodiesterase-5
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
PESA	Progression of Early Subclinical Atherosclerosis
PET	Positron emission tomography
PRECISE-DAPT	PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy
PRECOMBAT	Randomized Trial of Stents versus Bypass Surgery for Left Main Coronary Artery Disease (trial)
PRIZE	Precision Medicine with Zibotentan in Microvascular Angina
PROM	Patient-reported outcome measure
PROMISE	Prospective Multicenter Imaging Study for Evaluation of Chest Pain
PTP	Pre-test probability
QFR	Quantitative flow ratio
QoL	Quality of life
R3F	French FFR Registry
RAAS	Renin–angiotensin–aldosterone system
RCT	Randomized controlled trial
REVIVED-BCIS2	Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction
RF-CL	Risk-factor-weighted clinical likelihood
RFR	Relative flow reserve
RIPCORD	Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain trial
RR	Relative risk
RWTA	Regional systolic wall-thickening abnormalities
SAPT	Single antiplatelet therapy
SCORE2	Systematic Coronary Risk Estimation 2
SCORE2-OP	Systematic Coronary Risk Estimation 2–Older Persons
SCOT-HEART	Scottish Computed Tomography of the Heart
SELECT	Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity
SGLT2	Sodium–glucose cotransporter 2
SLE	Systemic lupus erythematosus
SPECT	Single-photon emission computed tomography
STEMI	ST-segment elevation myocardial infarction
STICH	Surgical Treatment for Ischemic Heart Failure
STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality
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
SYNTAX	SYNergy between PCI with TAXUS and Cardiac Surgery
THEMIS	The Effect of Ticagrelor on Health Outcomes in diabEtes Mellitus patients Intervention Study
TID	Transient ischaemic dilatation
TIMI	Thrombolysis In Myocardial Infarction
Tx	Thromboxane

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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

Classes of recommendations	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
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.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

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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.

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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

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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 bridging[4] and congenital arterial anomalies[5] 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 arteries[9] 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 test[36] 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*).

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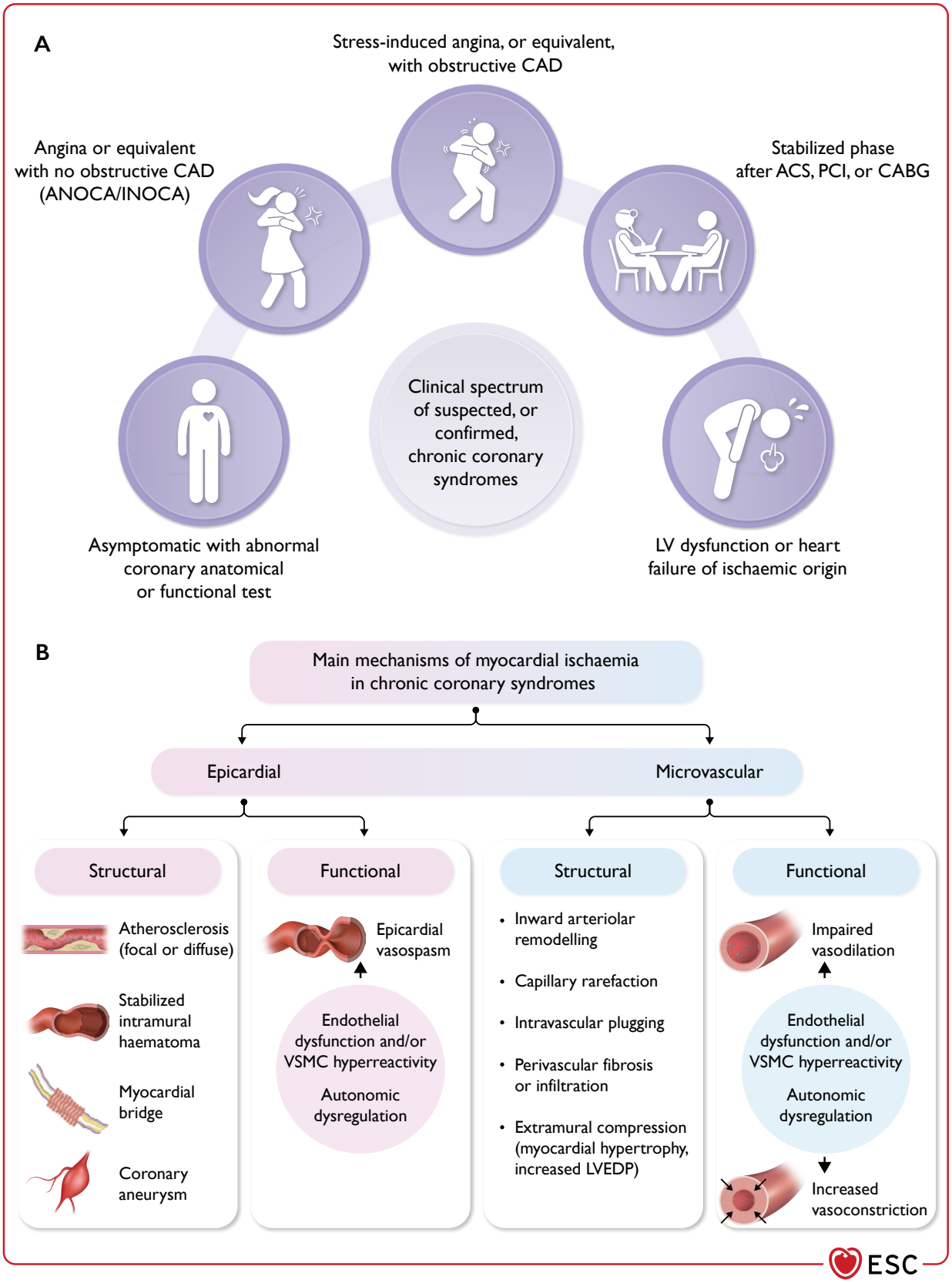


Figure 1 (Central Illustration) Clinical presentations of chronic coronary syndrome and mechanisms of myocardial ischaemia. ACS, acute coronary syndrome; ANOCA, angina with non-obstructive coronary arteries; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, chronic coronary syndrome; 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.

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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* (≤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 (≤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: • 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

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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: o Duke Treadmill Score < −10; • stress SPECT or PET perfusion imaging: o area of ischaemia ≥10% of the LV myocardium; • stress echocardiography: o ≥3 of 16 segments with stress-induced hypokinesia or akinesia; • stress CMR: o ≥2 of 16 segments with stress perfusion defects or o ≥3 dobutamine-induced dysfunctional segments; • CCTA: o left main disease with ≥50% stenosis, o three-vessel disease with ≥70 stenosis, or o two-vessel disease with ≥70% stenosis, including the proximal LAD or o one-vessel disease of the proximal LAD with ≥70% stenosis and FFR-CT ≤0.8	I	B
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

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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 *without* 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

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Management of chronic coronary syndrome patients with chronic heart failure—*Section 5*		
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.	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/ischaemia 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: • calcium channel blockers are recommended to control symptoms and to prevent ischaemia and potentially fatal complications;	I	A
• nitrates should be considered to prevent recurrent episodes.	IIa	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: • 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
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/ischaemia		
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, ischaemia 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.

[a]Class of recommendation.

[b]Level of evidence.

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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 *without* 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

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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_2DS_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_2DS_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: • early cessation of aspirin (≤1 week); • followed by continuation of OAC and clopidogrel: o up to 6 months in patients not at high ischaemic risk or o 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

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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					
In CCS patients with LV ejection fraction ≤35%					
In patients with one- or two-vessel disease, PCI should be considered as an alternative to CABG when complete revascularization can be achieved.	IIa	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.	IIa	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.	IIa	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.	IIa	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

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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; CHA_2DS_2-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.
[a]Class of recommendation.
[b]Level of evidence.

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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.

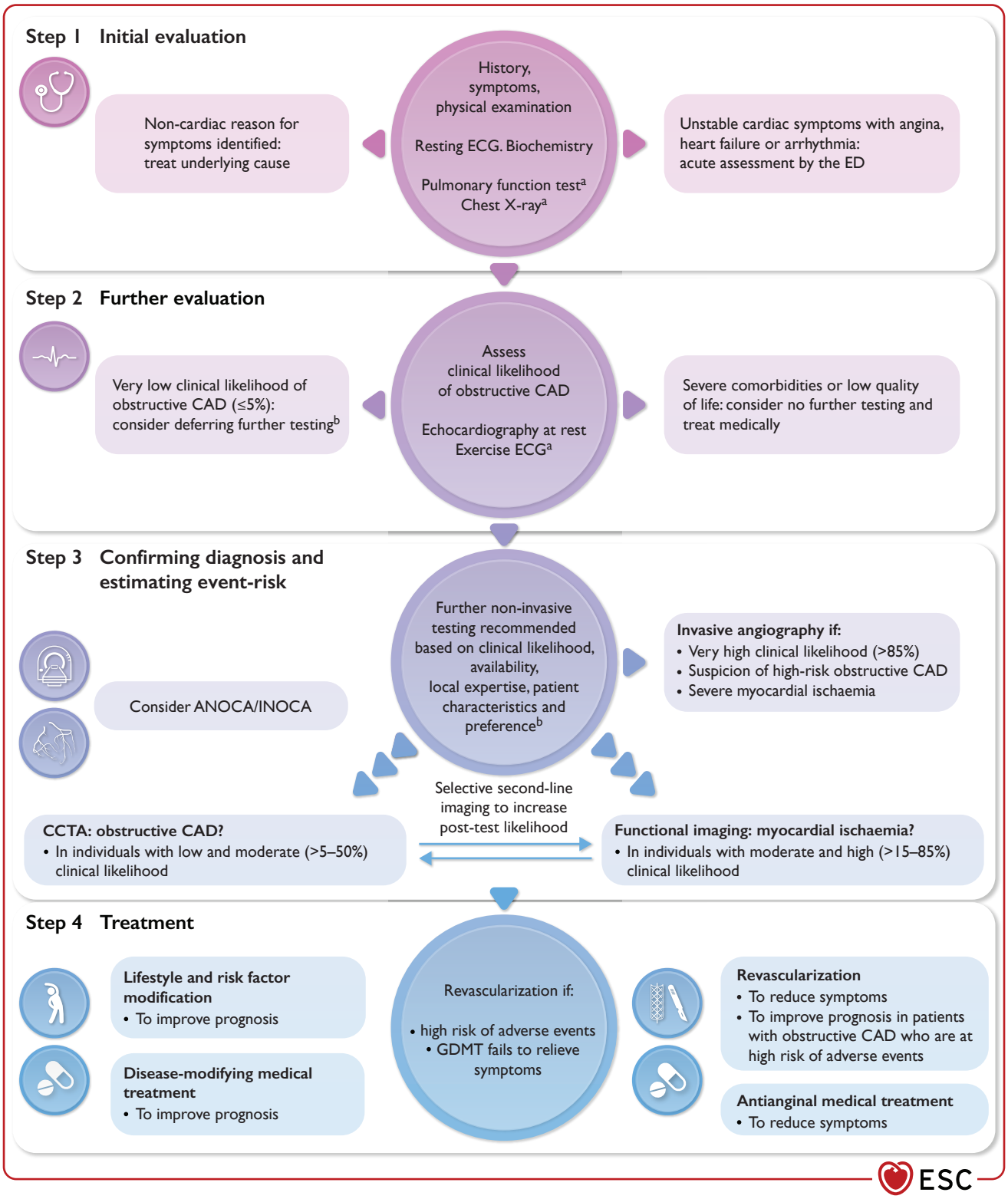


Figure 2 Stepwise approach to the initial management of individuals with suspected chronic coronary syndrome. ANOCA, angina with non-obstructive coronary arteries; CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; ECG, electrocardiogram; ED,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

