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ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)

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The disclosure forms of all experts involved in the development of these Guidelines are available on the ESC website www.escardio.org/guidelines

For the Supplementary Data which include background information and detailed discussion of the data that have provided the basis for the Guidelines see https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehz425#supplementary-data

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Abbreviations and acronyms

ABI	Ankle-brachial index
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome(s)
ACTION	A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
AUGUSTUS	An Open-label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention
BARI-2D	Bypass Angioplasty Revascularization Investigation 2 Diabetes
BEAUTIFUL	I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease and Left Ventricular Dysfunction
b.i.d.	Bis in die (twice a day)
BMI	Body mass index
BP	Blood pressure
b.p.m.	Beats per minute
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CAPRIE	Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events
CASS	Coronary Artery Surgery Study
CCB	Calcium channel blocker
CCS	Chronic coronary syndrome(s)
CFR	Coronary flow reserve
CHA_2DS_2-VASc	Cardiac failure, Hypertension, Age ≥75 [Doubled], Diabetes, Stroke [Doubled] – Vascular disease, Age 65–74 and Sex category [Female]
CHD	Coronary heart disease
CI	Confidence interval
CKD	Chronic kidney disease
CMR	Cardiac magnetic resonance
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
CPG	Committee for Practice Guidelines
CRT	Cardiac resynchronization therapy
CT	Computed tomography
CTA	Computed tomography angiography
CVD	Cardiovascular disease
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent(s)
DHP	Dihydropyridine
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
FAME 2	Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2
FFR	Fractional flow reserve

FFR_{CT}	Computed tomography-based fractional flow reserve
GEMINI-ACS	A Study to Compare the Safety of Rivaroxaban Versus Acetylsalicylic Acid in Addition to Either Clopidogrel or Ticagrelor Therapy in Participants With Acute Coronary Syndrome
GFR	Glomerular filtration rate
GLS	Global longitudinal strain
GOSPEL	Global secondary prevention strategies to limit event recurrence after myocardial infarction
HbA1c	Glycated haemoglobin
HF	Heart failure
ICA	Invasive coronary angiography
IMR	Index of microcirculatory resistance
IMT	Intima-media thickness
IONA	Impact Of Nicorandil in Angina
iwFR	Instantaneous wave-free ratio (instant flow reserve)
LAD	Left anterior descending
LBBB	Left bundle branch block
LDL-C	Low-density lipoprotein cholesterol
LM	Left main (coronary artery)
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
NOAC	Non-vitamin K antagonist oral anticoagulant
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OAC	Oral anticoagulant
o.d.	Omni die (once a day)
ORBITA	Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin-kexin type 9
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 54
PET	Positron emission tomography
PROMISE	Prospective Multicenter Imaging Study for Evaluation of Chest Pain
PTP	Pre-test probability
RAS	Renin-angiotensin system
RCT	Randomized clinical trial
REACH	Reduction of Atherothrombosis for Continued Health
RIVER-PCI	Ranolazine for Incomplete Vessel Revascularization Post-Percutaneous Coronary Intervention
SCORE	Systematic COronary Risk Evaluation
SCOT-HEART	Scottish Computed Tomography of the HEART
SIGNIFY	Study Assessing the Morbidity—Mortality Benefits of the If Inhibitor Ivabradine in Patients with Coronary Artery Disease
SPECT	Single-photon emission computed tomography
VKA	Vitamin K antagonist

1 Preamble

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in proposing the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC), as well as by other societies and organizations. Because of their impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines). The ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

The ESC carries out a number of registries which are essential to assess, diagnostic/therapeutic processes, use of resources and adherence to Guidelines. These registries aim at providing a better understanding of medical practice in Europe and around the world, based on data collected during routine clinical practice.

The guidelines are developed together with derivative educational material addressing the cultural and professional needs for cardiologists and allied professionals. Collecting high-quality observational data, at appropriate time interval following the release of ESC Guidelines, will help evaluate the level of implementation of the Guidelines, checking in priority the key end points defined with the ESC Guidelines and Education Committees and Task Force members in charge.

The Members of this Task Force were selected by the ESC, including representation from its relevant ESC sub-specialty groups, in order to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the riskbenefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in *Tables 1 and 2*.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as

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

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.

real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period were notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new Guidelines. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the European Heart Journal. The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC Guidelines also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards for non-specialists and an electronic version for digital applications (smartphones, etc.). These versions are abridged and thus, for more detailed information, the user should always access to the full text version of the Guidelines, which is freely available via the ESC website and hosted on the EHJ website. The National Societies of the ESC are encouraged to endorse, translate and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient 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.

2 Introduction

Coronary artery disease (CAD) is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries, whether obstructive or non-obstructive. This process can be modified by lifestyle adjustments, pharmacological therapies, and invasive interventions designed to achieve disease stabilization or regression. The disease can have long, stable periods but can also become unstable at any time, typically due to an acute atherothrombotic event caused by plaque rupture or erosion. However, the disease is chronic, most often progressive, and hence serious, even in clinically apparently silent periods. The dynamic nature of the CAD process results in various clinical presentations, which can be conveniently

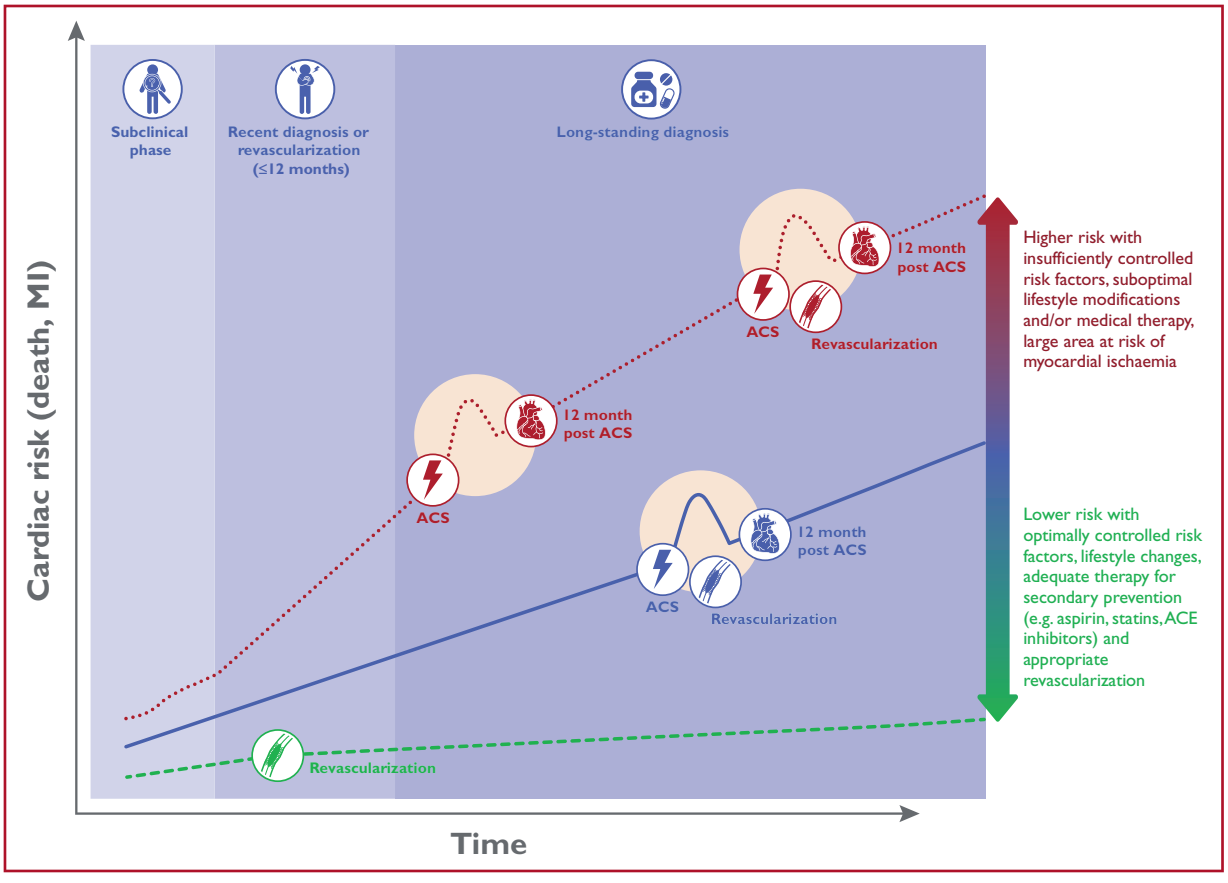

Figure 1 Schematic illustration of the natural history of chronic coronary syndromes. ACE = angiotensin-converting enzyme; ACS = acute coronary syndromes; CCS = chronic coronary syndromes; MI = myocardial infarction.

categorized as either acute coronary syndromes (ACS) or chronic coronary syndromes (CCS). The Guidelines presented here refer to the management of patients with CCS. The natural history of CCS is illustrated in *Figure 1*.

The most frequently encountered clinical scenarios in patients with suspected or established CCS are: (i) patients with suspected CAD and 'stable' anginal symptoms, and/or dyspnoea (see *section 3*); (ii) patients with new onset of heart failure (HF) or left ventricular (LV) dysfunction and suspected CAD (see *section 4*); (iii) asymptomatic and symptomatic patients with stabilized symptoms <1 year after an ACS, or patients with recent revascularization (see *section 5.1*); (iv) asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization (see *section 5.2*); (v) patients with angina and suspected vasospastic or microvascular disease (see *section 6*); and (vi) asymptomatic subjects in whom CAD is detected at screening (see *section 7*).

All of these scenarios are classified as a CCS but involve different risks for future cardiovascular events [e.g. death or myocardial infarction (MI)], and the risk may change over time. Development of an ACS may acutely destabilize each of these clinical scenarios. The risk may *increase* as a consequence of insufficiently controlled cardiovascular risk factors, suboptimal lifestyle modifications and/or medical therapy, or unsuccessful revascularization. Alternatively, the risk may *decrease* as a consequence of appropriate secondary prevention and successful revascularization. Hence, CCS are defined by the different evolutionary phases of CAD, excluding situations in which an acute coronary artery thrombosis dominates the clinical presentation (i.e. ACS).

In the present Guidelines, each section deals with the main clinical scenarios of CCS. This structure aims to simplify the use of the Guidelines in clinical practice. Additional information, tables, figures, and references are available in the Supplementary Data on the ESC website (www.escardio.org) as well as in *The ESC Textbook of Cardiovascular Medicine*.

2.1 What is new in the 2019 Guidelines?

New/revised concepts in 2019
The Guidelines have been revised to focus on CCS instead of stable CAD.
This change emphasizes the fact that the clinical presentations of CAD can be categorized as either ACS or CCS. CAD is a dynamic process of atherosclerotic plaque accumulation and functional alterations of coronary circulation that can be modified by lifestyle, pharmacological therapies, and revascularization, which result in disease stabilization or regression.
In the current Guidelines on CCS, six clinical scenarios most frequently encountered in patients are identified: (i) patients with suspected CAD and 'stable' anginal symptoms, and/or dyspnoea; (ii) patients with new onset of HF or LV dysfunction and suspected CAD; (iii) asymptomatic and symptomatic patients with stabilized symptoms <1 year after an ACS or patients with recent revascularization; (iv) asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization; (v) patients with angina and suspected vasospastic or microvascular disease; (vi) asymptomatic subjects in whom CAD is detected at screening.
The PTP of CAD based on age, gender and nature of symptoms have undergone major revisions. In addition, we introduced a new phrase 'Clinical likelihood of CAD' that utilizes also various risk factors of CAD as PTP modifiers. The application of various diagnostic tests in different patient groups to rule-in or rule-out CAD have been updated.
The Guidelines emphasize the crucial role of healthy lifestyle behaviours and other preventive actions in decreasing the risk of subsequent cardiovascular events and mortality.

ACS = acute coronary syndromes; CAD = coronary artery disease; CCS = chronic coronary syndromes; HF = heart failure; LV = left ventricular; PTP = pre-test probability.

New major recommendations in 2019	
Basic testing, diagnostics, and risk assessment	
Non-invasive functional imaging for myocardial ischaemia or coronary CTA is recommended as the initial test for diagnosing CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone.	I
It is recommended that selection of the initial non-invasive diagnostic test be based on the clinical likelihood of CAD and other patient characteristics that influence test performance, local expertise, and the availability of tests.	I
Functional imaging for myocardial ischaemia is recommended if coronary CTA has shown CAD of uncertain functional significance or is not diagnostic.	I
Invasive angiography is recommended as an alternative test to diagnose CAD in patients with a high clinical likelihood and severe symptoms refractory to medical therapy, or typical angina at a low level of exercise and clinical evaluation that indicates high event risk. Invasive functional assessment must be available and used to evaluate stenoses before revascularization, unless very high grade (>90% diameter stenosis).	I
Invasive coronary angiography with the availability of invasive functional evaluation should be considered for confirmation of the diagnosis of CAD in patients with an uncertain diagnosis on non-invasive testing.	IIa
Coronary CTA should be considered as an alternative to invasive angiography if another non-invasive test is equivocal or non-diagnostic.	IIa
Coronary CTA is not recommended when extensive coronary calcification, irregular heart rate, significant obesity, inability to cooperate with breath-hold commands, or any other conditions make good image quality unlikely.	III

Continued

Antithrombotic therapy in patients with CCS and sinus rhythm	
Addition of a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a **high risk** of ischaemic events and without high bleeding risk (see options in *section 3.3.2*).	IIa
Addition of a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a **moderately increased risk** of ischaemic events and without high bleeding risk (see options in *section 3.3.2*).	IIb
Antithrombotic therapy in patients with CCS and AF	
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
Long-term OAC therapy (a 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
Long-term OAC therapy (a 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
Antithrombotic therapy in post-PCI patients with AF or another indication for OAC	
In patients who are eligible for a NOAC, it is recommended that a NOAC (apixaban 5 mg b.i.d., dabigatran 150 mg b.i.d., edoxaban 60 mg o.d., or rivaroxaban 20 mg o.d.) is used in preference to a VKA in combination with antiplatelet therapy.	I
When rivaroxaban is used and concerns about high bleeding risk prevail over concerns about stent thrombosis or ischaemic stroke, rivaroxaban 15 mg o.d. should be considered in preference to rivaroxaban 20 mg o.d. for the duration of concomitant single or dual antiplatelet therapy.	IIa
When dabigatran is used and concerns about high bleeding risk prevail over concerns about stent thrombosis or ischaemic stroke, dabigatran 110 mg b.i.d. should be considered in preference to dabigatran 150 mg b.i.d. for the duration of concomitant single or dual antiplatelet therapy	IIa
After uncomplicated PCI, early cessation (≤1 week) of aspirin, and continuation of dual therapy with OAC and clopidogrel, should be considered if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used.	IIa
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 upon according to the assessment of these risks and clearly specified at hospital discharge.	IIa
In patients with an indication for a VKA in combination with aspirin and/or clopidogrel, the dose intensity of the VKA should be carefully regulated with a target international normalized ratio in the range of 2.0 - 2.5 and with time in therapeutic range >70%.	IIa
Dual therapy with an OAC and either ticagrelor or prasugrel may be considered as an alternative to triple therapy with an OAC, aspirin, and clopidogrel in patients with a moderate or high risk of stent thrombosis, irrespective of the type of stent used.	IIb
Other pharmacological therapy	
Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or OAC monotherapy who are at high risk of gastrointestinal bleeding.	I
Lipid-lowering drugs: if goals are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.	I
Lipid-lowering drugs: for patients at very high risk who do not achieve their goals on a maximum tolerated dose of statin and ezetimibe, combination with a PCSK9 inhibitor is recommended.	I
ACE inhibitors should be considered in CCS patients at very high risk of cardiovascular adverse events.	IIa
The sodium-glucose co-transporter 2 inhibitors empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with diabetes mellitus and CVD.	I
A glucagon-like peptide-1 receptor agonist (liraglutide or semaglutide) is recommended in patients with diabetes mellitus and CVD.	I
Screening for CAD in asymptomatic subjects	
Carotid ultrasound IMT for cardiovascular risk assessment is not recommended.	III
Recommendations for treatment options for refractory angina	
A reducer device for coronary sinus constriction may be considered to ameliorate symptoms of debilitating angina refractory to optimal medical and revascularization strategies.	IIb

[a]Class of recommendation.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndromes; AF = atrial fibrillation; b.i.d. = bis in die (twice a day); CAD = coronary artery disease; CCS = chronic coronary syndromes; CHA_2DS_2-VASc = Cardiac failure, Hypertension, Age ≥75 [Doubled], Diabetes, Stroke [Doubled] – Vascular disease, Age 65–74 and Sex category [Female]; CTA = computed tomography angiography; CVD = cardiovascular disease; HF = heart failure; IMT = intima-media thickness; LV = left ventricular; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; o.d. = omni die (once a day); PCI = percutaneous coronary intervention; PCSK9 = proprotein convertase subtilisin-kexin type 9; VKA = vitamin K antagonist.