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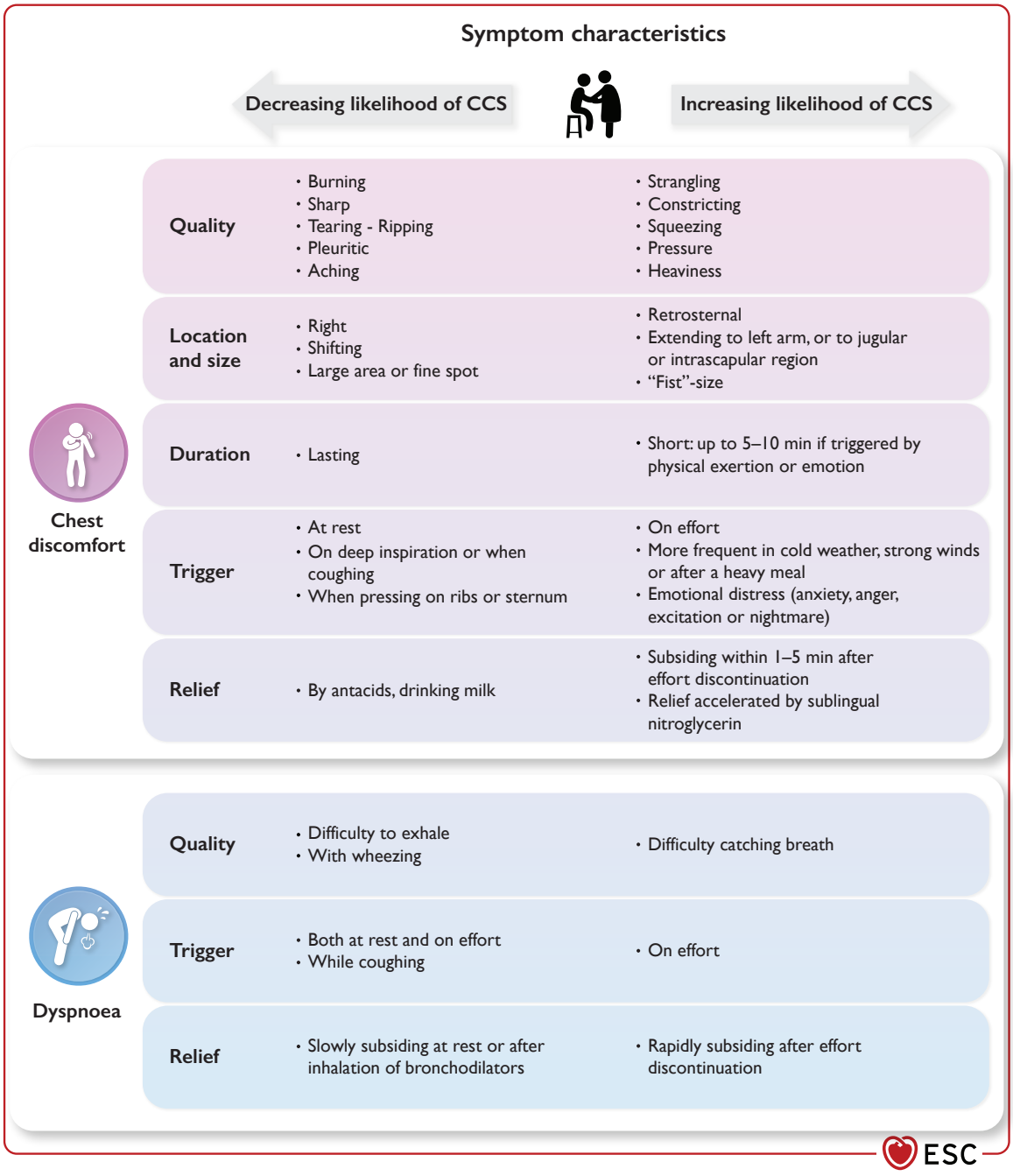


Figure 3 Main CCS symptoms: angina and exertional dyspnoea. CCS, chronic coronary syndrome.

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.

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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

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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 co-morbid 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

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ACS, acute coronary syndrome; CAD, coronary artery disease; CCS, chronic coronary syndrome; ECG, electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.

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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.
[a]Class of recommendation.
[b]Level 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

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symptoms) leads to improved prediction of obstructive CAD, down-classifies 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 (≤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 (≤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 (≤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* (≤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 (≤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.
[a]Class of recommendation.
[b]Level of evidence.

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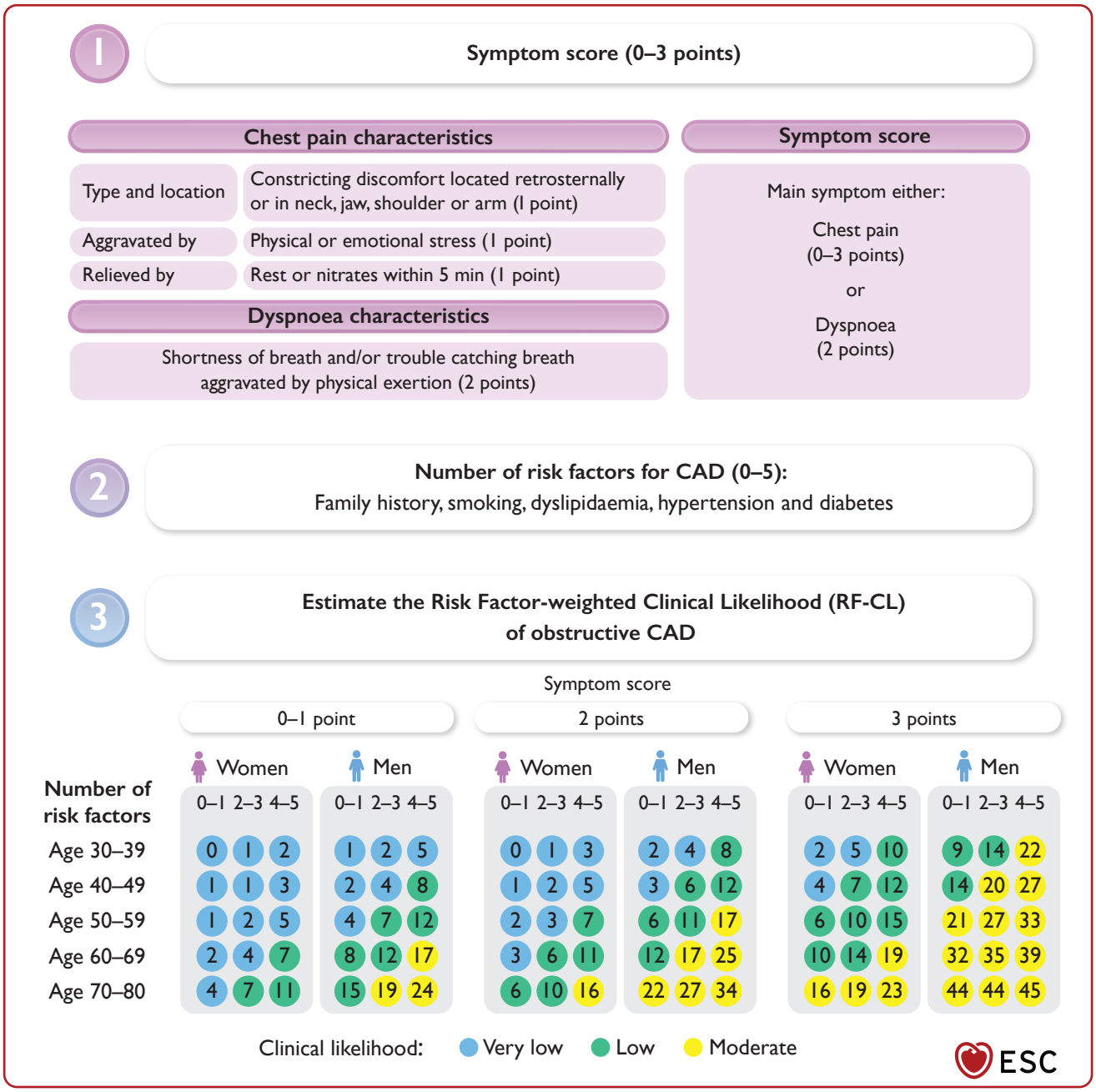


Figure 4 Estimation of the clinical likelihood of obstructive coronary artery disease. CAD, coronary artery disease; RF-CL, risk factor-weighted clinical likelihood. Data derived from Winther *et al.*[139] The symptom score replaces the previous, potentially misleading terminology, that defined presence of three chest pain characteristics as 'typical' angina (here = 3 points), two of three characteristics as 'atypical' angina (here = 2 points), and no or one characteristic as 'non-cardiac/non-anginal' (here = 0–1 point). Family history of CAD is defined as 1 or more first-degree relatives with early signs of CAD (men <55 and women <65 years of age); smoking, as current or past smoker; dyslipidaemia, hypertension, and diabetes, as present at the time of diagnosis. Values in the lower panel are the clinical likelihood estimates expressed as %.

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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 ≤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

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CMR, cardiac magnetic resonance; LVEF, left ventricular ejection fraction.
[a]Class of recommendation.
[b]Level 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 imaging[189] 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 CAD[148] and should mainly be used for risk stratification.

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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

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BP, blood pressure; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; ECG, electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.
[c]When 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: • 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

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[a]Class of recommendation.
[b]Level 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

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ECG, electrocardiogram.
[a]Class of recommendation.
[b]Level 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 significant[195] 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

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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.
[a]Class of recommendation.
[b]Level 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

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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
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.
[a]Class of recommendation.
[b]Level of evidence.

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 accuracy[260] and absolute quantification of MBF. Hence, its diagnostic performance for multivessel CAD has improved substantially.[261]

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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. ^{13}N-ammonia, ^{15}O-water, and ^{82}Rubidium) 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: • 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

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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

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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.
[a]Class of recommendation.
[b]Level 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 morbility/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 ≥50% left main stenosis, or ≥70% proximal LAD stenosis with single or two-vessel CAD, or ≥70% proximal three-vessel CAD[56,182,316,317]—or when any stress test shows moderate to severe inducible ischaemia[316] 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]

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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

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CAD, coronary artery disease; FFR, fractional flow reserve; ICA, invasive coronary angiography; iFR, instantaneous wave-free ratio; IVUS, intravascular ultrasound.
[a]Class of recommendation.
[b]Level of evidence.
[c]Typically 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

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recent studies (RIPCORD2 and FUTURE) did not demonstrate any clinical outcome improvement compared with angiography alone.[346,347] Therefore, intracoronary pressure measurement in patients with multivessel 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 study[355] 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.
[a]Class of recommendation.
[b]Level of evidence.
[c]Typically 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*.

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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 (≤5%) likelihood of obstructive CAD. Based on the CACS-CL model, in patients with a low (>5%–15%) likelihood of

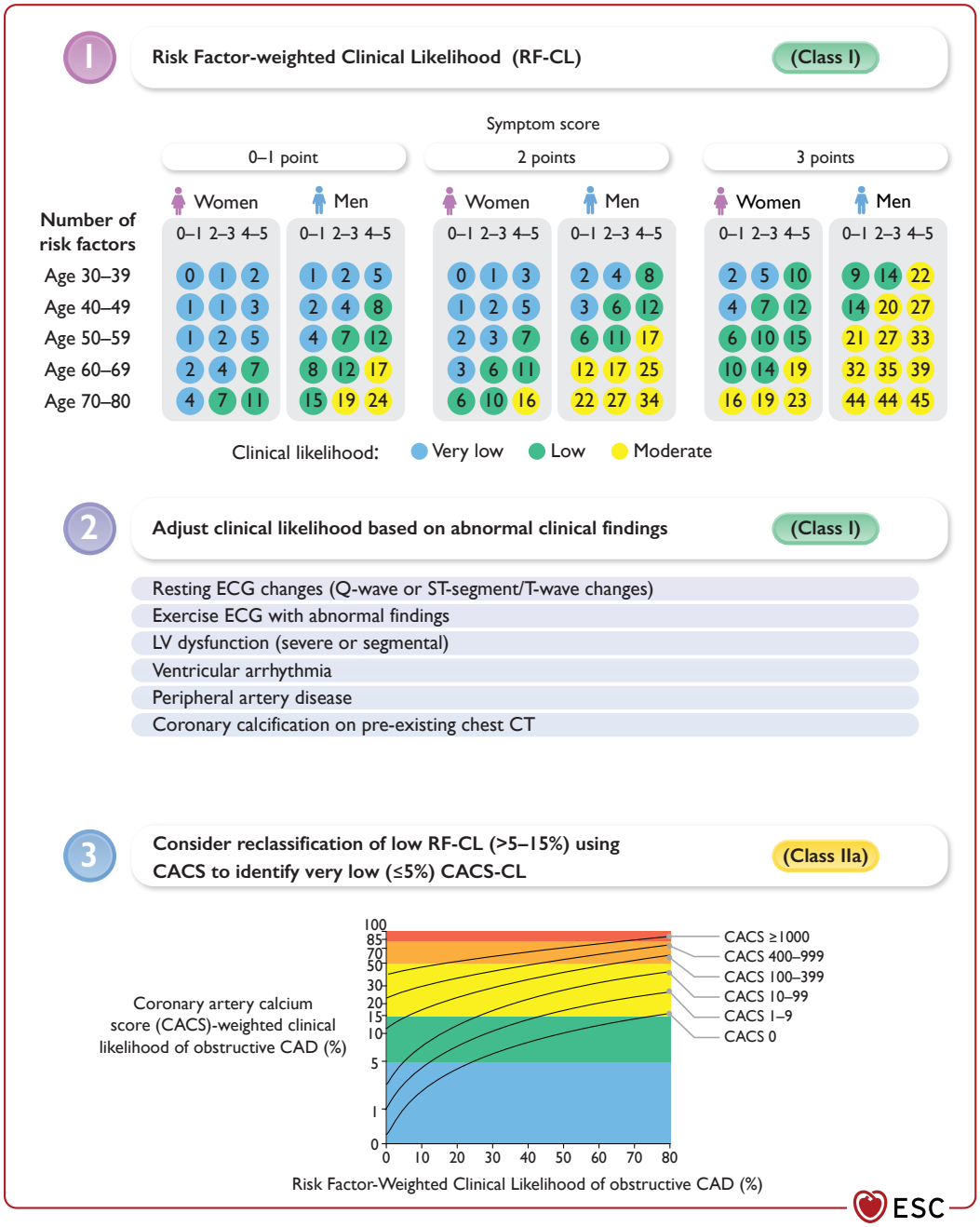


Figure 5 Adjustment and reclassification of the estimated clinical likelihood of obstructive coronary artery disease. CACS, coronary artery calcium score; CACS-CL, coronary artery calcium score + RF-CL model; CAD, coronary artery disease; CT, computed tomography; ECG, electrocardiogram; LV, left ventricular;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

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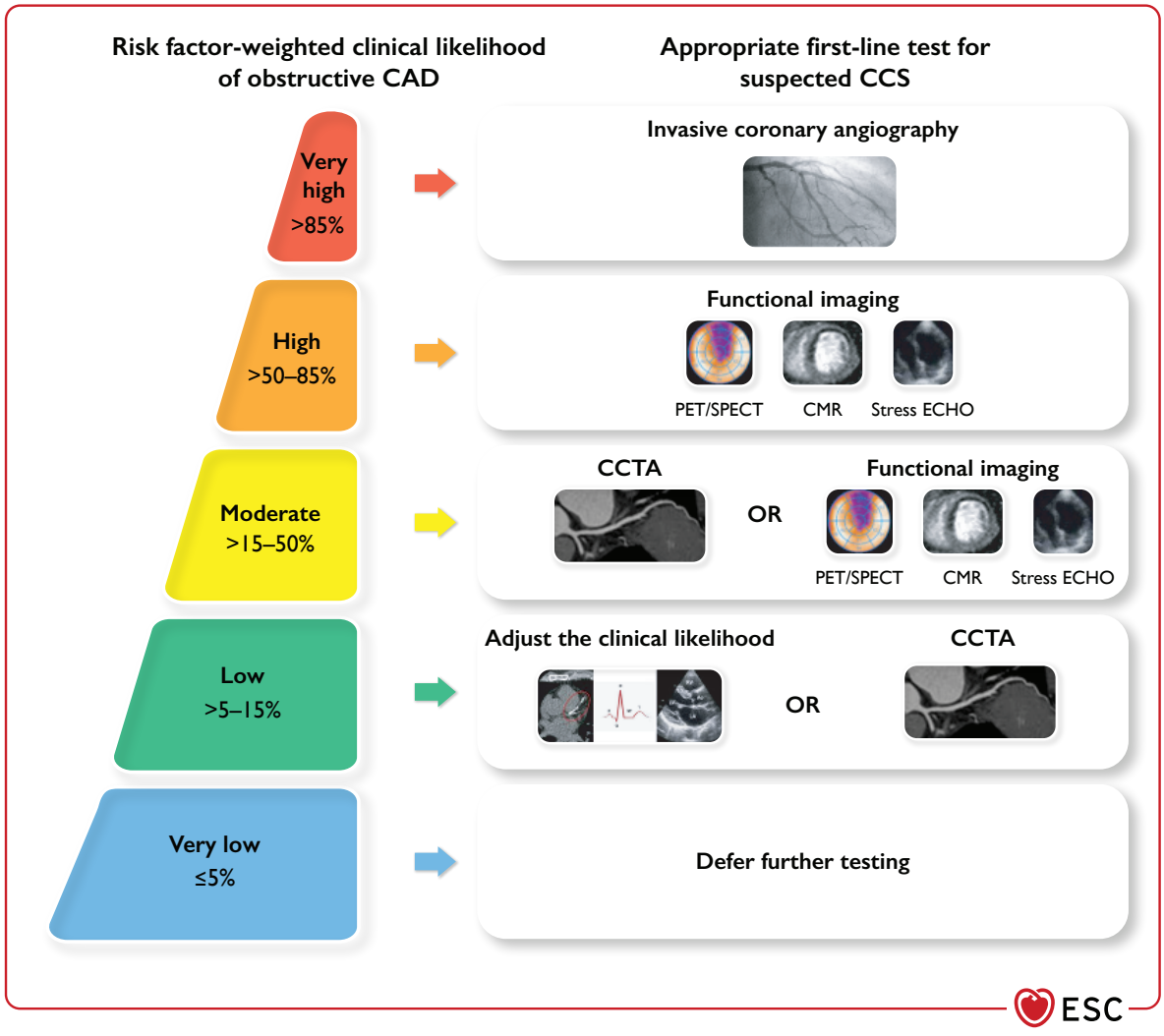


Figure 6 Appropriate first-line testing in symptomatic individuals with suspected chronic coronary syndrome. CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; ECHO, echocardiography; PET, positron emission tomography; 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 testing[33] 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*).

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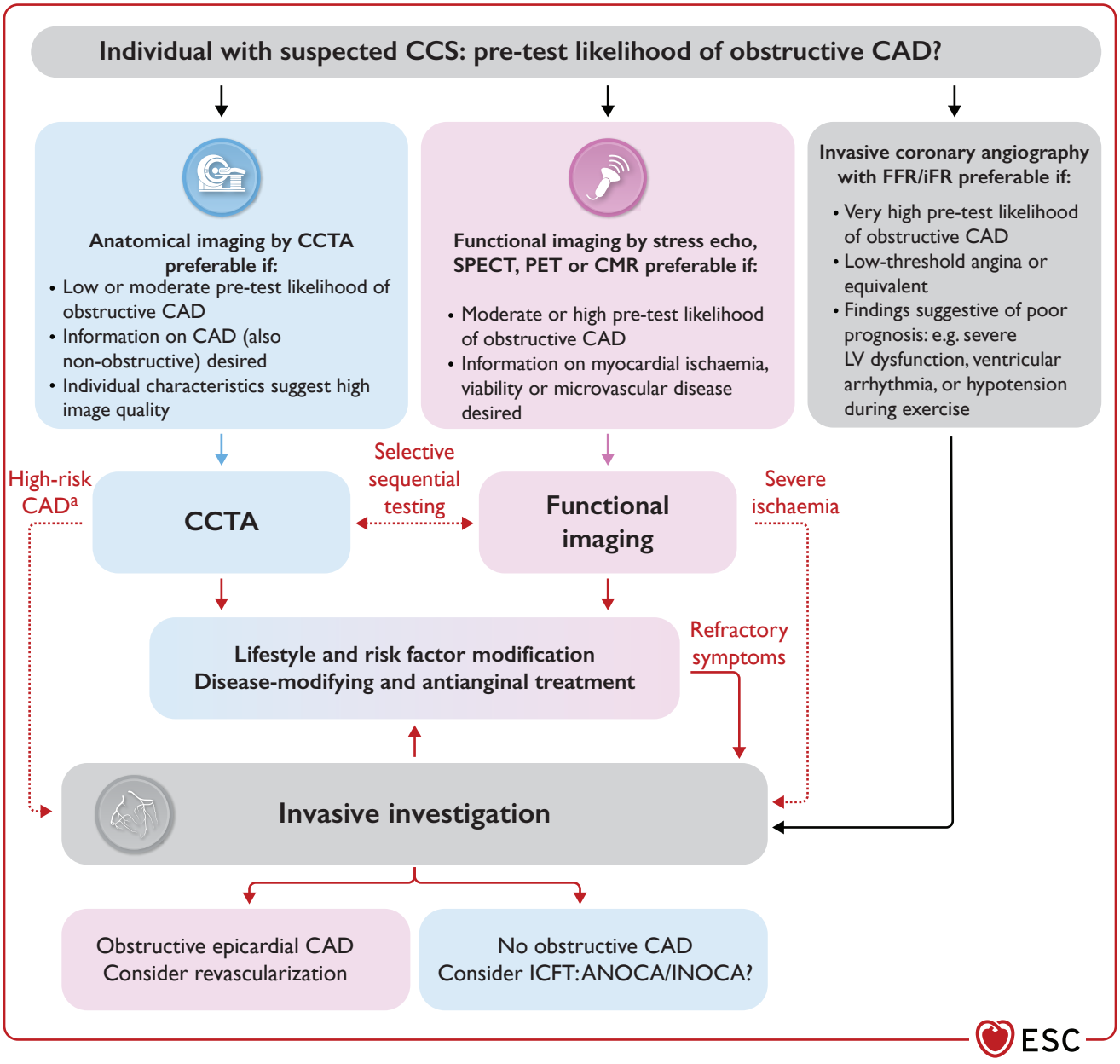