Changes in major recommendations			
2013	**Class[a]**	**2019**	**Class[a]**
Exercise ECG is recommendedas the initial test to establish a diagnosis of stable CAD in patients withsymptoms of angina and intermediate PTP of CAD (15–65%), free of anti-ischaemic drugs, unless they cannot exercise or display ECG changes that make the ECG non-evaluable.	I	Exercise ECG is recommended for the assessment of exercise tolerance, symptoms, arrhythmias, BP response, and event risk in selected patients.	I
		Exercise ECG may be considered as an alternative test to rule-in or rule-out CAD when other non-invasive or invasive imaging methods are not available.	IIb
Exercise ECG should be considered in patients on treatment to evaluate control of symptoms and ischaemia.	IIa	Exercise ECG may be considered in patients on treatment to evaluate control of symptoms and ischaemia.	IIb
For second-line treatment it is recommended that long-acting nitrates, ivabradine, nicorandil, or ranolazine are added according to heart rate, BP, and tolerance.	IIa	Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-CCB is contraindicated, poorly tolerated, or inadequate in controlling angina symptoms.	IIa
For second-line treatment, trimetazidine may be considered,	IIb	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
		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, BP, and tolerance.	IIb
In patients with suspected coronary microvascular angina: intracoronary acetylcholine and adenosine with Doppler measurements may be considered during coronary arteriography, if the arteriogram is visually normal, to assess endothelium-dependent and non-endothelium-dependent CFR, and detect microvascular/epicardial vasospasm.	IIb	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
		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
In patients with suspected coronary microvascular angina: transthoracic Doppler echocardiography of the LAD, with measurement of diastolic coronary blood flow following intravenous adenosine and at rest, may be considered for non-invasive measurement of CFR.	IIb	Transthoracic Doppler of the LAD, CMR, and PET may be considered for non-invasive assessment of CFR.	IIb

[a]Class of recommendation.
BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CFR = coronary flow reserve; CMR = cardiac magnetic resonance; DHP-CCB = dihydropyridine calcium channel blockers; ECG = electrocardiogram; FFR = fractional flow reserve; iwFR = instantaneous wave-free ratio (instant flow reserve); LAD = left anterior descending; PET = positron emission tomography; PTP = pre-test probability.

3 Patients with angina and/or dyspnoea, and suspected coronary artery disease

3.1 Basic assessment, diagnosis, and risk assessment

The general approach for the initial diagnostic management of patients with angina and suspected obstructive CAD is presented in *Figure 2*. The diagnostic management approach includes six steps. The first step is to assess the symptoms and signs, to identify patients with possible unstable angina or other forms of ACS (step 1). In patients without unstable angina or other ACS, the next step is to evaluate the patient's general condition and quality of life (step 2). Comorbidities that could potentially influence therapeutic decisions are assessed and other potential causes of the symptoms are considered. Step 3 includes basic testing and assessment of LV function. Thereafter, the clinical likelihood of obstructive CAD is estimated (step 4) and, on this basis, diagnostic testing is offered to selected patients to establish the diagnosis of CAD (step 5). Once a diagnosis of obstructive CAD has been confirmed, the patient's event risk will be determined (step 6) as it has a major impact on the subsequent therapeutic decisions.

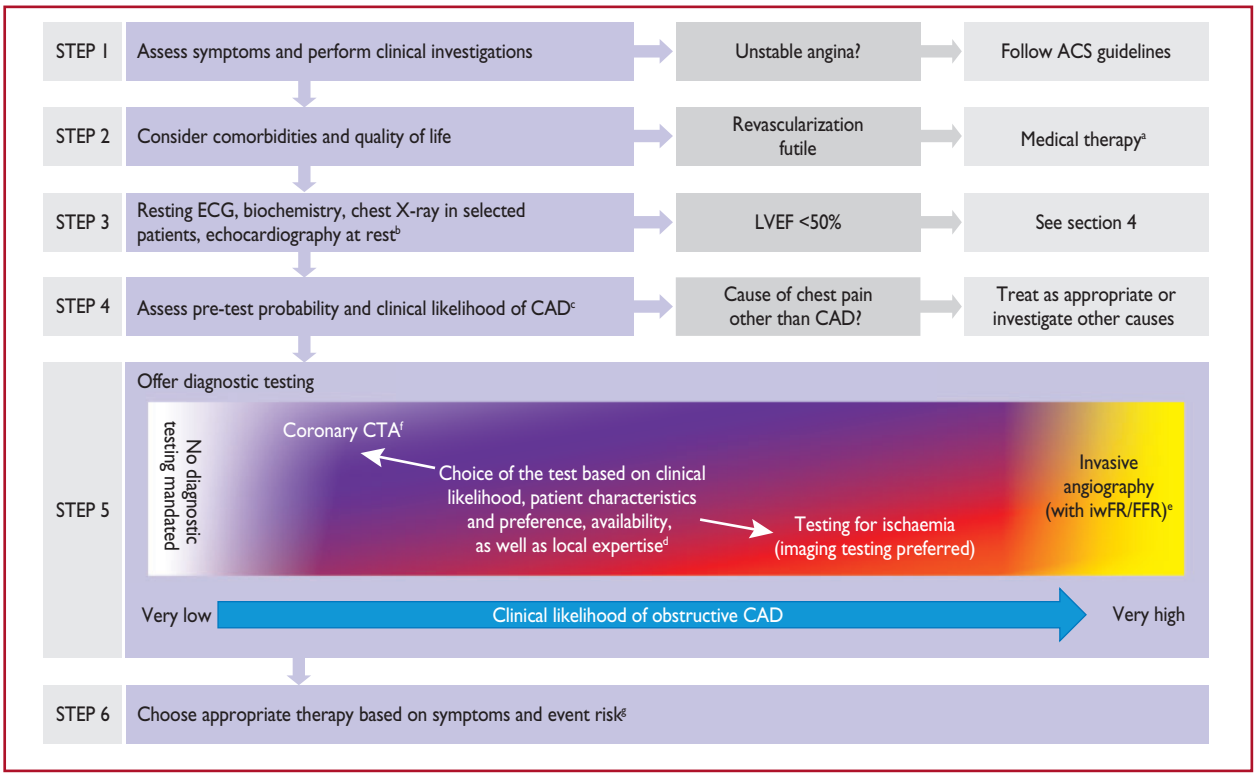

Figure 2 Approach for the initial diagnostic management of patients with angina and suspected coronary artery disease. ACS = acute coronary syndrome; BP = blood pressure; CAD = coronary artery disease; CTA = computed tomography angiography; ECG = electrocardiogram; FFR = fractional flow reserve; iwFR = instantaneous wave-free ratio; LVEF = left ventricular ejection fraction. [a]If the diagnosis of CAD is uncertain, establishing a diagnosis using non-invasive functional imaging for myocardial ischaemia before treatment may be reasonable. [b]May be omitted in very young and healthy patients with a high suspicion of an extracardiac cause of chest pain, and in multimorbid patients in whom the echocardiography result has no consequence for further patient management. [c]Consider exercise ECG to assess symptoms, arrhythmias, exercise tolerance, BP response, and event risk in selected patients. [d]Ability to exercise, individual test-related risks, and likelihood of obtaining diagnostic test result. [e]High clinical likelihood and symptoms inadequately responding to medical treatment, high event risk based on clinical evaluation (such as ST-segment depression, combined with symptoms at a low workload or systolic dysfunction indicating CAD), or uncertain diagnosis on non-invasive testing. [f]Functional imaging for myocardial ischaemia if coronary CTA has shown CAD of uncertain grade or is non-diagnostic. [g]Consider also angina without obstructive disease in the epicardial coronary arteries (see *section 6*).

After these steps, appropriate therapies are to be initiated, which include lifestyle management (see *section 3.2*), medical therapy (see *section 3.3*), and revascularization when indicated (see *section 3.4*).

3.1.1. Step 1: Symptoms and signs

A careful history is the cornerstone of the diagnosis of angina. It is possible to achieve a high degree of certainty on a diagnosis based on history alone, although physical examination and objective tests are most often necessary to confirm the diagnosis, exclude alternative diagnoses, and assess the severity of underlying disease. The history should include any manifestation of cardiovascular disease (CVD) and risk factors (i.e. family history of CVD, dyslipidaemia, diabetes, hypertension, smoking, and other lifestyle factors).

The characteristics of discomfort related to myocardial ischaemia (angina pectoris) may be divided into four categories: location, character, duration, and relationship to exertion, and other exacerbating or relieving factors. The discomfort caused by myocardial ischaemia is usually located in the chest, near the sternum, but may be felt anywhere from the epigastrium to the lower jaw or teeth, between the shoulder blades, or in either arm to the wrist and fingers. The discomfort is often described as pressure, tightness, or heaviness; sometimes strangling, constricting, or burning. It may be useful to ask the patient directly about the presence of 'discomfort' as many do not feel 'pain' or 'pressure' in their chest. Shortness of breath may accompany angina, and chest discomfort may also be accompanied by less-specific symptoms such as fatigue or faintness, nausea, burning, restlessness, or a sense of impending doom. Shortness of breath may be the sole symptom of CAD and it may be difficult to differentiate this from shortness of breath caused by other conditions.

The duration of the discomfort is brief—≤10 min in the majority of cases, and more commonly just a few minutes or less—and chest pain lasting for seconds is unlikely to be due to CAD. An important characteristic is the relationship to exercise. Symptoms

classically appear or become more severe with increased levels of exertion—such as walking up an incline or against a breeze, or in cold weather—and rapidly disappear within a few minutes when these causal factors abate. Exacerbations of symptoms after a heavy meal or after waking up in the morning are classic features of angina. Angina may paradoxically be reduced with further exercise (walk-through angina) or on second exertion (warm-up angina).[1] Sublingual nitrates rapidly relieve angina. Symptoms are unrelated to respiration or position. The angina threshold, and hence symptoms, may vary considerably from day to day and even during the same day.

Definitions of typical and atypical angina are summarized in *Table 3*. The classification, although subjective, is practical and of proven value in determining the likelihood of obstructive CAD.[2,3] Studies published since 2015 have reported that the majority of patients suspected of having CAD present with atypical or non-anginal chest pain,[4–6] with as few as 10 - 15% presenting with typical angina.[3,7,8] The Canadian Cardiovascular Society classification is still widely used as a grading system for angina,[9] to quantify the threshold at which symptoms occur in relation to physical activities (*Table 4*).

Physical examination of a patient with suspected CAD is important to assess the presence of anaemia, hypertension, valvular heart disease, hypertrophic cardiomyopathy, or arrhythmias. It is also recommended that practitioners obtain the body mass index (BMI) and search for evidence of non-coronary vascular disease, which may be asymptomatic [includes palpation of peripheral pulses, and auscultation of carotid and femoral arteries, as well as assessment of the ankle-brachial index (ABI)], and other signs of comorbid conditions such as thyroid disease, renal disease, or diabetes. This should be used in the context of other clinical information, such as the presence of cough or stinging pain, making CAD more unlikely. One should also try to reproduce the symptoms by palpation[10] and test the effect of sublingual nitroglycerin in order to classify the symptoms (*Table 3*).

Table 3 Traditional clinical classification of suspected anginal symptoms

Typical angina	Meets the following three characteristics: (i) Constricting discomfort in the front of the chest or in the neck, jaw, shoulder, or arm; (ii) Precipitated by physical exertion; (iii) Relieved by rest or nitrates within 5 min.
Atypical angina	Meets two of these characteristics.
Non-anginal chest pain	Meets only one or none of these characteristics.

3.1.1.1 Stable vs. unstable angina

Unstable angina may present in one of three ways: (i) as rest angina, i.e. pain of characteristic nature and location occurring at rest and for prolonged periods (>20 min); (ii) new-onset angina, i.e. recent (2 months) onset of moderate-to-severe angina (Canadian Cardiovascular Society grade II or III); or (iii) crescendo angina, i.e. previous angina, which progressively increases in severity and intensity, and at a lower threshold, over a short period of time. Management of angina fulfilling these criteria is dealt with in the ESC Guidelines for the management of ACS.[11,12] New-onset angina is generally regarded as unstable angina; however, if angina occurs for the first time with heavy exertion and subsides at rest, the suspected condition falls under the definition of CCS rather than unstable angina. In patients with unstable angina identified as being at low risk, it is recommended that the diagnostic and prognostic algorithms presented in these Guidelines be applied once the period of instability has subsided.[11] Low-risk patients with unstable angina are characterized by no recurrence of angina, no signs of HF, no abnormalities in the initial or subsequent electrocardiogram (ECG), and no rise in troponin levels.[11] In this setting, a non-invasive diagnostic strategy is recommended before deciding on an invasive strategy. Based on the definition above, stable and unstable angina may overlap, and many CCS patients pass through a period of experiencing unstable angina.

Table 4 Grading of effort angina severity according to the Canadian Cardiovascular Society

Grade	Description of angina severity	
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 cold, in 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 normal pace and conditions.
IV	Angina at rest	No exertion needed to trigger angina.

3.1.1.2 Distinction between symptoms caused by epicardial vs. microvascular/vasospastic disease

A distinction between symptoms caused by an epicardial stenosis and symptoms caused by microvascular or vasospastic disease cannot be made with reasonable certainty. Reliance on ischaemia testing or depiction of the coronary anatomy is often unavoidable to exclude obstructive CAD, which can be absent in symptomatic patients.[13,14] A diagnostic workup for microvascular or vasospastic disease is discussed in *section 6* of these Guidelines.