Figure 7 Initial management of symptomatic individuals with suspected chronic coronary syndrome. ANOCA, angina with non-obstructive coronary arteries; CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; Echo, echocardiography; 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. [a]High–risk CAD: obstructive CAD at high risk of adverse events by CCTA: ≥50% stenosis of the left main stem; three–vessel disease with severe stenoses (≥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 (>15-85%) likelihood of obstsructive 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*).

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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.
[a]Preventive measures are recommended for patients with eGFR <30 mL/min/1.73 m^2.[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]

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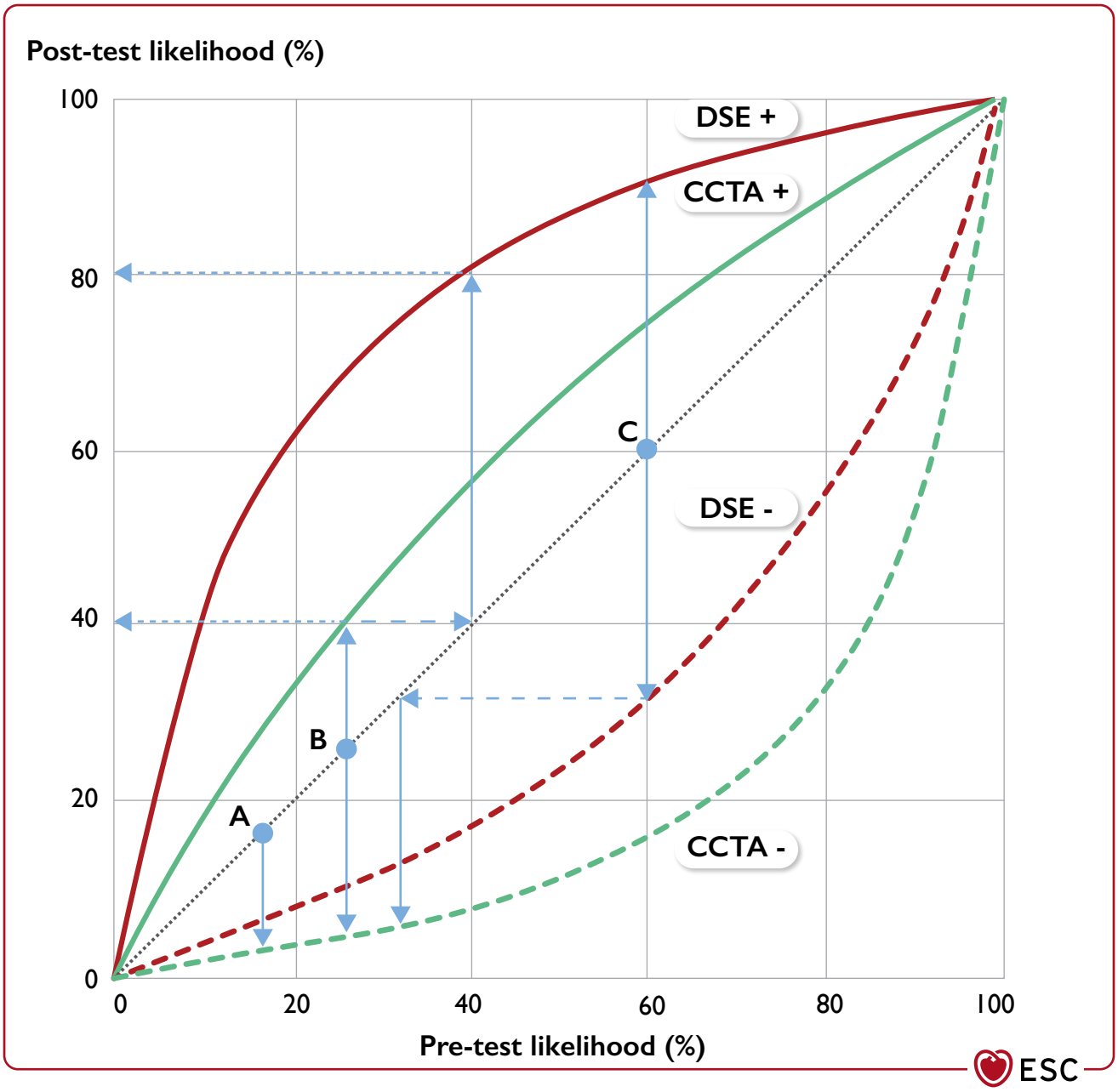


Figure 8 Ruling in and ruling out functionally significant obstructive coronary artery disease by sequential anatomical (coronary computed tomography angiography) and functional (dobutamine stress echocardiography) testing.[a] CAD, coronary artery disease; CCTA, coronary computed tomography angiography; 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] [a]Based on invasive FFR measurement or diameter stenosis of ≥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 (± 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).

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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

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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.
[a]Class of recommendation.
[b]Level of evidence.
[c]Characteristics determining ability to exercise, likelihood of good image quality, expected radiation exposure, and risks or contraindications.
[d]Typically 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 ≥50% stenosis of the left main stem, three-vessel or two-vessel disease including the proximal LAD artery with ≥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 ≥1% and ≤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 CCTA[317] confirms the very old observations of the Coronary Artery Surgery Study[182] 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

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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. ≥3/16 abnormal segments at stress echocardiography, ≥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 ISCHEMIA[317] 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 performed[341] and is not recommended as a routine, based on the RIPCORD2[347] and FUTURE results.[346] Recent methods using 3-dimensional image reconstruction and computational fluid dynamics enable FFR estimation with CCTA[432] 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] • exercise ECG: o Duke Treadmill Score < −10;[191] • stress SPECT or PET perfusion imaging: o area of ischaemia ≥10% of the LV myocardium;[287,315,422,423,435] • stress echocardiography: o ≥3 of 16 segments with stress-induced hypokinesia or akinesia;[435] • stress CMR: o ≥2 of 16 segments with stress perfusion defects or ≥3 dobutamine-induced dysfunctional segments;[435] • CCTA: o left main disease with ≥50% stenosis, three-vessel disease with ≥70 stenosis, or two-vessel disease with ≥70% stenosis, including the proximal LAD or[317] 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 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.
[a]Class of recommendation.
[b]Level 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

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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	• Vaccination against influenza, pneumococcal disease and other widespread infections, e.g. COVID-19
Sleep quality	• Treat sleep-related breathing disorders
Sexual activity	• 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	• Avoid psychosocial stress • Treat depression and anxiety by psychological or pharmacological interventions
Environment/pollution	• Avoid passive smoking • Reduce environmental noise • Avoid exposure to air pollution
Lifestyle interventions for risk-factor control	
Smoking and substance abuse	• Use pharmacological and behavioural strategies to assist in smoking cessation • Avoid e-cigarettes • Abstain from substance abuse
Obesity and being overweight	• Obtain and maintain a healthy weight (BMI 18.5–25 kg/m^2) • Reduce weight through recommended energy intake and increased physical activity and through pharmacological/surgical interventions in selected patients
Hyperlipidaemia	• Ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction in LDL-C vs. baseline is recommended
Diabetes	• HbA1c < 7.0% (53 mmol/mol)
Arterial hypertension	• SBP 120–129 mmHg, provided the antihypertensive treatment is well tolerated
Diet and alcohol consumption	• 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	• 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.

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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 marihuana 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/m^2).[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/m^2), 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/m^2), 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/m^2). 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/m^2), 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

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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 (%VO_2 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 VO_2 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 applications[490] and wearable activity trackers[491] 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.
[a]Class of recommendation.
[b]Level 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-blockers[507] 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

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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

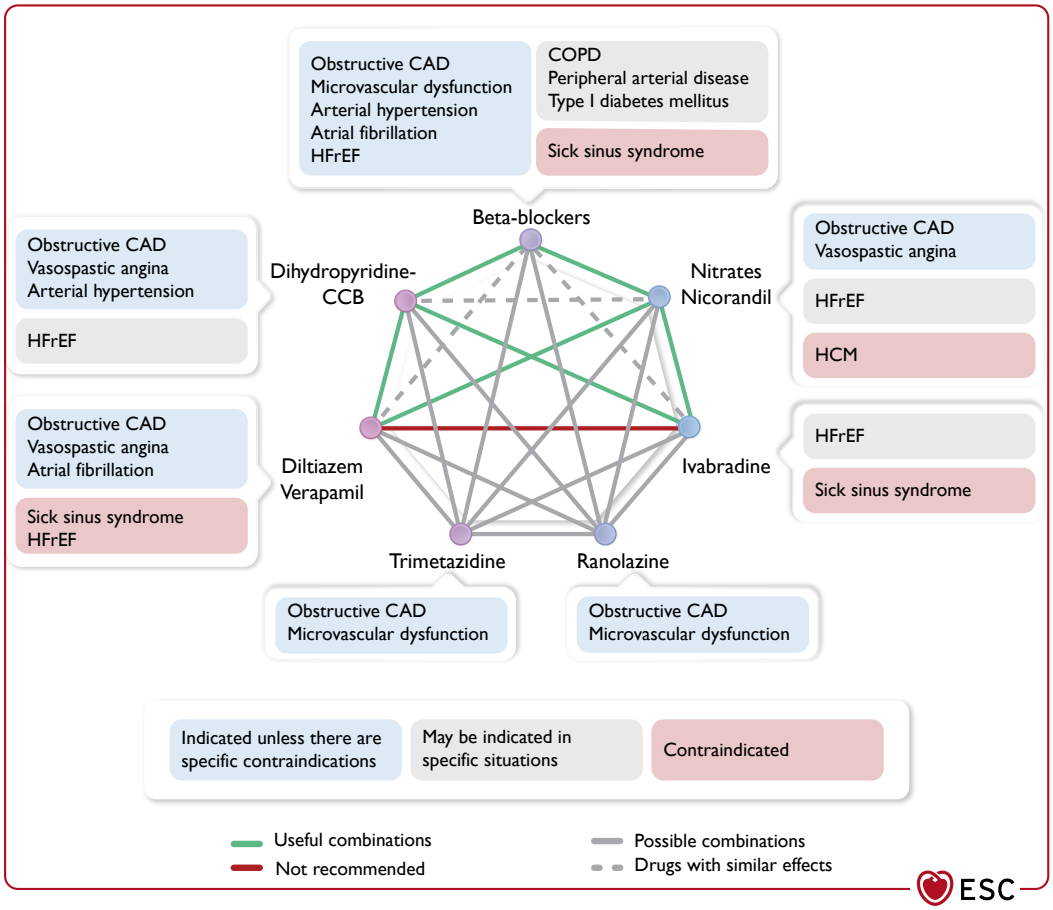


Figure 9 Possible combinations of antianginal drugs. CAD, coronary artery disease; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; HCM, hypertrophic cardiomyopathy; HFrEF, heart failure with reduced ejection fraction. The schematic shows useful combinations (green lines), combinations 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].

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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
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

Continued

CCB, calcium channel blocker; CCS, chronic coronary syndrome; CYP3A4, cytochrome P450 3A4; DHP, dihydropyridine; DM, diabetes mellitus; LVEF, left ventricular ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.
[c]These 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).
[d]Consideration 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

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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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibitor monotherapy.

4.3.1.1.2.1. Clopidogrel monotherapy. In addition to the cyclooxygenase-I pathway inhibited by aspirin, the platelet $P2Y_{12}$ 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 $P2Y_{12}$ inhibitor monotherapy [clopidogrel in 7545 (62.0%), ticagrelor in 4633 (38.0%)] and followed for 6–36 months.[562] $P2Y_{12}$ 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 $P2Y_{12}$ inhibitor. The treatment effect was consistent across pre-specified subgroups (ACS or CCS) and type of $P2Y_{12}$ 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

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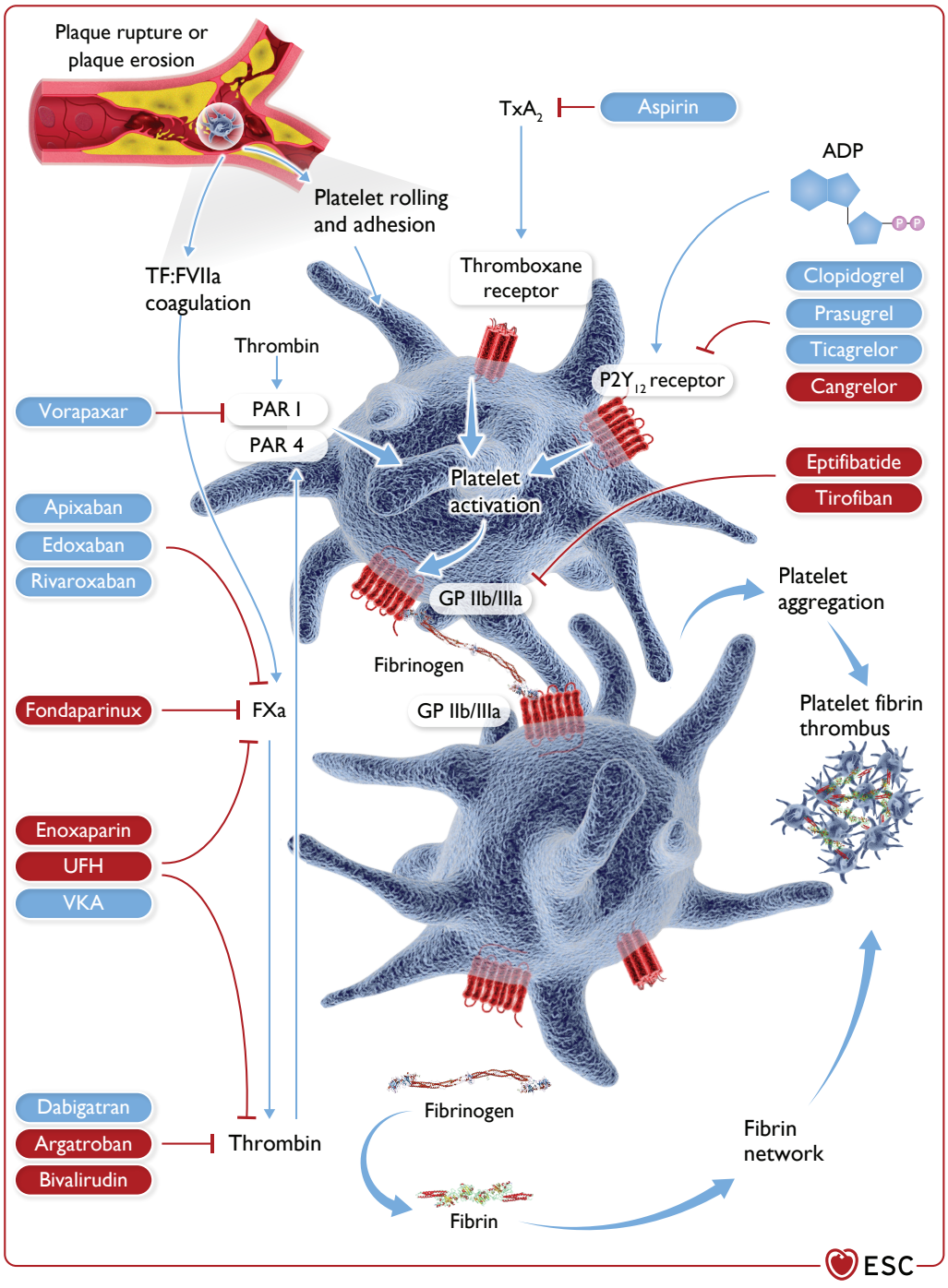


Figure 10 Antithrombotic drugs for chronic coronary syndromes: pharmacological targets. ADP, adenosine diphosphate; FVIIa, activated factor VII; FXa, activated factor X; GP, glycoprotein; PAR, protease-activated receptor; TF, tissue factor; TxA_2, thromboxane A2; UFH, unfractionated heparin; VKA, vitamin K antagonist. Orally administered drugs are shown on a blue background, parenterally administered ones on red. Aspirin prevents TxA2 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% NSTE (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]

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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 $P2Y_{12}$ 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.

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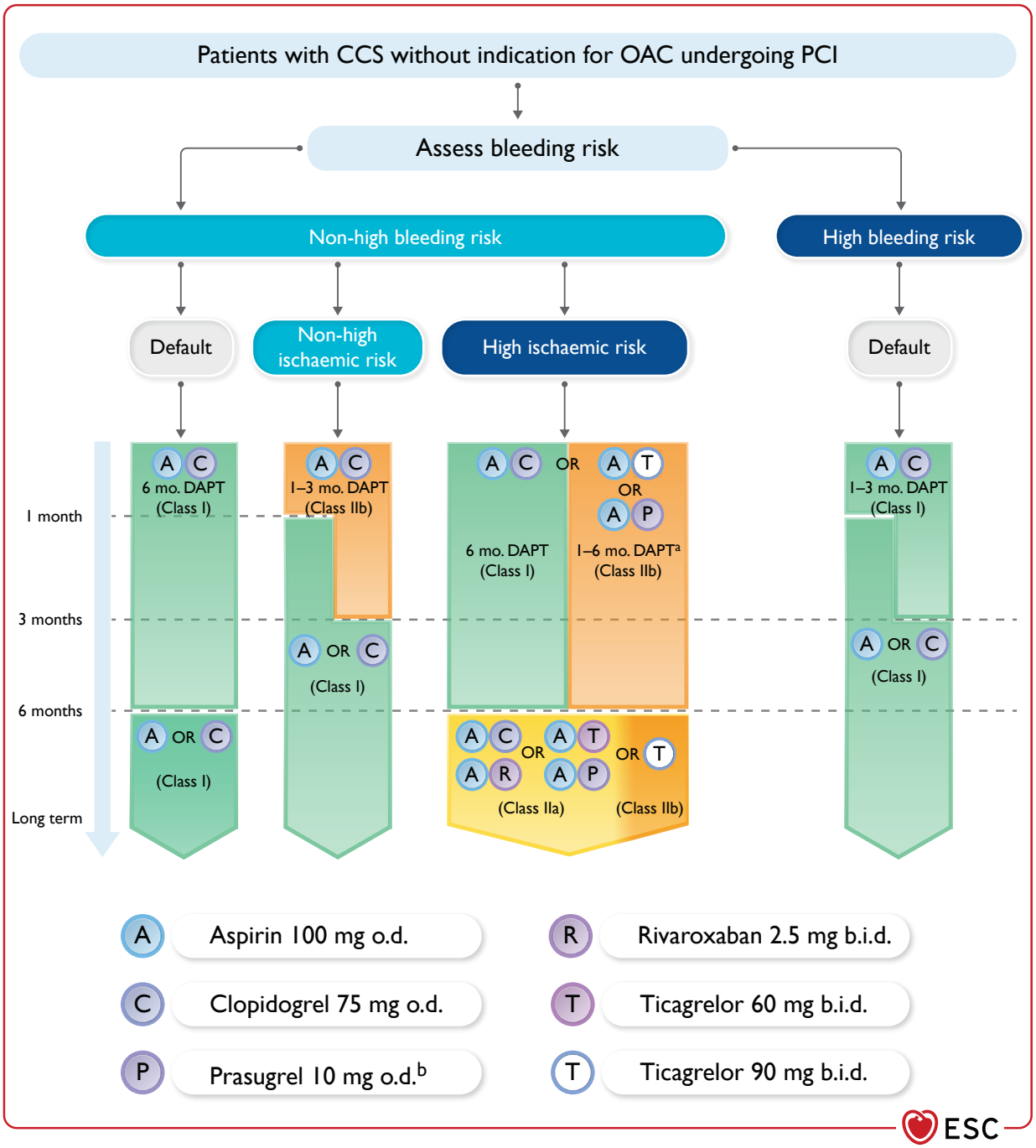


Figure 11 Antithrombotic treatment in chronic coronary syndrome patients undergoing percutaneous coronary intervention. ARC-HBR, Academic Research Consortium for High Bleeding Risk; b.i.d., bis in die (twice daily); CCS, chronic coronary syndrome; CYP2C19, cytochrome P450 2C19; DAPT, dual antiplatelet 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. [a]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. [b]Prasugrel 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

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Table 8 Options for extended intensified antithrombotic therapy

Drug	Dose	Clinical setting	NNT (ischaemic outcomes)	NNH (bleeding outcomes)
Co-administered with aspirin 100 mg o.d.				
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)
Co-administered with low-dose aspirin 75–162 mg o.d.				
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 $P2Y_{12}$ 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

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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 $P2Y_{12}$ 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 *without* 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

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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: • early cessation of aspirin (≤1 week); • followed by continuation of OAC and clopidogrel: o up to 6 months in patients not at high ischaemic risk;[c] or o 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.