3.1.2 Step 2: Comorbidities and other causes of symptoms

Before any testing is considered, one must assess the patient's general health, comorbidities, and quality of life. If revascularization is unlikely to be an acceptable option, further testing may be reduced to a clinically indicated minimum and appropriate therapy should be instituted, which may include a trial of antianginal medication even if a diagnosis of CAD has not been fully demonstrated. Non-invasive functional imaging for ischaemia may be an option if there is need to verify the diagnosis (*Figure 2*).

If the pain is clearly non-anginal, other diagnostic testing may be indicated to identify gastrointestinal, pulmonary, or musculoskeletal causes of chest pain. Nevertheless, these patients should also receive Guideline-based risk-factor modification based on commonly applied risk charts such as SCORE (Systematic COronary Risk Evaluation) (www.heartscore.org).[15]

3.1.3 Step 3: Basic testing

Basic (first-line) testing in patients with suspected CAD includes standard laboratory biochemical testing, a resting ECG, possible ambulatory ECG monitoring, resting echocardiography, and, in selected patients, a chest X-ray. Such testing can be done on an outpatient basis.

3.1.3.1 Biochemical tests

Laboratory investigations are used to identify possible causes of ischaemia, to establish cardiovascular risk factors and associated conditions, and to determine prognosis. Haemoglobin as part of a full blood count and—where there is a clinical suspicion of a thyroid disorder—thyroid hormone levels provide information related to possible causes of ischaemia. Fasting plasma glucose and glycated haemoglobin (HbA1c) should be measured in every patient with suspected CAD. If both are inconclusive, an additional oral glucose tolerance test is recommended.[16] Knowledge of glucose metabolism is important because of the well-recognized association between diabetes and adverse cardiovascular outcome. Patients with diabetes should be managed according to specific Guidelines.[15,16] A lipid profile, including total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides, should also be evaluated in any patient with suspected CAD to establish the patient's risk profile and ascertain the need for treatment.[15,17] To characterize severe dyslipidaemia or follow-up on high triglyceridaemia, fasting values are recommended.[17]

Peripheral artery disease (PAD) and renal dysfunction increase the likelihood of CAD, and have a negative impact on prognosis.[18–20] Hence, baseline renal function should be evaluated with estimation of the glomerular filtration rate (GFR). It may also be reasonable to measure the uric acid level, as hyperuricaemia is a frequent comorbid condition and may also 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 Guidelines for ACS without persistent ST-segment elevation.[11] If high-sensitivity assays are employed, low levels of troponin can be detected in many patients with stable angina. Increased troponin levels are associated with adverse outcome[21–25] and small studies have indicated a possible incremental value in diagnosing CAD,[26,27] but larger trials are needed to verify the utility of systematic assessment in patients suspected of CAD. While multiple biomarkers may be useful for prognostication (see *section 5*), they do not yet have a role in diagnosing obstructive CAD.

Basic biochemistry testing in the initial diagnostic management of patients with suspected coronary artery disease

Recommendations	Class[a]	Level[b]
If evaluation suggests clinical instability or ACS, repeated measurements of troponin, preferably using high-sensitivity or ultrasensitive assays, are recommended to rule-out myocardial injury associated with ACS.[28,29]	I	A
The following blood tests are recommended in all patients:		
• Full blood count (including haemoglobin);[30]	I	B
• Creatinine measurement and estimation of renal function;[31,32]	I	A
• A lipid profile (including LDL-C).[33,34]	I	A
It is recommended that screening for type 2 diabetes mellitus in patients with suspected and established CCS is implemented with HbA1c and fasting plasma glucose measurements, and that an oral glucose tolerance test is added if HbA1c and fasting plasma glucose results are inconclusive.[16,35]	I	B
Assessment of thyroid function is recommended in case of clinical suspicion of thyroid disorders.	I	C

ACS = acute coronary syndromes; CAD = coronary artery disease; CCS = chronic coronary syndromes; HbA1c = glycated haemoglobin; LDL-C = low-density lipoprotein cholesterol.

[a]Class of recommendation.

[b]Level of evidence.

3.1.3.2 Resting electrocardiogram and ambulatory monitoring

The paradigm of diagnosing myocardial ischaemia has, for almost a century, been based on the detection of repolarization abnormalities, mainly in the form of ST-segment depressions. Thus, the resting 12 lead ECG remains an indispensable component of the initial evaluation of a patient with chest pain without an obviously non-cardiac cause. Two scenarios of clinical evaluation are encountered: (i) a patient without symptoms of chest pain or discomfort, and (ii) a patient with ongoing anginal symptoms.

The former situation is far more prevalent and a normal resting ECG is frequently recorded. However, even in the absence of repolarization abnormalities, an ECG can demonstrate indirect signs of CAD, such as signs of previous MI (pathological Q waves) or conduction abnormalities [mainly left bundle branch block (LBBB) and impairment of atrioventricular conduction]. Atrial fibrillation (AF) is a frequent finding in patients with chest pain (usually atypical). ST-segment depression during supraventricular tachyarrhythmias is not predictive of obstructive CAD.[36–39]

The ECG can be crucial for diagnosing myocardial ischaemia if dynamic ST-segment changes are recorded during ongoing angina. The diagnosis of Prinzmetal and vasospastic angina is based on the detection of typical transient ST-segment elevation or depression during an angina attack (usually at rest).

Long-term ambulatory ECG monitoring and recording should not be used to replace exercise testing; however, 12 lead ECG monitoring can be considered in selected patients to detect anginal episodes unrelated to physical exercise. Ambulatory ECG monitoring may reveal evidence of silent myocardial ischaemia in patients with CCS, but rarely adds relevant diagnostic or prognostic information that cannot be derived from stress testing.[40] ECG changes suggesting ischaemia on ambulatory ECG monitoring are very frequent in women, but do not correlate with findings during stress testing.[41] Most importantly, therapeutic strategies targeting silent ischaemia detected by ambulatory monitoring have not demonstrated clear survival benefits.[42,43]

Resting electrocardiogram in the initial diagnostic management of patients with suspected coronary artery disease

Recommendations	Class[a]	Level[b]
A resting 12 lead ECG is recommended in all patients with chest pain without an obvious non-cardiac cause.	I	C
A resting 12 lead ECG is recommended in all patients during or immediately after an episode of angina suspected to be indicative of clinical instability of CAD.	I	C
ST-segment alterations recorded during supraventricular tachyarrhythmias should not be used as evidence of CAD.	III	C

CAD = coronary artery disease; CCS = chronic coronary syndromes; ECG = electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.

Ambulatory electrocardiogram monitoring in the initial diagnostic management of patients with suspected coronary artery disease

Recommendations	Class[a]	Level[b]
Ambulatory ECG monitoring is recommended in patients with chest pain and suspected arrhythmias.	I	C
Ambulatory ECG recording, preferably monitoring with 12 lead ECG, should be considered in patients with suspected vasospastic angina.	IIa	C
Ambulatory ECG monitoring should not be used as a routine examination in patients with suspected CCS.	III	C

CAD = coronary artery disease; CCS = chronic coronary syndromes; ECG = electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.

3.1.3.3 Echocardiography and magnetic resonance imaging at rest

An echocardiographic study will provide important information about cardiac function and anatomy. LV ejection fraction (LVEF) is often normal in patients with CCS.[44] A decreased LV function and/or regional wall motion abnormalities may increase the suspicion of ischaemic myocardial damage,[45] and a pattern of LV dysfunction following the theoretical distribution territory of the coronary arteries is typical in patients who have already had an MI.[46,47] The detection of regional wall motion abnormalities can challenging by visual assessment, and detection of early systolic lengthening, decreased systolic shortening, or post-systolic shortening by strain imaging techniques might be helpful in patients with apparently normal LV function but with clinical suspicion of CCS.[48–50] Decreased diastolic LV function has been reported to be an early sign of ischaemic myocardial dysfunction and could also be indicative of microvascular dysfunction.[51,52]

Echocardiography is an important clinical tool for the exclusion of alternative causes of chest pain and also aids in diagnosing concurrent cardiac diseases, such as valvular heart diseases, HF, and most cardiomyopathies,[53] but it is important to remember that these diseases often coexist with obstructive CAD. The use of an echocardiographic contrast agent can be useful in patients with poor acoustic windows.[54]

Cardiac magnetic resonance (CMR) may be considered in patients with suspected CAD when the echocardiogram (having used contrast) is inconclusive.[55] CMR will provide useful information on cardiac anatomy and systolic cardiac function, similar to that from an echocardiogram, in patients with no contraindications for CMR. CMR can assess global and regional function,[56] and the use of late gadolinium enhancement CMR can reveal a typical pattern of scarred myocardium in patients who have already experienced an MI.[57]

Assessment of LV function is important in all patients for risk stratification (see Supplementary Data *section 3.2*) and should therefore be performed in all symptomatic patients with suspected CAD.

Management of patients with either angina or HF symptoms, with reduced LVEF <40% or a mid-range reduced LVEF of 40-49%, is described in *section 4* of the Guidelines.

Resting echocardiography and cardiac magnetic resonance in the initial diagnostic management of patients with suspected coronary artery disease

Recommendations	Class[a]	Level[b]
A resting transthoracic echocardiogram is recommended in all patients for: (1) Exclusion of alternative causes of angina; (2) Identification of regional wall motion abnormalities suggestive of CAD; (3) Measurement of LVEF for risk stratification; and (4) Evaluation of diastolic function.[44,45,52,58]	I	B
Ultrasound of the carotid arteries should be considered, and be performed by adequately trained clinicians, to detect plaque in patients with suspected CCS without known atherosclerotic disease.	IIa	C
CMR may be considered in patients with an inconclusive echocardiographic test.	IIb	C

CAD = coronary artery disease; CCS = chronic coronary syndromes; CMR = cardiac magnetic resonance imaging; LVEF = left ventricular ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.

3.1.3.4 Chest X-ray

Chest X-ray is frequently used in the assessment of patients with chest pain. However, in CCS, it does not provide specific information for diagnosis or event risk stratification. The test may occasionally be helpful in assessing patients with suspected HF. Chest X-ray may also be useful in patients with pulmonary problems, which often accompany CAD, or to rule-out another cause of chest pain in atypical presentations.

Chest X-ray in the initial diagnostic management of patients with suspected coronary artery disease

Recommendation	Class[a]	Level[b]
Chest X-ray is recommended for patients with atypical presentation, signs and symptoms of HF, or suspicion of pulmonary disease.	I	C

HF = heart failure.
[a]Class of recommendation.
[b]Level of evidence.

3.1.4 Step 4: Assessment of pre-test probability and clinical likelihood of coronary artery disease

The performance of the available methods in diagnosing obstructive CAD (i.e. the likelihood that the patient has disease if the test is abnormal, and the likelihood that the patient does not have disease if the test is normal) depends on the prevalence of disease in the population studied and, thus, the likelihood that a given patient will actually have CAD. Diagnostic testing is most useful when the likelihood is intermediate. When likelihood is high, a large number of patients need to be studied to identify the few patients that do not have disease, and a negative test result can seldom rule out the presence of obstructive CAD (i.e. the negative predictive value is low). When the likelihood is low, a negative test can rule out the disease, but the lower the likelihood, the higher the likelihood of a false-positive test (i.e. a positive test in the absence of obstructive CAD). In patients at the extreme ends of the probability range, it is therefore reasonable to refrain from diagnostic testing, and assume that the patient does or does not have obstructive CAD based on clinical evaluation alone.

The likelihood of obstructive CAD is influenced by the prevalence of the disease in the population studied, as well as by clinical features of an individual patient. A simple predictive model can be used to estimate the pre-test probability (PTP) of obstructive CAD based on age, sex, and the nature of symptoms.[59] In the previous version of these Guidelines,[60] estimation of the PTP was based on data gathered by Genders *et al.*,[61] which updated previous data from Diamond and Forrester.[59] Notably, the prevalence of disease for a given constellation of age, sex, and nature of symptoms was lower than in the Diamond and Forrester data. Since the previous version of the Guidelines was published, several studies have indicated that the prevalence of obstructive disease among patients with suspected CAD is lower than in the previous update.[7,8,62,63]

A pooled analysis[64] of three contemporary study cohorts, including patients evaluated for suspected CAD,[7,8,62] has indicated that the PTP based on age, sex, and symptoms is approximately one-third of that predicted by the model used in the previous version of the Guidelines.[57,62] Overestimation of PTP is an important contributory factor to a low diagnostic yield of non-invasive and invasive testing. The new set of PTPs presented in *Table 5* may substantially reduce the need for non-invasive and invasive tests in patients with suspected stable CAD. The table now also includes patients presenting with dyspnoea as their main symptom. However, it should be noted that the PTPs presented in *Table 5* (as well as the PTP table in the previous version of the Guidelines) are based mainly on patients from countries with low CVD risk, and may vary between regions and countries.

Application of the new PTPs (*Table 5*) has important consequences for the referral of patients for diagnostic testing. If diagnostic testing was deferred in patients with a new PTP <15%, this would result in a large increase in the proportion of patients for whom diagnostic testing was not recommended, because more patients are classified as having a PTP <15%. In data derived from the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial, 50% of patients previously classified as having an intermediate likelihood of obstructive CAD were reclassified to a PTP <15% according to the new PTP.[62] In data derived from the pooled analysis[64] (*Table 5*), 57% of all patients were classified to a PTP <15%.

Studies have shown that outcomes in patients classified with the new PTP <15% is good (annual risk of cardiovascular death or MI is <1%).[7,62] Hence, it is safe to defer routine testing in patients with PTP <15%, thus reducing unnecessary procedures and costs.

Table 5 Pre-test probabilities of obstructive coronary artery disease in 15 815 symptomatic patients according to age, sex, and the nature of symptoms in a pooled analysis[64] of contemporary data[7,8,62]

	Typical		Atypical		Non-anginal		Dyspnoea[a]	
Age	Men	Women	Men	Women	Men	Women	Men	Women
30–39	3%	5%	4%	3%	1%	1%	0%	3%
40–49	22%	10%	10%	6%	3%	2%	12%	3%
50–59	32%	13%	17%	6%	11%	3%	20%	9%
60–69	44%	16%	26%	11%	22%	6%	27%	14%
70+	52%	27%	34%	19%	24%	10%	32%	12%

CAD = coronary artery disease; PTP = pre-test probability.
[a]In addition to the classic Diamond and Forrester classes,[59] patients with dyspnoea only or dyspnoea as the primary symptom are included. The regions shaded dark green denote the groups in which non-invasive testing is most beneficial (PTP >15%). The regions shaded light green denote the groups with PTPs of CAD between 5–15%, in which testing for diagnosis may be considered after assessing the overall clinical likelihood based on the modifiers of PTPs presented in *Figure 3*.

Recent studies have also demonstrated that, when tested, the true observed prevalence of obstructive CAD has been <5% in patients who had a PTP <15% according to the 2013 version of these Guidelines.[7,63] Therefore, this Task Force recognizes that the performance of diagnostic testing in patients with a new PTP of 5 - 15% more closely reflects current clinical practice and may be considered, particularly if symptoms are limiting and require clarification.[7,63] Patient preference, local resources and the availability of tests, clinical judgement, and appropriate patient information remain important when making a decision to proceed with non-invasive diagnostic testing for an individual patient when the PTP is 5 - 15%, and the higher likelihood of a false-positive test must be considered. Patients with a PTP ≤5% can be assumed to have such a low probability of disease that diagnostic testing should be performed only for compelling reasons. Implementation of the new PTPs also indicates that patients should not be routinely referred directly to invasive assessment unless clinical or other data indicate a high likelihood of obstructive CAD.