[a]Class of recommendation.

[b]Level of evidence.

[c]Enhanced 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.

[d]Bleeding-risk criteria according to PRECISE-DAPT or ARC-HBR (Supplementary data, *Table S2*).

[e]Anatomical/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.

[f]For example, stentectomy, endarterectomy, poor venous graft quality.

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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 dyslipidaemias[64] 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 trials 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.
[a]Class of recommendation.
[b]Level 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

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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 ≤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 diabetes[86] and the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[526] 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/m^2. 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.
[a]Class of recommendation.
[b]Level of evidence.
[c]Canaglifozin, dapagliflozin, empagliflozin, sotagliflozin (listed in alphabetical order).
[d]Dulaglutide, efpeglenatide, 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

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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 CAD[716] 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

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CAD, coronary artery disease; CCS, chronic coronary syndrome.
[a]Class of recommendation.
[b]Level 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

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ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCS, chronic coronary syndrome.
[a]Class of recommendation.
[b]Level 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 antianginal 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.

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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 (≥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 (≥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 ≤ 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 ≤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 disease[54] 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 ≤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 ≤ 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,

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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 events[727] 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 studies[326] 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 scores[783] and relevant to clinical decision-making.

The SYNTAX II score was developed by combining clinical and anatomic 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

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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-analysis[730] 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]

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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 *de novo* 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.

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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 FFR[838] 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, OCTOBER[810] 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,

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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.

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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

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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.
[a]Class of recommendation.
[b]Level of evidence.
[c]Age, frailty, cognitive status, diabetes, and any other comorbidities.
[d]Multivessel disease with/out left main stem involvement, high anatomical complexity, and likelihood of revascularization completeness.
[e]Local 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.
[a]Class of recommendation.
[b]Level of evidence.
[c]For example: absence of previous cardiac surgery, or severe morbidities, or frailty, or immobility precluding CABG.
[d]Multivessel disease is defined as the involvement of at least two main coronary arteries.

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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 CAD[905] 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

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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 ≤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 ≤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.
[a]Class of recommendation.
[b]Level 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.

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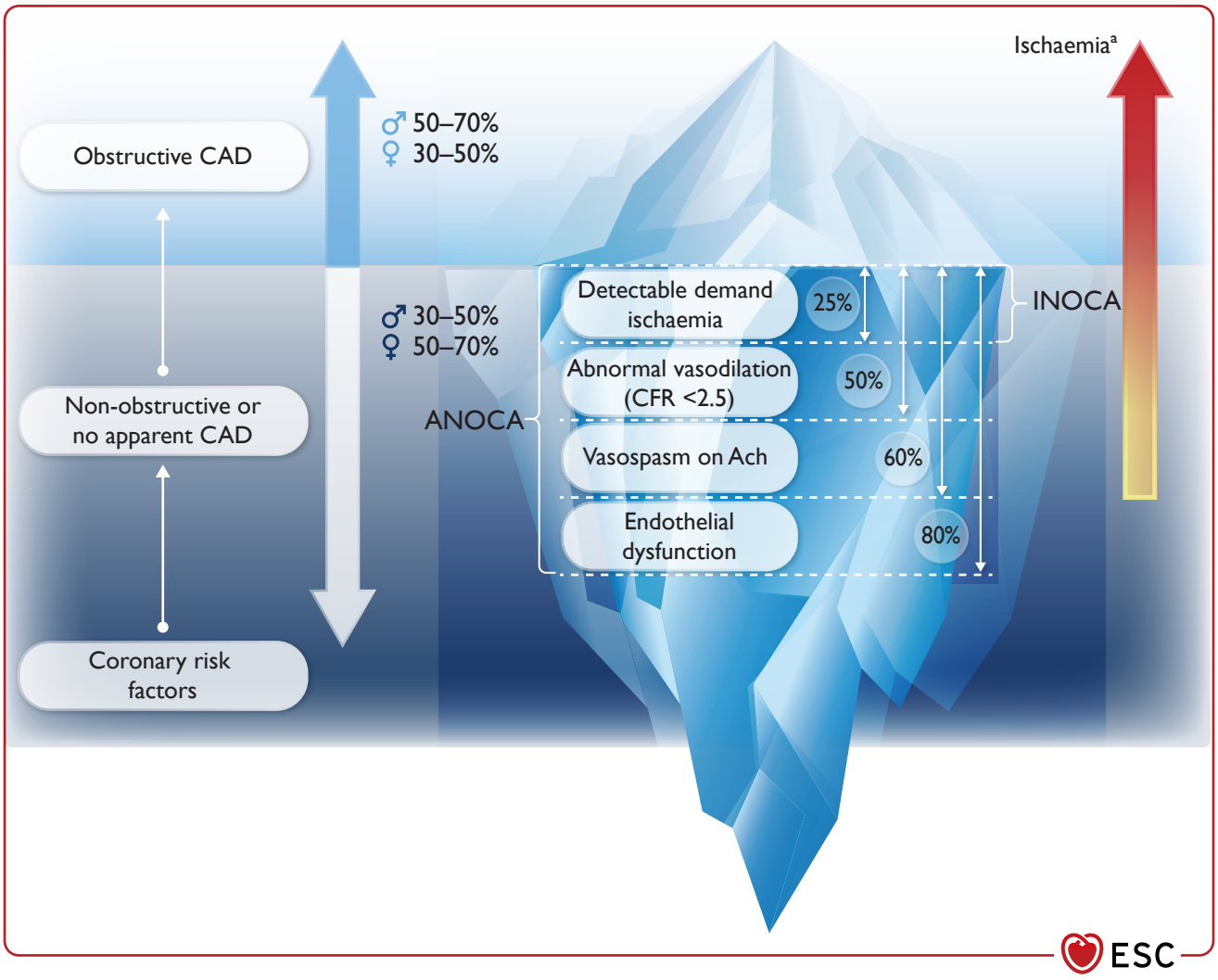


Figure 12 Prevalence of disease characteristics in patients with ANOCA/INOCA referred for invasive coronary functional testing. Ach, acetylcholine; ANOCA, angina with non-obstructive coronary arteries; CFR, coronary flow reserve; i.c., intracoronary; INOCA, ischaemia with non-obstructive coronary arteries. 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. [a]Prevalence 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]

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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 vascular 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

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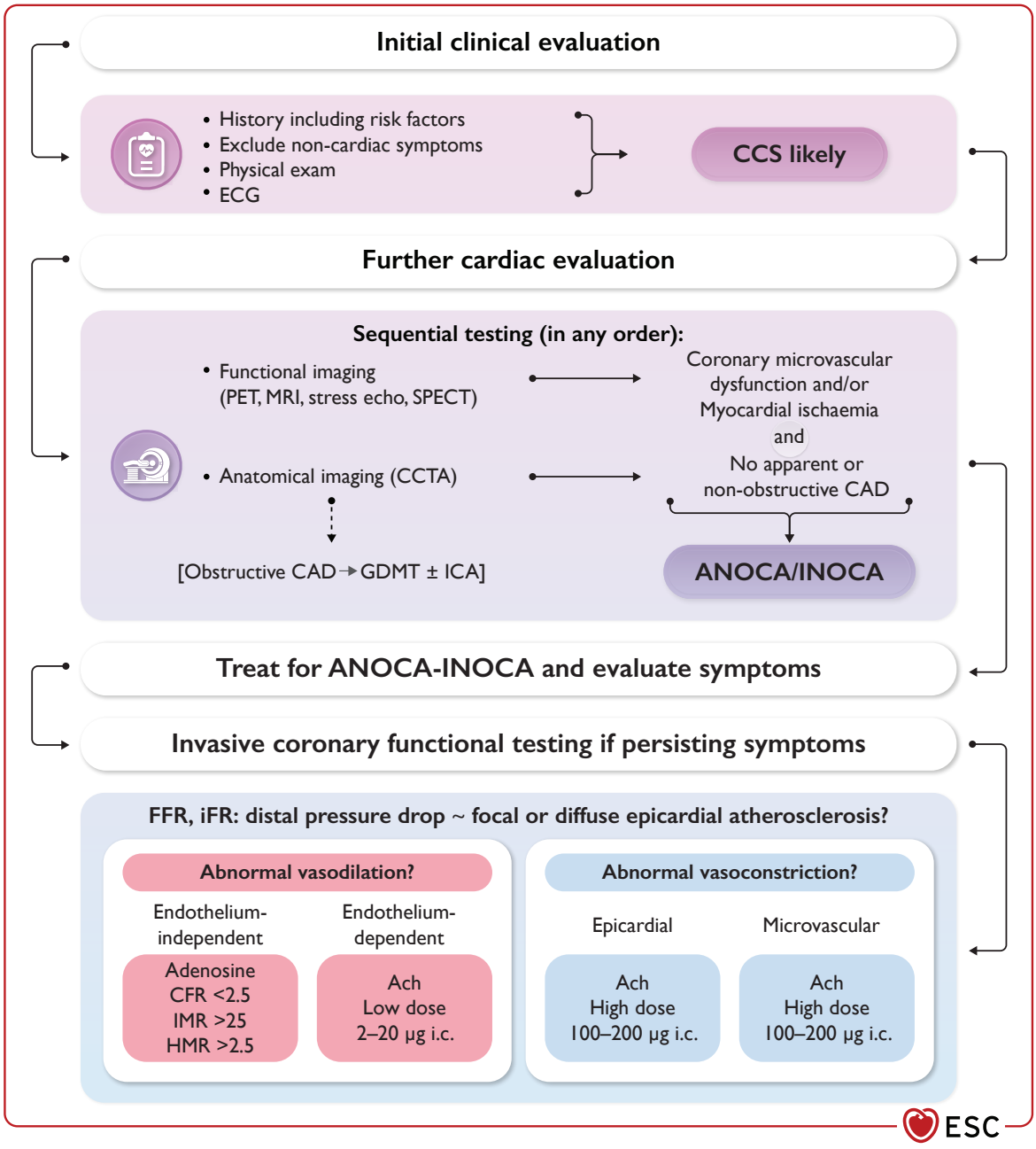


Figure 13 Diagnostic algorithm for patients with angina/ischaemia with non-obstructive coronary arteries. Ach, acetylcholine; ANOCA, angina with non-obstructive coronary arteries; CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CFR, coronary 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 ≥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