Clinical models that incorporate information on risk factors for CVD, resting ECG changes, or coronary calcification have improved the identification of patients with obstructive CAD compared with age, sex, and symptoms alone.[3,7,60,65–68] Therefore, the presence of risk factors for CVD (such as family history of CVD, dyslipidaemia, diabetes, hypertension, smoking, and other lifestyle factors) that increase the probability of obstructive CAD can be used as modifiers of the PTP estimate. If available, Q-wave, ST-segment, or T-wave changes on the ECG, LV dysfunction suggestive of ischaemia, and findings on exercise ECG, as well as information on coronary calcium obtained by computed tomography (CT), can be used to improve estimations of the PTP of obstructive CAD.[3,69] In particular, the absence of coronary calcium (Agatston score = 0) is associated with a low prevalence of obstructive CAD (<5%), and low risk of death or non-fatal MI (<1% annual risk).[69,70] However, it should be noted that coronary calcium imaging does not exclude coronary stenosis caused by a non-calcified atherosclerotic lesion,[70] and the presence of coronary calcium is a weak predictor of obstructive CAD.[69] Although the optimal use of these factors in improving PTP assessment has not yet been established, they should be considered in addition to the PTP based on sex, age, and the nature of symptoms to determine the overall clinical likelihood of obstructive CAD, as summarized in *Figure 3*. This is particularly important in refining the likelihood of CAD patients with a PTP of 5–15% based on age, sex, and the nature of symptoms.

3.1.5 Step 5: Selecting appropriate testing

In patients in whom revascularization is futile due to comorbidities and overall quality of life, the diagnosis of CAD can be made clinically and only medical therapy is required. If the diagnosis of CAD is uncertain, establishing a diagnosis using non-invasive functional imaging for myocardial ischaemia before treatment is reasonable (*Figure 2*).

In a patient with a high clinical likelihood of CAD, symptoms unresponsive to medical therapy or typical 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 invasive coronary angiography (ICA) without further diagnostic testing is a reasonable option. Under such circumstances, the indication for revascularization should be based on appropriate invasive confirmation of the haemodynamic significance of a stenosis.[71,72]

In other patients in whom CAD cannot be excluded by clinical assessment alone, non-invasive diagnostic tests are recommended to establish the diagnosis and assess the event risk. The current Guidelines recommend the use of either non-invasive functional imaging of ischaemia or anatomical imaging using coronary CT angiography (CTA) as the initial test for diagnosing CAD.

3.1.5.1 Functional non-invasive tests

Functional non-invasive tests for the diagnosis of obstructive CAD are designed to detect myocardial ischaemia through ECG changes, wall motion abnormalities by stress CMR or stress echocardiography, or perfusion changes by single-photon emission CT

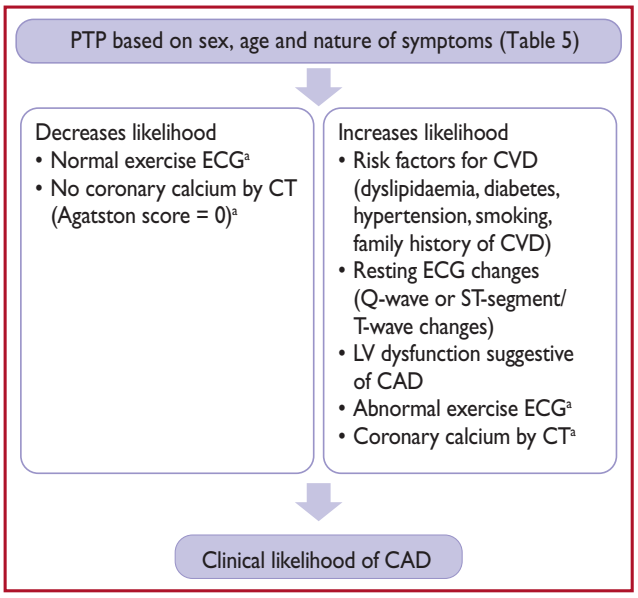

Figure 3 Determinants of the clinical likelihood of obstructive coronary artery disease. CAD = coronary artery disease; CT = computed tomography, CVD = cardiovascular disease, ECG = electrocardiogram, LV = left ventricular; PTP = pre-test probability. [a]When available.

(SPECT), positron emission tomography (PET), myocardial contrast echocardiography, or contrast CMR. Ischaemia can be provoked by exercise or pharmacological stressors, either by increased myocardial work and oxygen demand, or by heterogeneity in myocardial perfusion by vasodilatation. Non-invasive functional tests are associated with high accuracy for the detection of flow-limiting coronary stenosis compared with invasive functional testing [fractional flow reserve (FFR)].[73] However, lower-grade coronary atherosclerosis not linked with ischaemia remains undetected by functional testing and, in the presence of a negative functional test, patients should receive risk-factor modification based on commonly applied risk charts and recommendations.

3.1.5.2 Anatomical non-invasive evaluation

Anatomical non-invasive evaluation, by visualizing the coronary artery lumen and wall using an intravenous contrast agent, can be performed with coronary CTA, which provides high accuracy for the detection of obstructive coronary stenoses defined by ICA,[73] because both tests are based on anatomy. However, stenoses estimated to be 50–90% by visual inspection are not necessarily functionally significant, i.e. they do not always induce myocardial ischaemia.[73,74] Therefore, either non-invasive or invasive functional testing is recommended for further evaluation of angiographic stenosis detected by coronary CTA or invasive angiography, unless a very high-grade (>90% diameter stenosis) stenosis is detected via invasive angiography. The presence or absence of non-obstructive coronary atherosclerosis on coronary CTA provides prognostic information, and can be used to guide preventive therapy.[75] The SCOT-HEART (Scottish Computed Tomography of the HEART) trial demonstrated a significantly lower rate of the combined endpoint of cardiovascular death or non-fatal MI (2.3 vs. 3.9% during 5 year follow-up) in patients in whom coronary CTA was performed in addition to routine testing, which consisted predominantly of exercise ECG.[6] Other randomized, prospective clinical trials have demonstrated that diagnostic testing with coronary CTA is associated with clinical outcomes similar to those for functional imaging in patients with suspected CAD.[4,6,76] In patients with extensive CAD, coronary CTA complemented by CT-based FFR was non-inferior to ICA and FFR for decision-making, and the identification of targets for revascularization.[77]

3.1.5.3 Role of the exercise electrocardiogram

Exercise ECG has inferior diagnostic performance compared with diagnostic imaging tests, and has limited power to rule-in or rule-out obstructive CAD.[73] Since the publication of the previous version of these Guidelines, randomized clinical trials (RCTs) have compared the effects of diagnostic strategies based on exercise ECG or an imaging diagnostic test[6,78,79] on clinical outcomes. These studies have shown that the addition of coronary CTA[5,6,78,80] or functional imaging[79] clarifies the diagnosis, enables the targeting of preventive therapies and interventions, and potentially reduces the risk of MI compared with an exercise ECG. Some, although not all, registry studies have also shown similar benefits regarding the use of an imaging diagnostic test in patients treated in everyday clinical practice.[81,82] Therefore, these Guidelines recommend the use of an imaging diagnostic test instead of exercise ECG as the initial test for to diagnose obstructive CAD.

An exercise ECG alone may be considered as an alternative to diagnose obstructive CAD if imaging tests are not available, keeping in mind the risk of false-negative and false-positive test results.[73,83] An exercise ECG is of no diagnostic value in patients with ECG abnormalities 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 who are being treated with digitalis). An exercise ECG provides

complementary clinically useful information beyond ECG changes and valuable prognostic information. Therefore, application of an exercise ECG may be considered in selected patients to complement clinical evaluation for the assessment of symptoms, ST-segment changes, exercise tolerance, arrhythmias, blood pressure (BP) response, and event risk.

3.1.5.4 Selection of diagnostic tests

Either a functional or anatomical test can be used to establish a diagnosis of obstructive CAD. A summary of the main diagnostic pathways is displayed in *Figure 4*. For revascularization decisions, information on both anatomy and ischaemia is needed.

3.1.5.5 The impact of clinical likelihood on the selection of a diagnostic test

Each non-invasive diagnostic test has a particular range of clinical likelihood of obstructive CAD where the usefulness of its application is maximal. The likelihood ratios of the tests constitute useful parameters of their abilities to correctly classify patients, and can be used to facilitate the selection of the most useful test in any given patient.[73,84] Given a clinical likelihood of obstructive CAD and the likelihood ratio of a particular test, one can assess the post-test probability of obstructive CAD after performing such a test. Using this approach, one can estimate the optimal ranges of clinical likelihood for each test, where they can reclassify patients from intermediate to either low or high post-test probability of CAD (*Figure 5*).[73]

Coronary CTA is the preferred test in patients with a lower range of clinical likelihood of CAD, no previous diagnosis of CAD, and characteristics associated with a high likelihood of good image quality. It detects subclinical coronary atherosclerosis, but can also accurately rule out both anatomically and functionally significant CAD (*Figure 5*). It has higher accuracy values when low clinical likelihood populations are subjected to examination.[85] Trials evaluating outcomes after coronary CTA to date have mostly included patients with a low clinical likelihood.[4,5]

The non-invasive functional tests for ischaemia typically have better rule-in power. In outcome trials, functional imaging tests have been associated with fewer referrals for downstream ICA compared with a strategy relying on anatomical imaging.[55,76,86] Before revascularization decisions can be made, functional evaluation of ischaemia (either non-invasive or invasive) is required in most patients. Therefore, functional non-invasive testing may be preferred in patients at the higher end of the range of clinical likelihood if revascularization is likely or the patient has previously diagnosed CAD.

Patients in whom CAD is suspected, but who have a very low clinical likelihood (≤5%) of CAD, should have other cardiac causes of chest pain excluded and their cardiovascular risk factors adjusted, based on a risk-score assessment. In patients with repeated, unprovoked attacks of anginal symptoms mainly at rest, vasospastic angina should be considered, diagnosed, and treated appropriately (see *section 6*).

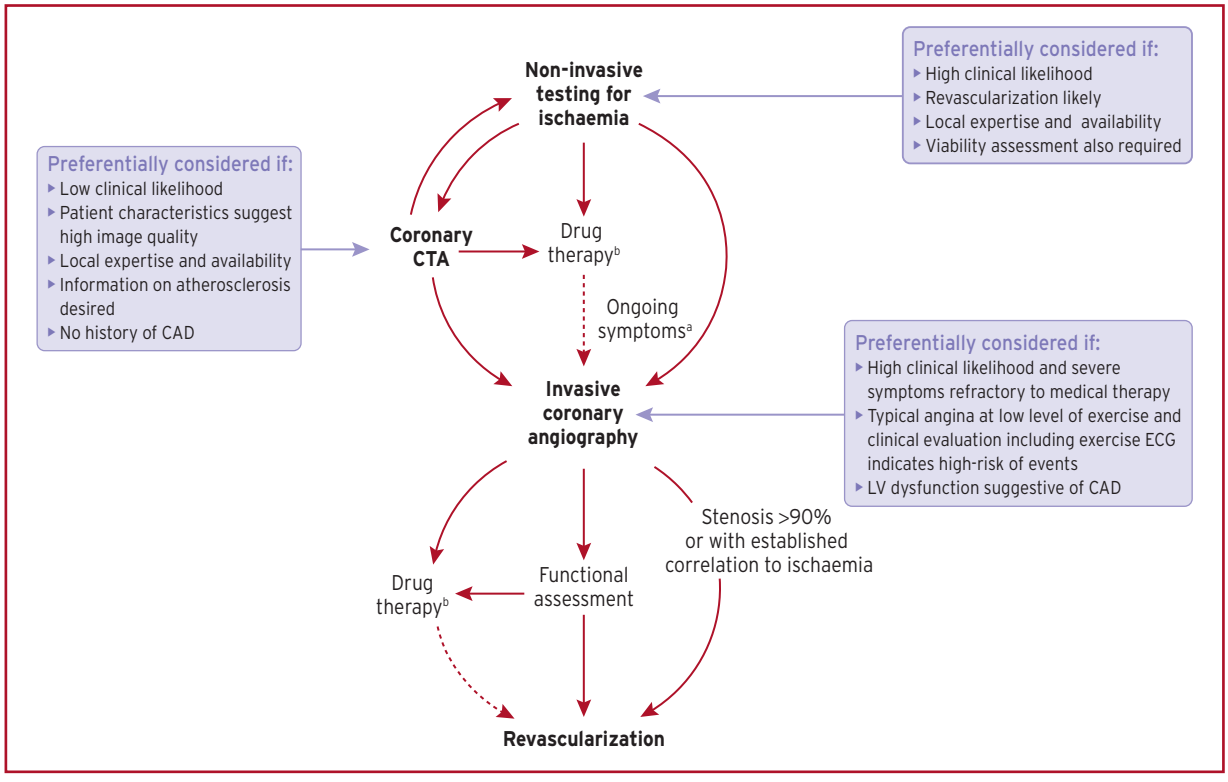

Figure 4 Main diagnostic pathways in symptomatic patients with suspected obstructive coronary artery disease. Depending on clinical conditions and the healthcare environment, patient workup can start with either of three options: non-invasive testing, coronary computed tomography angiography, or invasive coronary angiography. Through each pathway, both functional and anatomical information is gathered to inform an appropriate diagnostic and therapeutic strategy. Risk-factor modification should be considered in all patients. CAD = coronary artery disease; CTA = computed tomography angiography; ECG = electrocardiogram; LV = left ventricular. [a]Consider microvascular angina. [b]Antianginal medications and/or risk-factor modification.

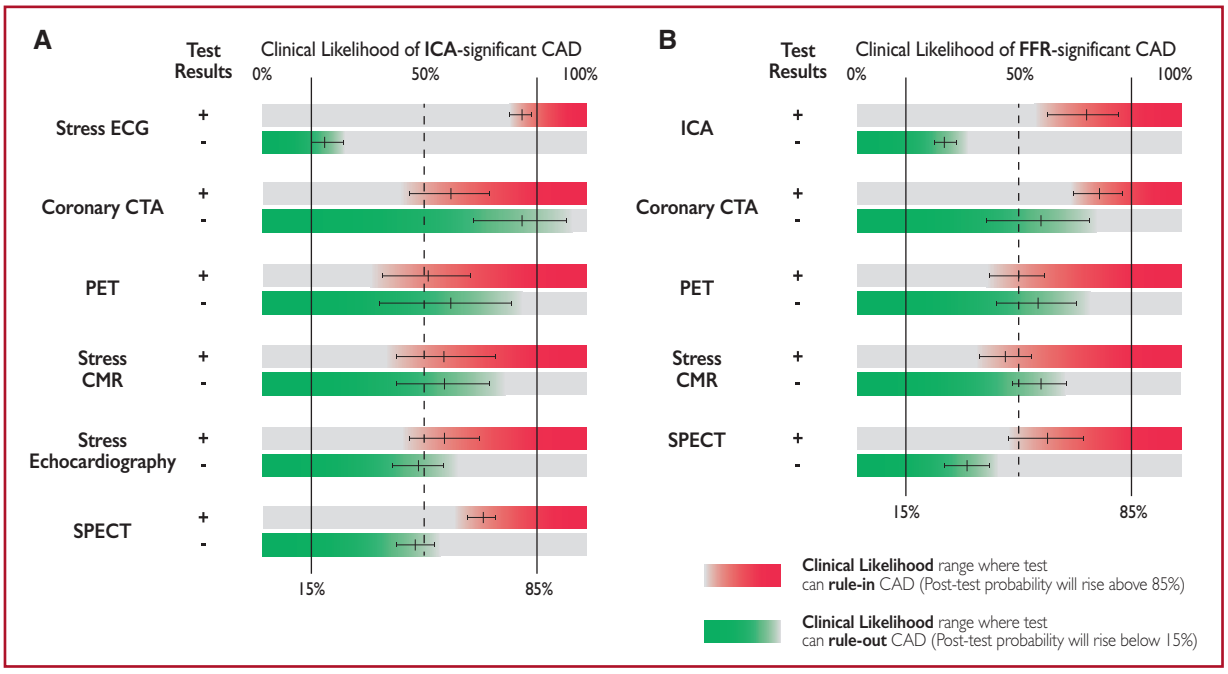

Figure 5 Ranges of clinical likelihood of coronary artery disease in which a given test can rule-in (red) or rule-out (green) obstructive coronary artery disease. (*A*) Reference standard is anatomical assessment using invasive coronary angiography. (*B*) Reference standard is functional assessment using fractional flow reserve. Note in (B) that the data with stress echocardiography and single-photon emission computed tomography are more limited than with the other techniques.[73] The crosshairs mark the mean values and their 95% confidence intervals. Figure adapted from Knuuti *et al.*[73] CAD = coronary artery disease; CMR = cardiac magnetic resonance; CTA = computed tomography angiography; ECG = electrocardiogram; FFR = fractional flow reserve; ICA = invasive coronary angiography; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

In addition to diagnostic accuracy and clinical likelihood, the selection of a non-invasive test depends on other patient characteristics, local expertise, and the availability of tests. Some diagnostic tests may perform better in some patients than others. For example, irregular heart rate and the presence of extensive coronary calcification are associated with increased likelihood of non-diagnostic image quality of coronary CTA, and it is not recommended in such patients.[85] Stress echocardiography or SPECT perfusion imaging can be combined with dynamic exercise testing, and may be preferred if additional information available from the exercise test, such as exercise tolerance or heart rate response to exercise, is considered important. Exercise ECG cannot be used for diagnostic purposes in the presence of ECG abnormalities that prevent the evaluation of ischaemia. Risks related to different diagnostic tests need to be weighed against the benefits to the individual.[87] For example, exposure to ionizing radiation associated with coronary CTA and nuclear perfusion imaging needs to be taken into account, especially in young individuals.[87] Similarly, contraindications to pharmacological stressors and contrast agents (iodine-based contrast agents and gadolinium-based chelates) need to be taken into account. When testing is used appropriately, the clinical benefit from accurate diagnosis and therapy exceeds the projected risks of testing itself.[87]

3.1.5.6 Invasive testing

For diagnostic purposes, ICA is only necessary in patients with suspected CAD in cases of inconclusive non-invasive testing or, exceptionally, in patients from particular professions, due to regulatory issues.[88] However, ICA may be indicated if non-invasive assessment suggests high event risk for determination of options for revascularization.[88]

In a patient with a high clinical likelihood of CAD, and symptoms unresponsive to medical therapy or with typical angina at a low level of exercise, and initial clinical evaluation indicates a high event risk, early ICA without previous non-invasive risk stratification may be reasonable to identify lesions potentially amenable to revascularization (*Figure 4*). Invasive functional assessment should complement ICA, especially in patients with coronary stenoses of 50 - 90% or multivessel disease, given the frequent mismatch between the angiographic and haemodynamic severities of coronary stenoses.[89–91] Systematic integration of ICA with FFR has been shown to result in changes to the management strategies of 30 - 50% of patients undergoing elective ICA.[92,93] Methods used to perform ICA have improved substantially, resulting in a reduction of complication rates with rapid ambulation. This is especially true for ICA performed via the radial artery.[94] The composite rate of major complications associated with routine femoral diagnostic catheterization—mainly bleeding requiring blood transfusions—is still 0.5–2%.[95] The composite rate of death, MI, or stroke is of the order of 0.1–0.2%.[96] ICA should not be performed in patients with angina who refuse invasive procedures, prefer to avoid revascularization, who are not candidates for percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), or in whom revascularization is not expected to improve functional status or quality of life. Intracoronary techniques for the diagnostic assessment of coronary anatomy are briefly mentioned in the Supplementary Data of this document.

Use of diagnostic imaging tests in the initial diagnostic management of symptomatic patients with suspected coronary artery disease

Recommendations	Class[a]	Level[b]
Non-invasive functional imaging for myocardial ischaemia[c] or coronary CTA is recommended as the initial test to diagnose CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone.[4,5,55,73,78–80]	I	B
It is recommended that selection of the initial non-invasive diagnostic test is done based on the clinical likelihood of CAD and other patient characteristics that influence test performance,[d] local expertise, and the availability of tests.	I	C
Functional imaging for myocardial ischaemia is recommended if coronary CTA has shown CAD of uncertain functional significance or is not diagnostic.[4,55,73]	I	B
Invasive coronary angiography is recommended as an alternative test to diagnose CAD in patients with a high clinical likelihood, severe symptoms refractory to medical therapy or typical angina at a low level of exercise, and clinical evaluation that indicates high event risk. Invasive functional assessment must be available and used to evaluate stenoses before revascularization, unless very high grade (>90% diameter stenosis).[71,72,74]	I	B
Invasive coronary angiography with the availability of invasive functional evaluation should be considered for confirmation of the diagnosis of CAD in patients with an uncertain diagnosis on non-invasive testing.[71,72]	IIa	B
Coronary CTA should be considered as an alternative to invasive angiography if another non-invasive test is equivocal or non-diagnostic.	IIa	C
Coronary CTA is not recommended when extensive coronary calcification, irregular heart rate, significant obesity, inability to cooperate with breath-hold commands, or any other conditions make obtaining good image quality unlikely.	III	C
Coronary calcium detection by CT is not recommended to identify individuals with obstructive CAD.	III	C

CAD = coronary artery disease; CT = computed tomography; CTA = computed tomography angiography.
[a]Class of recommendation.
[b]Level of evidence
[c]Stress echocardiography, stress cardiac magnetic resonance, single-photon emission CT, or positron emission tomography.
[d]Characteristics determining ability to exercise, likelihood of good image quality, expected radiation exposure, and risks or contraindications.

Use of exercise electrocardiogram in the initial diagnostic management of patients with suspected coronary artery disease

Recommendations	Class[a]	Level[b]
Exercise ECG is recommended for the assessment of exercise tolerance, symptoms, arrhythmias, BP response, and event risk in selected patients.[c]	I	C
Exercise ECG may be considered as an alternative test to rule-in and rule-out CAD when non-invasive imaging is not available.[73,83]	IIb	B
Exercise ECG may be considered in patients on treatment to evaluate control of symptoms and ischaemia.	IIb	C
Exercise ECG is not recommended for diagnostic purposes in patients with ≥0.1 mV ST-segment depression on resting ECG or who are being treated with digitalis.	III	C

BP = blood pressure; CAD = coronary artery disease; ECG = electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.
[c]When this information will have an impact on diagnostic strategy or management.

3.1.6 Step 6: Assessment of event risk

Assessment of event risk is recommended in every patient being evaluated for suspected CAD or with a newly diagnosed CAD, as it has major impacts on therapy decisions. The process of risk stratification serves to identify patients at high event risk who will benefit from revascularization beyond the amelioration of symptoms. Event risk stratification is usually based on the assessments used to make a diagnosis of CAD. All patients should undergo cardiovascular event risk stratification using clinical evaluation, the assessment of LV function by resting echocardiography, and, in the majority of cases, non-invasive assessment of ischaemia or coronary anatomy. Although the diagnostic value of an exercise ECG is limited,[73] the occurrence of ST-segment depression at a low workload combined with exertional symptoms (angina or dyspnoea), low exercise capacity, complex ventricular ectopy, or arrhythmias and abnormal BP response are markers of a high risk of cardiac mortality.[97–100] Patients with typical

Table 6 Definitions of high event risk for different test modalities in patients with established chronic coronary syndromes[a] [102–104]

Exercise ECG	Cardiovascular mortality >3% per year according to Duke Treadmill Score
SPECT or PET perfusion imaging	Area of ischaemia ≥10% of the left ventricle myocardium
Stress echocardiography	≥3 of 16 segments with stress-induced hypokinesia or akinesia
CMR	≥2 of 16 segments with stress perfusion defects or ≥3 dobutamine-induced dysfunctional segments
Coronary CTA or ICA	Three-vessel disease with proximal stenoses, LM disease, or proximal anterior descending disease
Invasive functional testing	FFR ≤0.8, iwFR ≤0.89

CTA = computed tomography angiography; CMR = cardiac magnetic resonance; ECG = electrocardiogram; FFR = fractional flow reserve; ICA = invasive coronary angiography; iwFR = instantaneous wave-free ration (instant flow reserve); LM = left main; PET = positron emission tomography; SPECT; single-photon emission computed tomography.
[a]For detailed explanations, refer to the Supplementary Data.

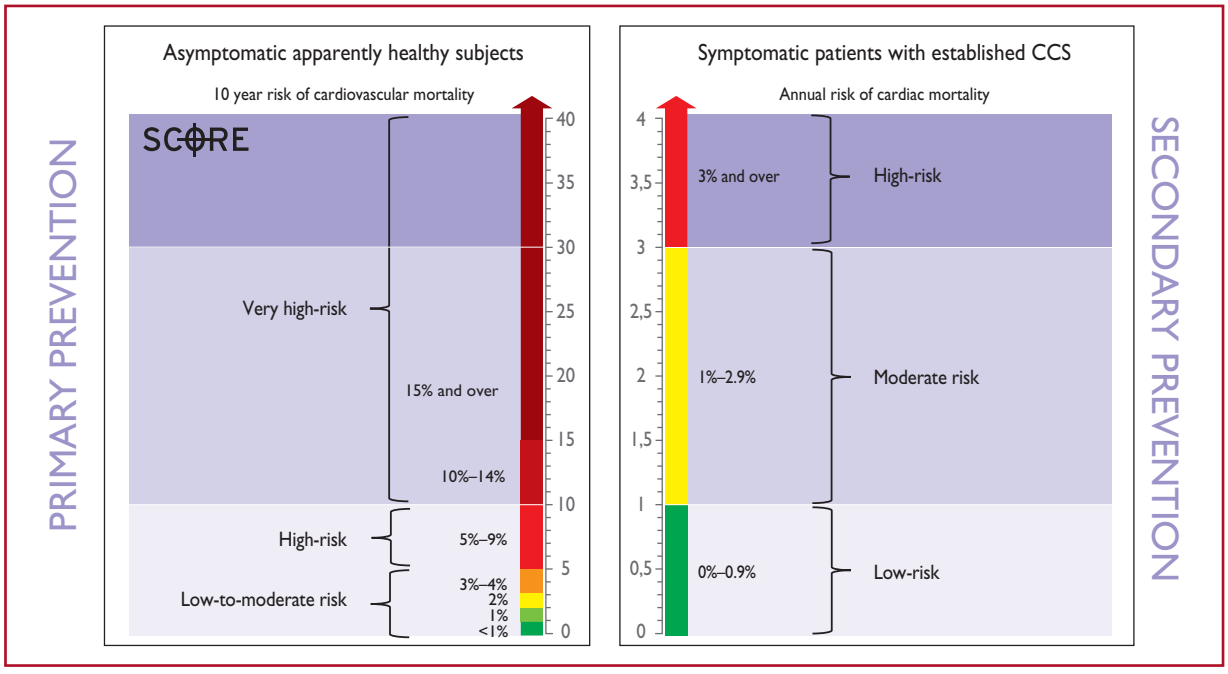

Figure 6 Comparison of risk assessments in asymptomatic apparently healthy subjects (primary prevention) and patients with established chronic coronary syndromes (secondary prevention). Note that in asymptomatic subjects (left panel), SCORE estimates 10 year cardiovascular mortality, while in symptomatic patients (right panel), annual cardiac mortality is estimated. CCS = chronic coronary syndromes; SCORE = Systematic COronary Risk Evaluation.

angina and LV systolic dysfunction in a pattern that indicates CAD are also at high risk of cardiac mortality.[101] ICA for risk stratification will only be required in a selected subgroup of patients and additional FFR may be required for event risk stratification as appropriate (*Figure 4*). Risk assessment in patients with HF and LV dysfunction, asymptomatic patients with known CAD, and patients with recurrent symptoms after previous coronary intervention is discussed in *sections 4* and *5*.

3.1.6.1 Definition of levels of risk

In patients with established CCS, the risk of annual cardiac mortality is used to describe the event risk. As in the previous version of the Guidelines,[60] high event risk is defined as a cardiac mortality rate >3% per year and low event risk as a cardiac mortality rate <1% per year. The definitions of high event risk based on findings of diagnostic tests in symptomatic patients or in patients with established CCS are shown in *Table 6*.

Notably, the level of risk is different from the risk assessment based on SCORE in asymptomatic individuals without diabetes who are apparently healthy (see *section 7*). SCORE defines 10 year cardiovascular mortality in asymptomatic subjects. Differences in these risk-assessment tools and the scales are illustrated in *Figure 6*. The findings of different test modalities that correspond to high event risk are presented in *Table 6* and are discussed in more detail in the Supplementary Data (sections 1.1 and 1.2).[102–104] For all non-invasive tests presented in *Table 6*, a normal test result is associated with a low event risk.[105]

Recommendations on risk assessment

Recommendations	Class[a]	Level[b]
Risk stratification is recommended based on clinical assessment and the result of the diagnostic test initially employed to diagnose CAD.[6,75,102,103]	I	B
Resting echocardiography is recommended to quantify LV function in all patients with suspected CAD.	I	C
Risk stratification, preferably using stress imaging or coronary CTA (if permitted by local expertise and availability), or alternatively exercise stress ECG (if significant exercise can be performed and the ECG is amenable to the identification of ischaemic changes), is recommended in patients with suspected or newly diagnosed CAD.[6,75,102,106]	I	B
In symptomatic patients with a high-risk clinical profile, ICA complemented by invasive physiological guidance (FFR) is recommended for cardiovascular risk stratification, particularly if the symptoms are responding inadequately to medical treatment and revascularization is considered for improvement of prognosis.[104,107]	I	A
In patients with mild or no symptoms, ICA complemented by invasive physiological guidance (FFR/iwFR) is recommended for patients on medical treatment, in whom non-invasive risk stratification indicates a high event risk and revascularization is considered for improvement of prognosis.[104,107]	I	A
ICA complemented by invasive physiological guidance (FFR) should be considered for risk-stratification purposes in patients with inconclusive or conflicting results from non-invasive testing.[74]	IIa	B
If coronary CTA is available for event risk stratification, additional stress imaging should be performed before the referral of a patient with few/no symptoms for ICA.[108,109]	IIa	B
Echocardiographic assessment of global longitudinal strain provides incremental information to LVEF and may be considered when LVEF is >35%.[110–114]	IIb	B
Intravascular ultrasound may be considered for the risk stratification of patients with intermediate LM stenosis.[115,116]	IIb	B
ICA is not recommended solely for risk stratification.	III	C

CAD = coronary artery disease; CTA = computed tomography angiography; ECG = electrocardiogram; FFR = fractional flow reserve; ICA = invasive coronary angiography; iwFR = instantaneous wave-free ratio; LM = left main; LV = left ventricular; LVEF = LV ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.