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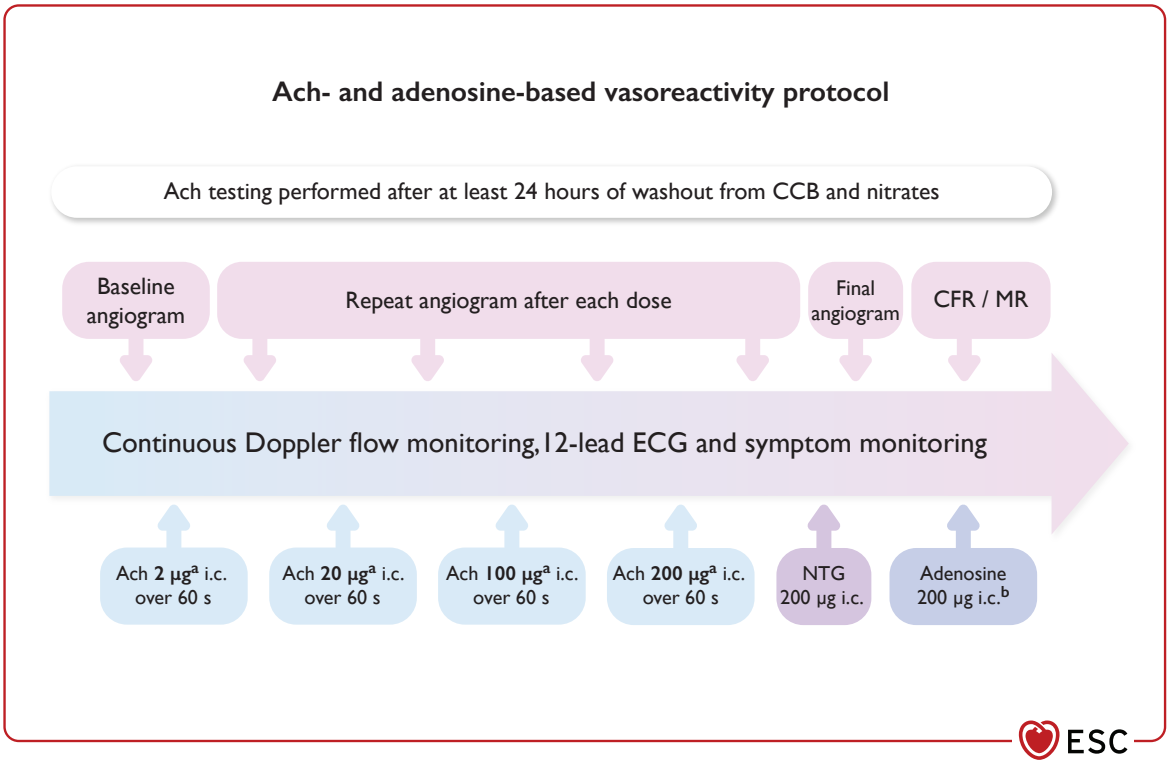


Figure 14 Spasm provocation and functional testing protocol. Ach, acetylcholine; CCB, calcium channel blocker; CFR, coronary flow reserve; ECG, electrocardiogram; i.c., intracoronary; i.v., intravenous; MR, microvascular resistance; NTG, nitroglycerine. i.c. bolus injections of Ach over 60s to assess: (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. [a]The incremental administration of Ach is stopped whenever a coronary vasospasm is induced. [b]i.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 adenosine[973] is assessed and CFR, IMR, HMR, or MRR are measured. In patients with contraindications to the use of adenosine, papaverine can be used[974] 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/ischaemia 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

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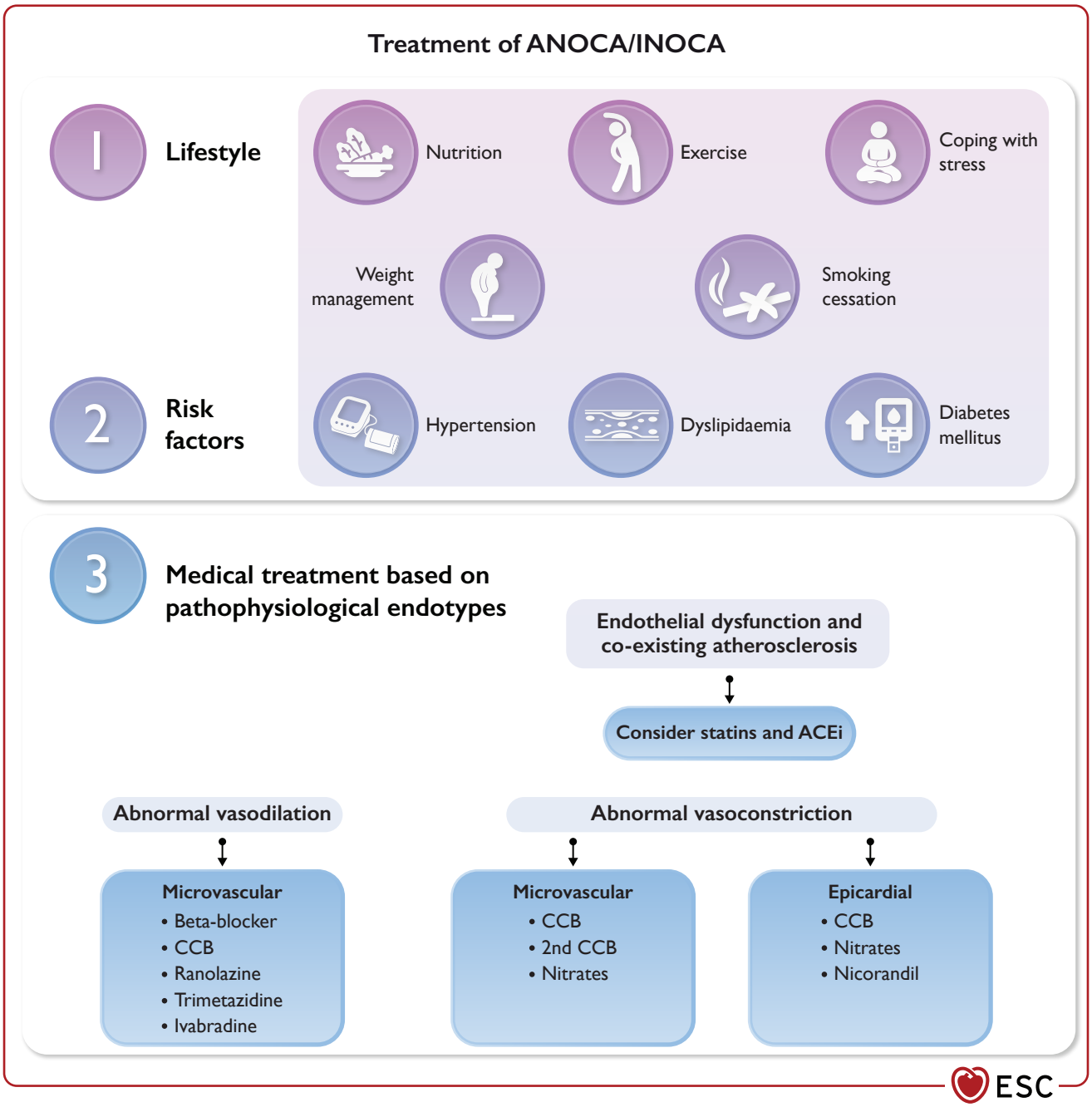


Figure 15 Treatment of angina/ischaemia with non-obstructive coronary arteries. ACE-I, angiotensin-converting enzyme inhibitor; ANOCA, angina with non-obstructive coronary arteries; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; INOCA, ischaemia with non-obstructive coronary arteries. 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.

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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
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.
[a]Class of recommendation.
[b]Level 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

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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 PCI[1021] 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 disease[1015] 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 Guidelines[1064], 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]

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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 m^2 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 m^2.[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 thrombocytopaenia, 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 mortality[1084] 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 prevalently 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.

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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: • 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

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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.
[a]Class of recommendation.
[b]Level 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

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CACS, coronary artery calcium scoring; CT, computed tomography; SCORE2, Systematic Coronary Risk Estimation 2; SCORE-OP, Systematic Coronary Risk Estimation 2–Older Persons.
[a]Class of recommendation.
[b]Level of evidence.

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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

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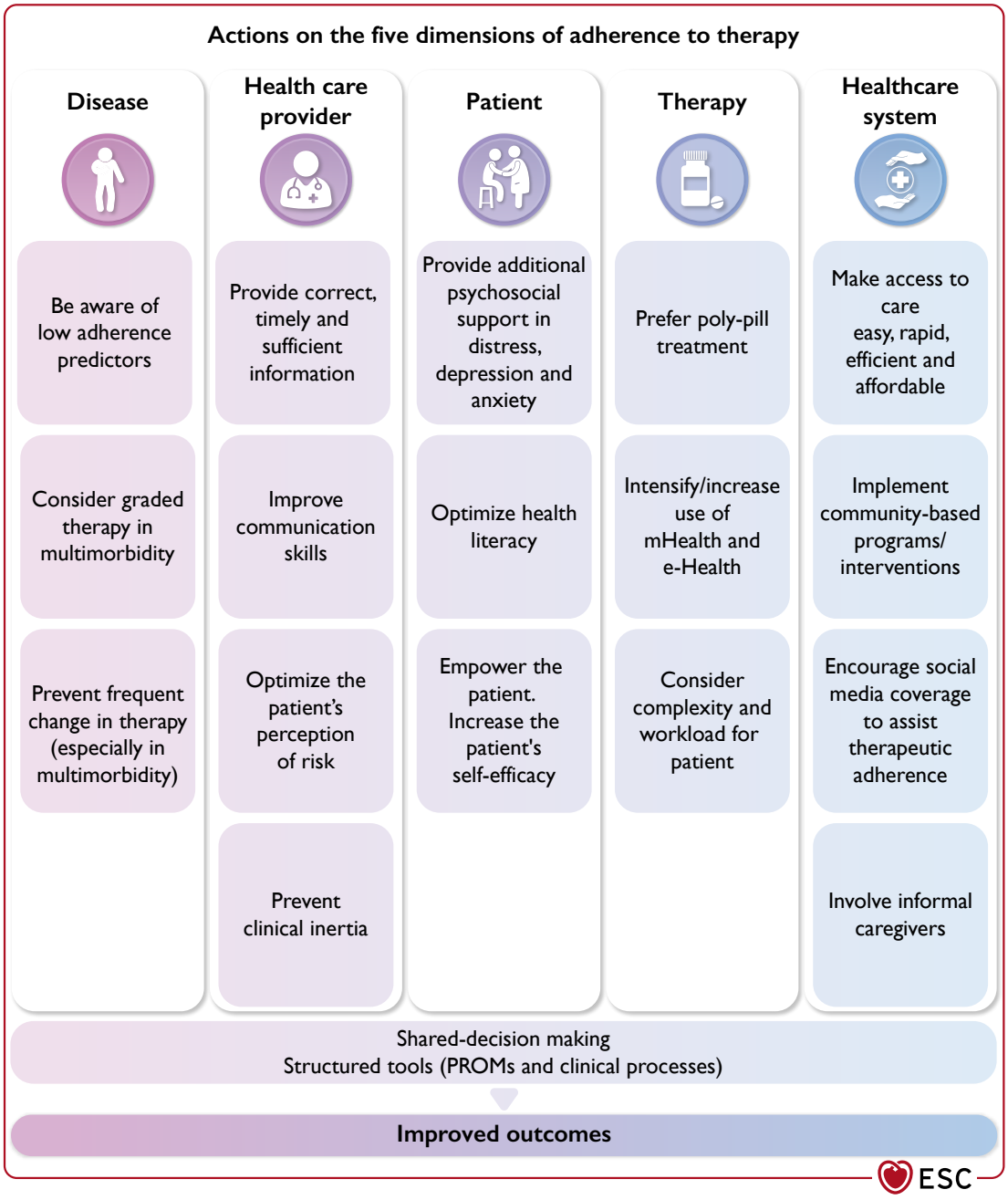


Figure 16 Actions on the five dimensions of adherence to therapy. e-Health, healthcare services provided electronically; mHealth, mobile device-based healthcare; PROMs, patient-reported outcome measures. Adapted from Pedretti *et al.*[1139].