3.2 Lifestyle management

3.2.1 General management of patients with coronary artery disease

General management of CCS aims to reduce symptoms and improve prognosis through appropriate medications and interventions, and to control risk factors including lifestyle behaviours. Optimal medical therapy in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial included the promotion of medication adherence, behavioural counselling, and support for the managing lifestyle risk factors delivered by nurse case managers.[117] Achievement of optimal management may be best accomplished through a multidisciplinary team approach that can provide tailored and flexible support to patients.

Patient-reported outcome measures can provide relevant and systematic information about patients' symptoms, functioning, and concerns. Patient-reported outcome measures are increasingly being implemented sequentially in healthcare, and have been shown to improve clinical care and patient experiences, communication between providers and patients (including sensitive subjects), save time in consultations, and improve provider satisfaction.[118]

3.2.2 Lifestyle modification and control of risk factors

Implementing healthy lifestyle behaviours decreases the risk of subsequent cardiovascular events and mortality, and is additional to appropriate secondary prevention therapy. Lifestyle recommendations and interventions are described in more detail in the 2016 ESC Guidelines on CVD prevention in clinical practice.[15] Lifestyle factors are important and the implementation of healthy behaviours (including smoking cessation, recommended physical activity, a healthy diet, and maintaining a healthy weight; see *Table 7*) significantly decreases the risk of future cardiovascular events and death, even when controlling for evidence-based secondary prevention therapy and interventions.[119–122] Benefits are evident as early as 6 months after an index event.[119]

Primary care providers have an important role to play in prevention. The primary care arm of the EUROACTION cluster randomized trial demonstrated that a nurse-co-ordinated programme in primary care was more effective in helping patients achieve lifestyle and risk-factor goals than usual care.[123] Practice nurses in the Netherlands were found to be as effective as general practitioners in decreasing cardiovascular risk in another randomized study.[123]

3.2.2.1 Smoking

Smoking cessation improves the prognosis in patients with CCS, including a 36% risk reduction in mortality for those who quit.[124] Measures to promote smoking cessation include brief advice, counselling and behavioural interventions, and pharmacological therapy including nicotine replacement. Patients should also avoid passive smoking.

Brief advice, relative to no treatment, doubles the likelihood of smoking cessation in the short-term, but more intensive advice and support (behavioural interventions, telephone support, or self-help measures) is more effective than brief advice, especially if continued over 1 month.[125,126] All forms of nicotine-replacement therapy, bupropion, and varenicline are more effective in increasing smoking cessation than control, and combining behavioural and pharmacological approaches is effective and highly recommended.[125] A network meta-analysis of 63 clinical trials (including eight trials in CVD patients) found no increase in major adverse cardiovascular events linked to nicotine-replacement therapy, bupropion, or varenicline.[127] Nicotine-replacement therapy was associated with minor events such as arrhythmias and angina, and bupropion appeared to have a protective effect against major adverse cardiovascular events.[127] The use of e-cigarettes is considered to be a reduced-harm alternative to conventional cigarettes, but they are not harm-free. Newer devices can deliver higher nicotine contents, and e-cigarettes emit other constituents such as carbonyls and fine and ultrafine particulates.[128] Although previous systematic reviews have found very limited and inconsistent evidence that e-cigarettes (primarily first-generation devices) are useful in improve smoking cessation compared with placebo or nicotine-replacement therapy, a recent large clinical trial found e-cigarettes to be more effective than nicotine-replacement therapy in smoking cessation.[129–133] In this randomised trial of 886 smokers, those assigned to e-cigarettes had a sustained 1 year abstinence rate of 18% compared with 9.9% for nicotine-replacement therapy [relative risk, 1.83; 95% confidence interval (CI) 1.30 to 2.58; $P < 0.001$].[133]

In clinical encounters with smokers, clinicians should follow the 'Five As': ask about smoking, advise to quit, assess readiness to quit, assist with smoking cessation (pharmacological support and referral for behavioural counselling), and arrange follow-up (*Figure 7*).

Table 7 Lifestyle recommendations for patients with chronic coronary syndromes

Lifestyle factor	
Smoking cessation	Use pharmacological and behavioural strategies to help patients quit smoking. Avoid passive smoking.
Healthy diet	Diet high in vegetables, fruit, and wholegrains. Limit saturated fat to <10% of total intake. Limit alcohol to <100 g/week or 15 g/day.
Physical activity	30 - 60 min moderate physical activity most days, but even irregular activity is beneficial.
Healthy weight	Obtain and maintain a healthy weight (<25 kg/m^2), or reduce weight through recommended energy intake and increased physical activity.
Other	Take medications as prescribed. Sexual activity is low risk for stable patients not symptomatic at low-to-moderate activity levels.

Figure 7 The five As of smoking cessation.

Table 8 Healthy diet characteristics[134,137,141,142]

Characteristics
Increase consumption of fruits and vegetables (≥200 g each per day).
35–45 g of fibre per day, preferably from wholegrains.
Moderate consumption of nuts (30 g per day, unsalted).
1–2 servings of fish per week (one to be oily fish).
Limited lean meat, low-fat dairy products, and liquid vegetable oils.
Saturated fats to account for <10% of total energy intake; replace with polyunsaturated fats.
As little intake of trans unsaturated fats as possible, preferably no intake from processed food, and <1% of total energy intake.
≤5–6 g of salt per day.
If alcohol is consumed, limiting intake to ≤100 g/week or <15 g/day is recommended.
Avoid energy-dense foods such as sugar-sweetened soft drinks.

3.2.2.2 Diet and alcohol

Unhealthy diets are a leading contributor to CAD and its progression, and changes to healthy eating patterns in patients with CCS have resulted in a reduction in mortality and cardiovascular events[134] (recommended diet characteristics are detailed in *Table 8*).

A Mediterranean dietary pattern high in fruit, vegetables, legumes, fibre, polyunsaturated fats, nuts, and fish, avoiding or limiting refined carbohydrates, red meat, dairy, and saturated fat, is advocated.[135–138] Although light-to-moderate alcohol intake (1–2 drinks per day) does not increase risk of MI, levels >100 g per week were associated with higher all-cause and other CVD mortality in a large individual-data meta-analysis.[139] The Global Burden of Disease 1990–2016 analysis concluded that zero alcohol intake was the level at which risk for death and disability was minimized.[140]

3.2.2.3 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 (20 - 25 kg/m^2). Obesity was associated with a shorter overall lifespan, and overweight was associated with developing CVD at an earlier age.[143] Waist circumference is a marker of central obesity and is strongly associated with developing CVD and diabetes. Waist circumference ≤94 cm for men (<90 cm for South Asian and Asian men) and ≤80 cm for women is recommended.

In subjects with CAD, intentional weight loss is associated with a significantly lower risk of adverse clinical outcomes.[144] Although there has been much argument regarding the relative benefits of low-fat vs. low-carbohydrate diets, Gardner *et al.*[145] found similar weight loss and benefits in patients randomized to either healthy low-fat or low-carbohydrate diets. This finding held, regardless of patients' genotype patterns and baseline insulin secretion. Healthy diets with energy intake limited to the amount needed to obtain and maintain a healthy weight (BMI <25 kg/m^2), and increasing physical activity, are recommended for weight management.

3.2.2.4 Physical activity

Exercise has been referred to as a 'polypill' due to its numerous beneficial effects on cardiovascular risk factors and cardiovascular system physiology.[146,147] Exercise improves angina through enhanced oxygen delivery to the myocardium, and increasing exercise capacity is an independent predictor of increased survival among men and women with CCS, even among those with a regimen consistent with evidence-based management.[122,147,148]

Every 1 mL/kg/min increase in exercise peak oxygen consumption was associated with a 14–17% reduction of risk for cardiovascular and all-cause death in women and men.[122]

Physical activity recommendations for patients with CCS are 30–60 min of moderate-intensity aerobic activity ≥5 days per week.[147] Even irregular leisure-time physical activity decreases mortality risk among previously sedentary patients,[149] and increasing activity is associated with lower cardiovascular mortality.[150] Previously sedentary patients will need support to work up to 30–60 min most days, reassurance that exercise is beneficial, and education regarding what to do if angina occurs while being active. Resistance exercises maintain muscle mass, strength, and function and, with aerobic activity, have benefits regarding insulin sensitivity and control of lipids and BP.

3.2.2.5 Cardiac rehabilitation

Exercise-based cardiac rehabilitation has consistently demonstrated its effectiveness in reducing cardiovascular mortality and hospitalizations compared with no exercise controls in patients with CAD, and this benefit persists into the modern era.[151–153] Most patients participating in cardiac rehabilitation are referred following an acute MI or after revascularization, with 0 - 24% of patients found to be referred for CCS in 12 European countries.[154] Importantly, the benefits of cardiac rehabilitation occur across diagnostic categories.[151–153]

3.2.2.6 Psychosocial factors

Patients with heart disease have a two-fold increased risk of mood and anxiety disorders compared with people without heart disease.[155,156] Psychosocial stress, depression, and anxiety are associated with worse outcomes, and make it difficult for patients to make positive changes to their lifestyles or adhere to a therapeutic regimen.

The ESC Prevention Guidelines recommend assessment for psychosocial risk factors.[15] 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.[157–159]

3.2.2.7 Environmental factors

Air pollutants are estimated to be one of the 10 leading risk factors for global mortality. Exposure to air pollution increases risk of MI, as well as hospitalization and death from heart failure, stroke, and arrhythmia.[160] Patients with CCS should avoid heavily traffic-congested areas. Air purifiers with high-efficiency particulate air ('HEPA') filters reduce indoor pollution, and wearing N95 respirator face masks in heavily polluted areas has been shown to be protective.[160] Environmental noise also increases the risk of CVD.[161] Policies and regulations that reduce air pollution and environmental noise should be supported, and patients should be advised about these risks.

3.2.2.8 Sexual activity

Patients with CCS often worry about the cardiovascular risk associated with sexual activity and/or experience sexual dysfunction.[162] The risk of triggering sudden death or an acute MI is very low, especially when sexual activity is with a stable partner in a familiar environment without stress, or excessive intake of food or alcohol beforehand.[163,164] Although sexual activity transiently increases the risk of MI, it is the cause of <1% of acute MIs and <1–1.7% of sudden deaths occur during sexual activity.[164] The energy expenditure during sexual activity is generally low-to-moderate (3 - 5 metabolic equivalents) and climbing two flights of stairs is often used as an equivalent activity in terms of energy expended.[163,164] Regular physical activity decreases the risk of adverse events during sexual activity.[165] Sexual dysfunction in patients with CCS includes decreased libido and sexual activity, and a high prevalence of erectile dysfunction. Sexual dysfunction may be caused by underlying vascular conditions, psychosocial factors, specific medications, number of medications, and changes in relationships.[166] Thiazide diuretics and beta-blockers (except nebivolol) may negatively influence erectile function, but studies published since 2011 have not found a consistent relationship between most contemporary cardiovascular medications and erectile dysfunction.[162,164,165] Phosphodiesterase-5 inhibitors to treat erectile dysfunction are generally safe in CCS patients, but should not be used in those taking nitrates.[164] Healthcare providers should ask patients about sexual activity, and offer advice and counselling.

3.2.2.9 Adherence and sustainability

Adherence to lifestyle modifications and to medications is a challenge. A systematic review of epidemiological studies indicated that a substantial proportion of patients do not adhere to cardiovascular medications, and that 9% of cardiovascular events in Europe were attributable to poor adherence.[167] In older men with ischaemic heart disease, greater adherence to medication guidelines appears to be positively associated with better clinical outcomes, independent of other conditions.[168] Polypharmacy plays a negative role in adherence to treatment,[169] and complexity of drug regimen is associated with non-adherence and higher rates of hospitalizations.[170] Drug prescriptions should prioritize medications that have proved their benefit with the highest level of evidence and those for whom the amplitude of benefit is largest. Simplifying medication regimens may help, and there is some evidence of benefits of cognitive educational strategies, electronically monitored feedback, and support by nurse case managers. Medication reviews by primary care providers may be helpful in patients with multiple comorbidities to minimize the risk of adverse interactions and to simplify medication regimens.[117,171–173]

Promoting behaviour change and medication adherence should be part of each clinical encounter in primary care and specialist follow-up, emphasising its importance, referring for support when needed, and congratulating patients for their achievements. Long-term support (intensive in the first 6 months, then every 6 months for 3 years) in the GOSPEL (Global secondary prevention strategies to limit event recurrence after myocardial infarction) trial resulted in significant improvements in risk factors, and decreases in several clinical mortality and morbidity endpoints.[121] The Multicenter Lifestyle Demonstration Project showed that CCS patients could make intensive lifestyle changes and improve their risk factors and fitness, with changes sustained at 12 months.[174]

3.2.2.10 Influenza vaccination

An annual influenza vaccination can improve prevention of acute MI in patients with CCS,[175,176] change HF prognosis,[177] and decrease cardiovascular mortality in adults aged ≥65 years.[178–180] Therefore, annual influenza vaccination is recommended for patients with CAD, especially in the elderly.

Recommendations on lifestyle management

Recommendations	Class[a]	Level[b]
Improvement of lifestyle factors in addition to appropriate pharmacological management is recommended.[119–122,124,148–153]	I	A
Cognitive behavioural interventions are recommended to help individuals achieve a healthy lifestyle.[181–183]	I	A
Exercise-based cardiac rehabilitation is recommended as an effective means for patients with CCS to achieve a healthy lifestyle and manage risk factors.[151–153]	I	A
Involvement of multidisciplinary healthcare professionals (e.g. cardiologists, GPs, nurses, dieticians, physiotherapists, psychologists, and pharmacists) is recommended.[121,123,181,184]	I	A
Psychological interventions are recommended to improve symptoms of depression in patients with CCS.[126,157]	I	B
Annual influenza vaccination is recommended for patients with CCS, especially in the elderly.[175,176,178,179,185–187]	I	B

CCS = chronic coronary syndrome; GPs = general practitioners.
[a]Class of recommendation.
[b]Level of evidence.

3.3 Pharmacological management

The aims of pharmacological management of CCS patients are to reduce angina symptoms and exercise-induced ischaemia, and to prevent cardiovascular events.

Immediate relief of anginal symptoms, or the prevention of symptoms under circumstances likely to elicit angina, is usually obtained with rapidly acting formulations of nitroglycerin. Anti-ischaemic drugs—but also lifestyle changes, regular exercise training, patient education, and revascularization—all play a role in minimizing or eradicating symptoms over the long-term (long-term prevention).