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]

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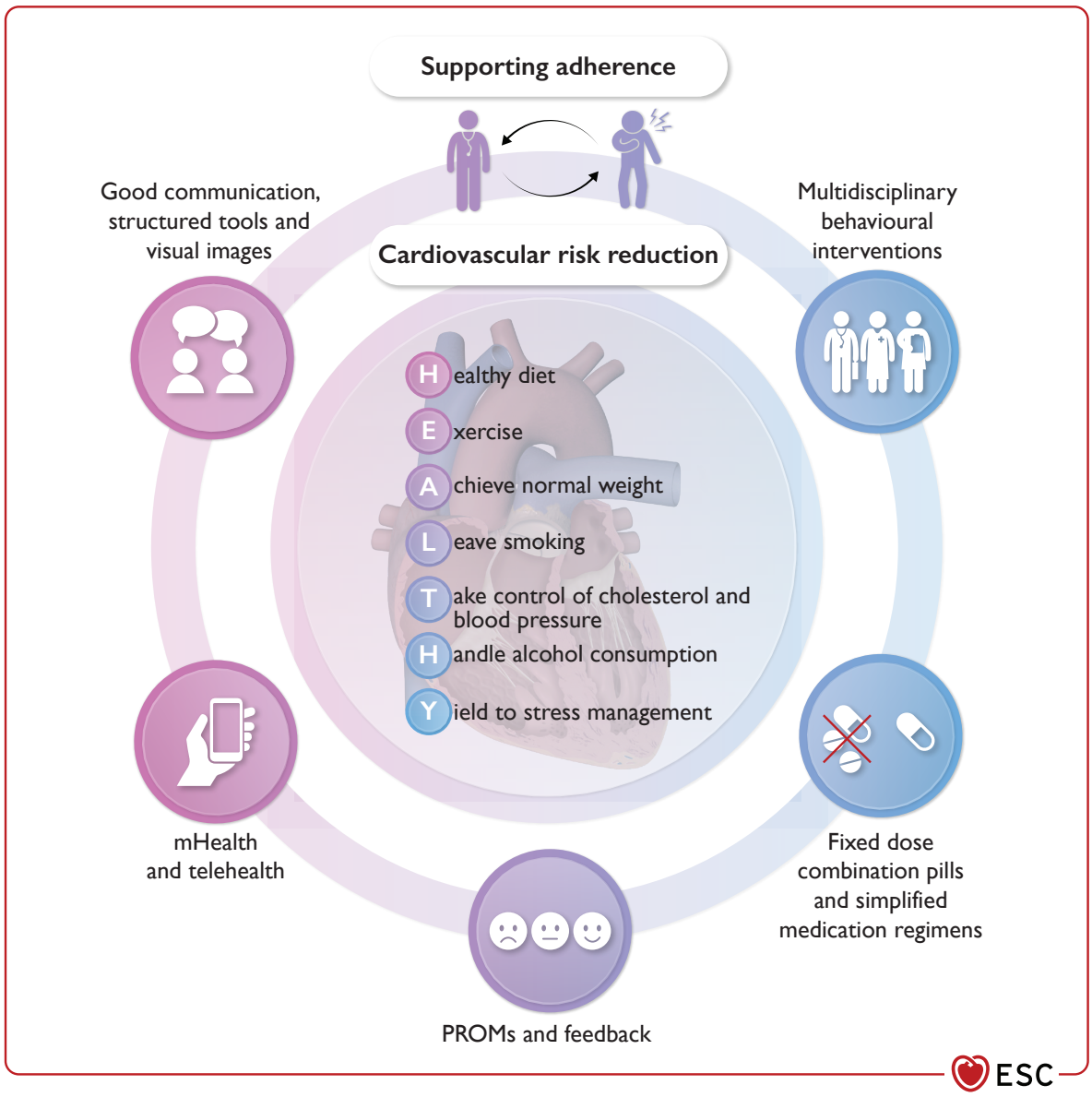


Figure 17 Strategies for long-term adherence to a healthy lifestyle. mHealth, mobile device-based healthcare; PROMs, patient-reported outcome measures.

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

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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 VO_2 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.[1146] 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

[a]Class of recommendation.
[b]Level 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

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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.

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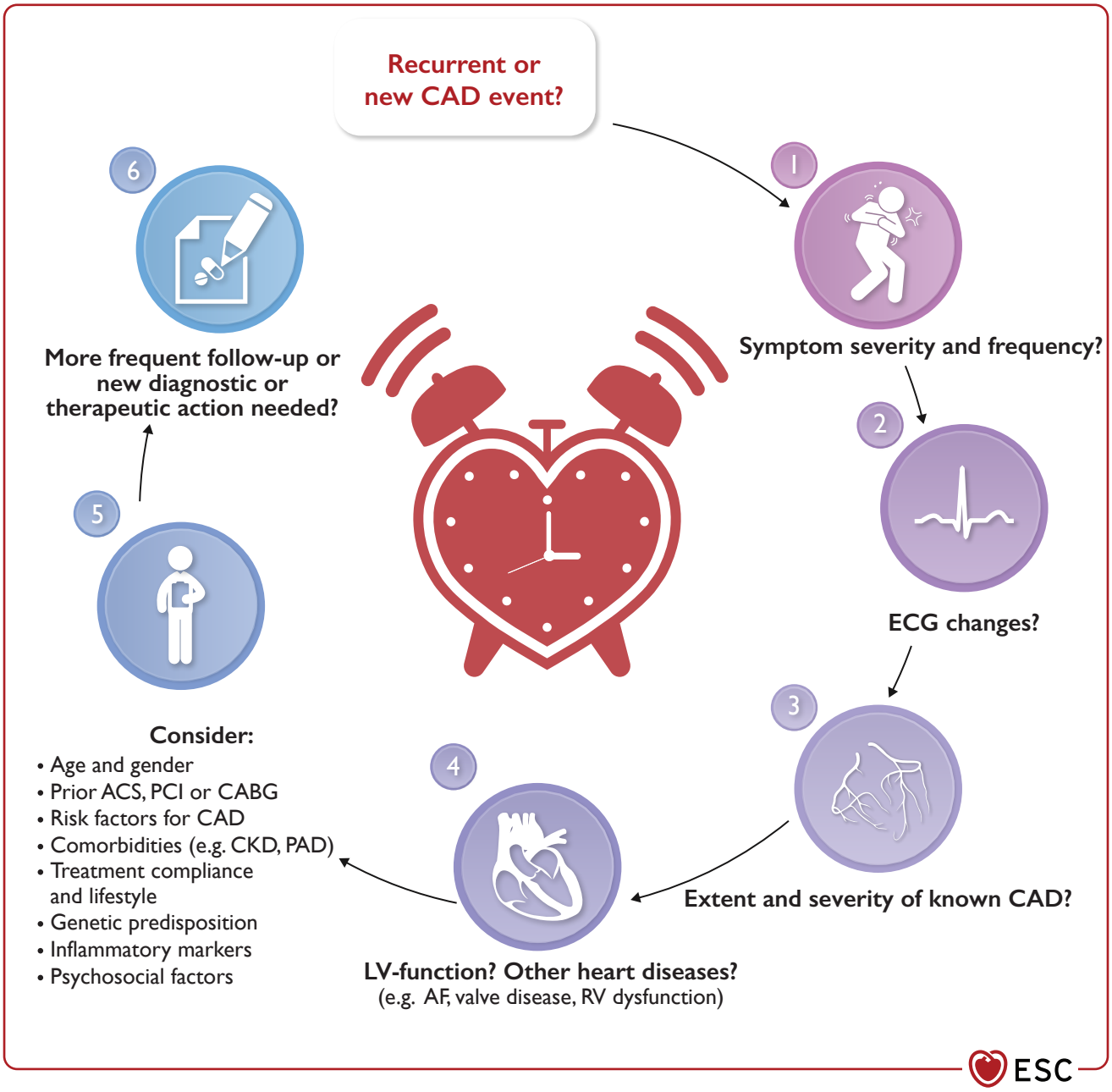


Figure 18 Approach for the follow-up of patients with established chronic coronary syndrome. ACS, acute coronary syndrome; AF, atrial fibrillation; CABG, coronary aortic bypass grafting; CAD, coronary artery disease; CCS, chronic coronary syndrome; CKD, chronic kidney disease; ECG, electrocardiogram; 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.

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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

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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.
[a]Class of recommendation.
[b]Level 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 implantation[1182] 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

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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

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CABG, coronary artery bypass grafting; DES, drug-eluting stent; LAD, left anterior descending; LIMA, left internal mammary artery; PCI, percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level 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

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ANOCA, angina with non-obstructive coronary arteries; CAD, coronary artery disease; INOCA, ischaemia with non-obstructive coronary arteries.
[a]Class of recommendation.
[b]Level of evidence.

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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 (≤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.

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- 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.

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 anginal 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.
- 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.

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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: • 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

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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: • 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:		
• FFR/iFR (significant ≤0.8 or ≤0.89, respectively);	I	A
• QFR (significant ≤0.8).	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

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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: • Exercise ECG: o Duke Treadmill Score < −10; • stress SPECT or PET perfusion imaging: o Area of ischaemia ≥10% of the LV myocardium; • Stress echocardiography: o ≥3 of 16 segments with stress-induced hypokinesia or akinesia; • stress CMR: o ≥2 of 16 segments with stress perfusion defects or ≥3 dobutamine-induced dysfunctional segments; • CCTA: o 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 *without* 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

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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: • early cessation of aspirin (≤1 week); • followed by continuation of OAC and clopidogrel: o up to 6 months in patients not at high ischaemic risk; or o 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 ≥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 ≤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

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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.	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: • 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
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 ≤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

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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 ≤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 ≤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

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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/ischaemia		
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.

[a]Class of recommendation.

[b]Level of evidence.

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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—INSELSPITAL, 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, Complexo 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 McInerny (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.*

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 Mitevska; **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,

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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.*

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