Prevention of cardiovascular events targets MI and death associated with CAD, and focuses primarily on reducing the incidence of acute thrombotic events and the development of ventricular dysfunction. Strategies include pharmacological and lifestyle interventions, as detailed in the 2016 European Guidelines on CVD prevention in clinical practice.[15]

3.3.1 Anti-ischaemic drugs

3.3.1.1 General strategy

Optimal treatment can be defined as the treatment that satisfactorily controls symptoms and prevents cardiac events associated with CCS, with maximal patient adherence and minimal adverse events.[188–191] However, there is no universal definition of an optimal treatment in patients with CCS, and drug therapies must be adapted to each patient's characteristics and preferences.[192] Initial drug therapy usually consists of one or two antianginal drugs, as necessary, plus drugs for secondary prevention of CVD.[193] The initial choice of antianginal drug(s) depends on the expected tolerance related to the individual patient's profile and comorbidities, potential drug interactions with co-administered therapies, the patient's preferences after being informed of potential adverse effects, and drug availability. Whether combination therapy with two antianginal drugs [e.g. a beta-blocker and a calcium channel blocker (CCB)] is superior to monotherapy with any class of antianginal drug in reducing clinical events remains unclear.[194–197]

Beta-adrenergic blockers or CCBs are recommended as the first choice, although no RCT to date has compared this strategy to an alternative strategy using initial prescription of other anti-ischaemic drugs, or the combination of a beta-blocker and a CCB.[191,195] The results of a network meta-analysis of 46 studies and 71 treatment comparisons supported the initial combination of a beta-blocker and a CCB.[198] The same meta-analysis suggested that several second-line add-on anti-ischaemic drugs (long-acting nitrates, ranolazine, trimetazidine, and, to a lesser extent, ivabradine) may prove beneficial in combination with a beta-blocker or a CCB as first-line therapy, while no data were available for nicorandil. However, it should be noted that the study pooled RCTs using endpoints of nitrate use, angina frequency, time to angina or to ST-segment depression, and total exercise time, and no study or meta-analysis has yet assessed with sufficient power the influence of combining a beta-blocker or a CCB with a second-line anti-ischaemic drug on morbidity or mortality events.[198] Regardless of the initial strategy, response to initial antianginal therapy should be reassessed after 2–4 weeks of treatment initiation.

3.3.1.2 Available drugs

Anti-ischaemic drugs have proved benefits regarding symptoms associated with myocardial ischaemia but do not prevent cardiovascular events in most patients with CCS. *Supplementary Table 3* in the Supplementary Data summarizes the principal major side effects, contraindications, drug–drug interactions, and precautions relating to anti-ischaemic drugs. *Supplementary Table 2* summarizes the main mechanisms of action of anti-ischaemic drugs.

3.3.1.2.1 Nitrates.

Short-acting nitrates for acute effort angina

Sublingual and spray nitroglycerin formulations provide immediate relief of effort angina. Spray nitroglycerin acts more rapidly than sublingual nitroglycerin.[199] At the onset of angina symptoms, the patient should rest in a sitting position (standing promotes syncope, and lying down enhances venous return and preload) and take nitroglycerin (0.3–0.6 mg tablet sublingually and not swallowed, or 0.4 mg spray to the tongue and not swallowed or inhaled) every 5 min until the pain disappears, or a maximum of 1.2 mg has been taken within 15 min. During this time frame, if angina persists, immediate medical attention is needed. Nitroglycerin can be administered for prophylaxis before physical activities known to provoke angina. Isosorbide dinitrate (5 mg sublingually) has a slightly slower onset of action than nitroglycerin due to hepatic conversion to mononitrate. The effect of isosorbide dinitrate may last ≤1 h if the drug is taken sublingually or persist for several hours if the drug is taken by oral ingestion.

Long-acting nitrates for angina prophylaxis

Long-acting nitrate formulations (e.g. nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate) should be considered as second-line therapy for angina relief when initial therapy with a beta-blocker or non-dihydropyridine (non-DHP) CCB is contraindicated, poorly tolerated, or insufficient to control symptoms. In fact, there is a paucity of data comparing nitrates with beta-blockers or CCB from which to draw firm conclusions about their relative efficacies.[200] When taken over a prolonged period, long-acting nitrates provoke tolerance with loss of efficacy, which requires prescription of a nitrate-free or nitrate-low interval of ∼10–14 h.[201] Nitroglycerin can be administered orally or transdermally through slow-release patch systems. Bioavailability of isosorbide dinitrate depends on the interindividual variability in hepatic conversion and is generally lower than the bioavailability of isosorbide mononitrate (its active metabolite), which is 100% bioavailable. Titration of dose is essential with all formulations to obtain the maximal control of symptoms at a tolerable dose. Discontinuation should be tapered and not abrupt to avoid a rebound increase in angina.[202] The most common side effects are hypotension, headache, and flushing. Contraindications include hypertrophic obstructive cardiomyopathy, severe aortic valvular stenosis, and co-administration of phosphodiesterase inhibitors (e.g. sildenafil, tadalafil, or vardenafil) or riociguat.

3.3.1.2.2 Beta-blockers. The dose of beta-blockers should be adjusted to limit the heart rate to 55–60 b.p.m. (beats per minute) at rest.[203,204] Discontinuation should be tapered and not abrupt. Beta-blockers can be combined with DHP CCBs to reduce DHP-induced tachycardia, but with uncertain incremental clinical value.[205–208] Caution is warranted when a beta-blocker is combined with verapamil or diltiazem due to the potential for developing worsening of HF, excessive bradycardia, and/or atrioventricular block. Combination of a beta-blocker with a nitrate attenuates the reflex tachycardia of the latter. The principal side effects of beta-blockers are fatigue, depression, bradycardia, heart block, bronchospasm, peripheral

vasoconstriction, postural hypotension, impotence, and masking of hypoglycaemia symptoms.

In certain patients with recent MI and those with chronic HF with reduced ejection fraction, beta-blockers have been associated with a significant reduction in mortality and/or cardiovascular events,[209–215] but the protective benefit in patients with CAD without prior MI or HF is less well established and lacks placebo-controlled trials.[216] A retrospective analysis of 21 860 matched patients from the REACH (REduction of Atherothrombosis for Continued Health) Registry showed no reduction in cardiovascular mortality with beta-blockers in patients with either CAD with risk factors only, known prior MI, or known CAD without MI.[217] In a retrospective national registry of 755 215 patients aged ≥65 years with a history of CAD without prior MI or HF with reduced ejection fraction undergoing elective PCI, beta-blocker use at discharge was not associated with any reduction in cardiovascular morbidity or mortality at 30 day and 3 year follow-up.[218] However, in patients with or without previous MI undergoing CABG, beta-blockers were associated with lower risk of long-term mortality and adverse cardiovascular events.[219] Other observational studies and meta-analyses have questioned the benefit of long-term (>1 year) beta-blocker therapy in patients with a previous MI.[216,220–224] This is still a matter for debate,[225] and uncertainties remain on the comparative role of beta-blockers and angiotensin-converting enzyme (ACE) inhibitors.

3.3.1.2.3 Calcium channel blockers. While CCBs improve symptoms and myocardial ischaemia, they have not been shown to reduce major morbidity endpoints or mortality in patients with CCS.[192,226–228]

Non-dihydropyridine agents (heart rate-lowering calcium channel blockers)

Verapamil. Verapamil has a large range of approved indications, including all varieties of angina (effort, vasospastic, and unstable), supraventricular tachycardias, and hypertension. Indirect evidence suggests good safety but with risks of heart block, bradycardia, and HF. Compared with metoprolol, the antianginal activity was similar.[229] Compared with atenonol in hypertension with CAD, verapamil is associated with fewer cases of diabetes, fewer anginal attacks,[230] and less psychological depression.[231] Beta-blockade combined with verapamil is not advised (due to risk of heart block).

Diltiazem. Diltiazem, with its low-side effect profile, has advantages compared with verapamil in the treatment of effort angina. Like verapamil, it acts by peripheral vasodilation, relief of exercise-induced coronary constriction, a modest negative inotropic effect, and sinus node inhibition. There have been no outcome studies comparing diltiazem and verapamil.

In some selected patients, non-DHP agents may be combined with beta-blockers for the treatment of angina. However, on such occasions they must be used under close monitoring of patients' tolerance regarding excessive bradycardia or signs of HF. Use of non-DHP CCBs in patients with LV dysfunction is not advised.

Dihydropyridine agents

Long-acting nifedipine. This agent is a powerful arterial vasodilator with few serious side effects. Long-acting nifedipine has been especially well tested in hypertensive anginal patients when added to beta-blockade.[232] In the large placebo-controlled ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system) trial, addition of long-acting nifedipine [60 mg o.d. (once a day)] to conventional treatment of angina had no effect on major cardiovascular event-free survival. Long-acting nifedipine proved to be safe, and reduced the need for coronary angiography and cardiovascular interventions.[232] Relative contraindications to nifedipine are few (severe aortic stenosis, hypertrophic obstructive cardiomyopathy, or HF), and careful combination with beta-blockade is usually feasible and desirable. Vasodilatory side effects include headache and ankle oedema.

Amlodipine. The very long half-life of amlodipine and its good tolerability make it an effective once-a-day antianginal and antihypertensive agent, setting it apart from drugs that are taken either twice or three times daily. Side effects are few, mainly ankle oedema. In patients with CCS and normal BP (~75% receiving a beta-blocker), amlodipine 10 mg/day reduced coronary revascularizations and hospitalizations for angina in a 24 month trial.[233] Exercise-induced ischaemia is more effectively reduced by amlodipine, 5 mg titrated to 10 mg/day, than by the beta-blocker atenolol, 50 mg/day, and their combination is even better.[234] However, the CCB–beta-blocker combination is often underused, even in some studies reporting 'optimally treated' stable effort angina.

3.3.1.2.4 Ivabradine. Ivabradine has been reported to be non-inferior to atenolol or amlodipine in the treatment of angina and ischaemia in patients with CCS.[235,236] Adding ivabradine 7.5 mg b.i.d. [bis in die (twice a day)] to atenolol therapy gave better control of heart rate and anginal symptoms.[237] In 10 917 patients with limiting previous angina enrolled in the morbidity–mortality evaluation of the BEAUTIFUL (I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease and Left Ventricular Dysfunction) trial, ivabradine did not reduce the composite primary endpoint of cardiovascular death, hospitalization with MI, or HF.[238] Also, in the SIGNIFY (Study Assessing the Morbidity–Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease) study, consisting of 19 102 patients with CAD without clinical HF and a heart rate ≥70 b.p.m., there was no significant difference between the ivabradine group and the placebo group in the incidence of the primary composite endpoint of death from cardiovascular causes or non-fatal MI.[239] Ivabradine was associated with an increase in the incidence of the primary endpoint among 12 049 patients with activity-limiting angina but not among those without activity-limiting angina (P=0.02 for interaction). In 2014, the European Medicines Agency issued recommendations to reduce the risk of bradycardia and placed ivabradine under additional monitoring.[240] In aggregate, these results support the use of ivabradine as a second-line drug in patients with CCS.

3.3.1.2.5 Nicorandil. Nicorandil is a nitrate derivative of nicotinamide, with antianginal effects similar to those of nitrates or beta-blockers.[241–244] Side effects include nausea, vomiting, and potentially severe oral, intestinal, and mucosal ulcerations.[245]

In the placebo-controlled IONA (Impact Of Nicorandil in Angina) trial (n = 5126), nicorandil significantly reduced the composite of coronary heart disease (CHD) death, non-fatal MI, or unplanned hospital admission for suspected anginal symptoms in patients with CCS, but there was no effect on death from ischaemic heart disease or non-

fatal MI.[246] These results support the use of nicorandil as a second-line drug in patients with CCS.

3.3.1.2.6 Ranolazine. Ranolazine is a selective inhibitor of the late inward sodium current. Side effects include dizziness, nausea, and constipation. In addition, ranolazine increases QTc, and should therefore be used carefully in patients with QT prolongation or on QT-prolonging drugs.

In a placebo-controlled trial of 6560 patients with non-ST-segment elevation ACS, the addition of ranolazine to standard treatment did not prove effective in reducing the primary efficacy endpoint of cardiovascular death, MI, or recurrent ischaemia.[247] However, in the relatively large subgroup of patients with chronic angina (n = 3565), significant reductions in recurrent ischaemia, worsening angina, and intensification of antianginal therapy were observed.[248] In another placebo-controlled trial of patients with diabetes and CAD receiving one or two antianginal drugs, ranolazine reduced angina and sublingual nitroglycerin use with good tolerability.[249] In the RIVER-PCI (Ranolazine for Incomplete Vessel Revascularization Post-Percutaneous Coronary Intervention) trial, ranolazine did not reduce the composite of ischaemia-driven revascularization or hospitalization without revascularization in 2651 patients with a history of chronic angina and incomplete revascularization after PCI, including those with and without PCI for a CAD indication, nor did it reduce angina symptoms at 1 year.[250,251]

These results support the use of ranolazine as a second-line drug in CCS patients with refractory angina despite commonly used antianginal agents such as beta-blockers, CCBs, and/or long-acting nitrates. Conversely, there is a lack of evidence to support the use of ranolazine in patients with CCS following PCI with incomplete revascularization.

3.3.1.2.7 Trimetazidine. Trimetazidine appears to have a haemodynamically neutral side effect profile.[252] Trimetazidine (35 mg b.i.d.) added to beta-blockade (atenolol) improved effort-induced myocardial ischaemia, as reviewed by the European Medicines Agency in June 2012.[253,254] It remains contraindicated in Parkinson's disease and motion disorders, such as tremor (shaking), muscle rigidity, walking disorders, and restless leg syndrome. A 2014 meta-analysis of 13, mostly Chinese, studies consisting of 1628 patients showed that treatment with trimetazidine on top of other antianginal drugs was associated with a smaller weekly mean number of angina attacks, lower weekly

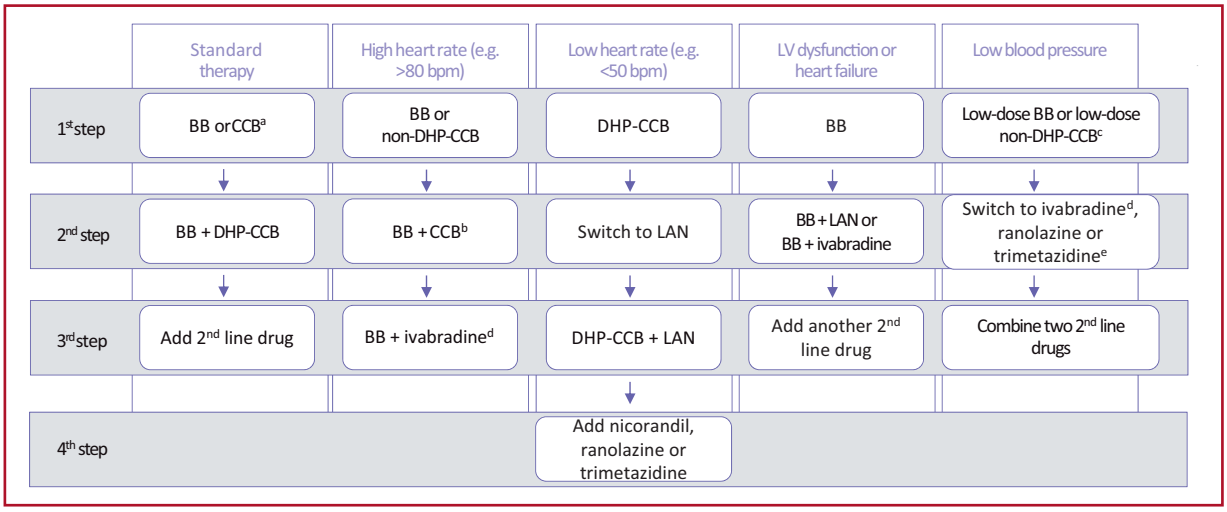

Figure 8 Suggested stepwise strategy for long term anti-ischaemic drug therapy in patients with chronic coronary syndromes and specific baseline characteristics. The proposed stepwise approach must be adapted to each patient's characteristics and preferences. Given the limited evidence on various combinations of drugs in different clinical conditions, the proposed options are only indicative of potential combinations and do not represent formal recommendations. BB = beta-blocker; bpm = beats per minute; CCB = [any class of] calcium channel blocker; DHP-CCB = dihydropyridine calcium channel blocker; HF = heart failure; LAN = long-acting nitrate; LV = left ventricular; non-DHP-CCB = non-dihydropyridine calcium channel blocker. [a]Combination of a BB with a DHP-CCB should be considered as first step; combination of a BB or a CCB with a second-line drug may be considered as a first step; [b]The combination of a BB and non-DHP-CCB should initially use low doses of each drug under close monitoring of tolerance, particularly heart rate and blood pressure; [c]Low-dose BB or low-dose non-DHP-CCB should be used under close monitoring of tolerance, particularly heart rate and blood pressure; [d]Ivabradine should not be combined with non-DHP-CCB; [e]Consider adding the drug chosen at step 2 to the drug tested at step 1 if blood pressure remains unchanged.

nitroglycerin use, longer time to 1 mm ST-segment depression, higher total work, and longer exercise duration at peak exercise than treatment with the other antianginal drugs for stable angina pectoris.[255] These results support the use of trimetazidine as a second-line drug in patients with CCS whose symptoms are not adequately controlled by, or who are intolerant to, other medicines for angina pectoris.

3.3.1.2.8 Allopurinol. In 2010, a randomized crossover study of 65 patients with CAD showed that allopurinol 600 mg/day increased times to ST-segment depression and to angina.[256] An observational study of 29 298 episodes of incident allopurinol use found an association of allopurinol use with a reduction in the risk of incident MI in the elderly, particularly when used for >2 years.[257] However, the role of allopurinol in reducing clinical events in CVD remains unclear.[258]

A stepwise strategy for anti-ischaemic drug therapy in CCS is proposed, depending on some baseline patient characteristics (*Figure 8*). Incomplete responses or poor tolerance at each step justify moving to the next step. The strategy must be adapted to each patient's characteristics and preferences, and does not necessarily follow the steps indicated in the figure.

3.3.1.3 Patients with low blood pressure

In patients with low BP, it is recommended to start antianginal drugs at very low doses, with preferential use of drugs with no or limited effects on BP. A low-dose beta-blocker or low-dose non-DHP-CCB can be tested first under close monitoring of tolerance. Ivabradine (in patients with sinus rhythm), ranolazine, or trimetazidine can also be used.

3.3.1.4 Patients with low heart rate

Increased heart rate correlates linearly with cardiovascular events, and the benefit of heart-rate reduction as a treatment goal in subgroups of CCS patients has been demonstrated using various drugs.[203,259–261] However, in patients with baseline bradycardia (e.g. heart rate <60 b.p.m.) heart rate-lowering drugs (beta-blockers, ivabradine, and heart-rate lowering CCBs) should be avoided or used with caution, and—if needed—started at very low doses. Antianginal drugs without heart rate-lowering effects should preferably be given.

Recommendations on anti-ischaemic drugs in patients with chronic coronary syndromes

Recommendations	Class[a]	Level[b]
General considerations		
Medical treatment of symptomatic patients requires one or more drug(s) for angina/ischaemia relief in association with drug(s) for event prevention.	I	C
It is recommended that patients are educated about the disease, risk factors, and treatment strategy.	I	C
Timely review of the patient's response to medical therapies (e.g. 2–4 weeks after drug initiation) is recommended.[262]	I	C
Angina/ischaemia[c] relief		
Short-acting nitrates are recommended for immediate relief of effort angina.[195,263]	I	B
First-line treatment is indicated with beta-blockers and/or CCBs to control heart rate and symptoms.[205,264]	I	A
If angina symptoms are not successfully controlled on a beta-blocker or a CCB, the combination of a beta-blocker with a DHP-CCB should be considered.	IIa	C
Initial first-line treatment with the combination of a beta-blocker and a DHP-CCB should be considered.[194,198,264]	IIa	B
Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-CCB is contraindicated, poorly tolerated, or inadequate to control angina symptoms.[200,201]	IIa	B
When long-acting nitrates are prescribed, a nitrate-free or low-nitrate interval should be considered to reduce tolerance.[201]	IIa	B
Nicorandil,[241–244,246] ranolazine,[248,265] ivabradine,[235–237] or trimetazidine[252,255] 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
In subjects with baseline low heart rate and low BP, ranolazine or trimetazidine may be considered as a first-line drug to reduce angina frequency and improve exercise tolerance.	IIb	C
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, BP, and tolerance.[198]	IIb	B
Nitrates are not recommended in patients with hypertrophic obstructive cardiomyopathy[266] or co-administration of phosphodiesterase inhibitors.[267]	III	B

BP = blood pressure; CCB = calcium channel blocker; CCS = chronic coronary syndromes; DHP-CCB = dihydropyridine calcium channel blocker.
[a]Class of recommendation.
[b]Level of evidence.
[c]No demonstration of benefit on prognosis.

3.3.2 Event prevention

3.3.2.1 Antiplatelet drugs

Platelet activation and aggregation is the driver for symptomatic coronary thrombosis, forming the basis for the use of antiplatelet drugs in patients with CCS in view of a favourable balance between the prevention of ischaemic events and increased risk of bleeding. Dual antiplatelet therapy (DAPT) with aspirin and an oral $P2Y_{12}$ inhibitor is the mainstay of antithrombotic therapy after MI and/or PCI.

3.3.2.1.1 Low-dose aspirin. Aspirin acts via irreversible inhibition of platelet cyclooxygenase-1 and thus thromboxane production, which is normally complete with chronic dosing ≥75 mg/day. The gastrointestinal side effects of aspirin increase at higher doses, and current evidence supports a daily dose of 75–100 mg for the prevention of ischaemic events in CAD patients with or without a history of MI.[268–270] As cyclooxygenase-1 inhibition by aspirin is consistent and predictable in adherent patients, no platelet function testing is required to monitor individual response.[271] Although other non-selective non-steroidal anti-inflammatory drugs, such as ibuprofen, reversibly inhibit cyclooxygenase-1, their adverse effects on cardiovascular risk indicate that they cannot be recommended as an alternative treatment in patients with aspirin intolerance.[272]

3.3.2.1.2 Oral $P2Y_{12}$ inhibitors. $P2Y_{12}$ inhibitors block the platelet $P2Y_{12}$ receptor, which plays a key role in platelet activation and the amplification of arterial thrombus formation. Clopidogrel and prasugrel are thienopyridine prodrugs that irreversibly block $P2Y_{12}$ via active metabolites. Ticagrelor is a reversibly-binding $P2Y_{12}$ inhibitor that does not require metabolic activation.

The CAPRIE (Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events) trial showed an overall slight benefit of clopidogrel compared with aspirin, with a similar safety profile, in preventing cardiovascular events in patients with previous MI, previous stroke, or PAD.[273] Subgroup analysis suggested greater benefit of clopidogrel in patients with PAD. Despite its lesser antiplatelet efficacy, clopidogrel demonstrated equivalent efficacy to ticagrelor in patients with PAD.[274] Clopidogrel is limited by variable pharmacodynamic effects related to variable efficiency of conversion to its active metabolite, partly associated with loss-of-function variants in the *CYP2C19* gene, leading to a lack of efficacy in some patients.[271] Drugs that inhibit CYP2C19, such as omeprazole, may reduce the response to clopidogrel.[275]

Prasugrel has more rapid, more predictable, and, on average, greater antiplatelet effect compared with clopidogrel, and is not susceptible to drug interactions or the effect of *CYP2C19* loss-of-function variants. Prasugrel has greater efficacy than clopidogrel in aspirin-treated patients with ACS undergoing PCI, but not in medically-managed patients with ACS.[276,277] Prasugrel has been associated with more non-fatal and fatal bleeding events than clopidogrel in ACS patients undergoing PCI, leading to apparent harm in those with a history of ischaemic stroke, and a lack of apparent benefit in those aged >75 years or with body weight <60 kg.[276]

Ticagrelor has the most predictable and consistently high level of $P2Y_{12}$ inhibition during maintenance therapy in adherent patients,[219] and also has more rapid onset, as well as more rapid and predictable offset of action compared with clopidogrel.[278–280] Ticagrelor as monotherapy appears to have similar efficacy and safety to aspirin monotherapy in patients with previous PCI.[281] Ticagrelor, with a 180 mg loading dose followed by 90 mg b.i.d., achieved greater reduction of ischaemic events compared with clopidogrel in aspirin-treated ACS patients, regardless of revascularization strategy, at the expense of more non-fatal bleeding.[282,283] Ticagrelor at doses of 90 or 60 mg b.i.d. reduced the 3 year combined incidence of MI, stroke, or cardiovascular death compared with placebo in stable aspirin-treated patients with a history of MI 1–3 years previously.[284] Both ticagrelor doses increased non-fatal but not fatal bleeding. The equivalent efficacies and similar safeties of the two ticagrelor doses were explained by similar levels of platelet inhibition.[285] Ticagrelor may cause dyspnoea, which is often transient and most often mild and tolerable, but occasionally necessitates switching to a thienopyridine.[286,287] Ticagrelor is metabolized via *CYP3A*, and consequently should not be used with strong CYP3A inhibitors or inducers.

The optimal timing of initiation of $P2Y_{12}$ inhibition before coronary angiography and possible PCI in patients with CCS is uncertain, but increasing use of a radial artery approach and clinical experience has allowed consideration of clopidogrel pre-treatment in patients who have a high chance of requiring PCI.[284] Limited pharmacodynamic studies support the unlicensed use of prasugrel or ticagrelor in stable patients undergoing elective PCI who have a high risk of stent thrombosis, but the safety/efficacy balance of this approach, compared with clopidogrel, has not been established.[288]

3.3.2.1.3 Duration of dual antiplatelet therapy. After PCI for stable angina, 6 months of DAPT achieves the optimum balance of efficacy and safety in most patients.[284] Premature discontinuation of a $P2Y_{12}$ inhibitor is associated with an increased risk of stent thrombosis and is discouraged.[284] However, a shorter duration of DAPT may be considered in those at high risk of life-threatening bleeding in view of the very low risk of stent thrombosis after 1–3 months.[284] On the basis of phase III trials, 12 months is the recommended default duration of DAPT after ACS, but shorter duration may again be considered in those at high bleeding risk.[11,284] A DAPT study of patients undergoing PCI showed that extended therapy beyond 12 months with clopidogrel or prasugrel reduced ischaemic events and stent thrombosis, but without mortality benefit and at the expense of increased bleeding.[289] A greater benefit of extended clopidogrel or prasugrel was seen in patients who were treated for MI.[290]

The 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 54) trial demonstrated that long-term therapy with ticagrelor 60 or 90 mg b.i.d., commenced in stable patients ≥1 year after MI, reduced ischaemic events at the expense of more non-fatal bleeding.[284] The 60 mg dose appeared better tolerated and is approved in many countries for this indication. Subgroup analysis demonstrated greater absolute reductions in ischaemic events with long-term ticagrelor (60 mg b.i.d.) in higher-risk post-MI patients with diabetes, PAD, or multivessel CAD.[291–293]

3.3.2.2 Anticoagulant drugs in sinus rhythm

Anticoagulant drugs inhibit the action and/or formation of thrombin, which plays a pivotal role in both coagulation and platelet activation. Consequently, anticoagulants have been shown to reduce the risk of arterial thrombotic events. The superior efficacy and safety of DAPT,

compared with aspirin and anticoagulation, in preventing stent thrombosis led to the latter strategy being abandoned in favour of DAPT following PCI.[284] Combination of antiplatelet therapy and standard anticoagulant doses of warfarin or apixaban for secondary prevention after ACS was associated with an unfavourable balance of efficacy and bleeding.[294,295] However, recently reported studies have renewed interest in combining lower anticoagulant doses with antiplatelet therapy.

3.3.2.2.1 Low-dose rivaroxaban. Rivaroxaban is a factor Xa inhibitor that has been studied at a low dose of 2.5 mg b.i.d. in several populations of patients in sinus rhythm, this dose being one-quarter of the standard dose used for anticoagulation in patients with AF. Rivaroxaban 2.5 mg b.i.d., compared with placebo, reduced the composite of MI, stroke, or cardiovascular death in stabilized patients treated predominantly with aspirin and clopidogrel following ACS, at the expense of increased bleeding but with evidence of a reduction in cardiovascular death.[296] Subsequently, in the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial, the same regimen in combination with aspirin was compared with aspirin alone, as well as rivaroxaban 5 mg b.i.d. alone, in patients with CCS or PAD, and showed reduced ischaemic events at the expense of increased risk of predominantly non-fatal bleeding.[297] Of note, the pre-specified significance thresholds for cardiovascular mortality and all-cause mortality were not met. Greater absolute risk reductions were seen in higher-risk patients with diabetes, PAD, or moderate chronic kidney disease (CKD), as well as current smokers. In GEMINI-ACS (A Study to Compare the Safety of Rivaroxaban Versus Acetylsalicylic Acid in Addition to Either Clopidogrel or Ticagrelor Therapy in Participants With Acute Coronary Syndrome), rivaroxaban 2.5 mg b.i.d. was compared with aspirin in patients treated with a $P2Y_{12}$ inhibitor who were stable following PCI. The results suggested similar safety of rivaroxaban to aspirin in this setting, but larger studies are required to substantiate this finding.[298] In addition, the safety of performing PCI without aspirin pre-treatment is unknown.

3.3.2.3 Anticoagulant drugs in atrial fibrillation

Anticoagulant therapy is recommended in patients with AF and CCS for reduction of ischaemic stroke and other ischaemic events. Anticoagulants in AF patients have demonstrated superiority over aspirin monotherapy or clopidogrel-based DAPT for stroke prevention, and are therefore recommended for this indication.[299] When oral anticoagulation is initiated in a patient with AF who is eligible for a non-vitamin K antagonist oral anticoagulant (NOAC; apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a vitamin K antagonist (VKA).[299]

3.3.2.3.1 Combination anticoagulant and antiplatelet therapy following percutaneous coronary intervention for patients with atrial fibrillation or another indication for oral anticoagulation. No studies to date have specifically focused on CCS patients with AF undergoing PCI and clinical decisions must be based on clinical trials that have included a large proportion of patients with ACS. For peri-procedural management, it is recommended that interruption of VKA is avoided, if feasible, whereas it is recommended that NOAC therapy is stopped for 12–48 h before elective PCI, depending on renal function and the particular NOAC regimen.[300] Radial artery access is preferred along with intraprocedural unfractionated heparin either at a standard dose (70–100 U/kg) or, in those with uninterrupted VKA, at a lower dose of 30–50 U/kg.[300] Pre-treatment with aspirin 75–100 mg daily is recommended, and clopidogrel (300–600 mg loading dose if not on long-term maintenance therapy) is recommended in preference to prasugrel or ticagrelor.[300] VKA-treated patients receiving aspirin and clopidogrel post-PCI should have a target international normalized ratio in the range of 2.0–2.5, aiming for high time in therapeutic range (>70%).[300] Subsequent to post-PCI trials of different antithrombotic regimens considered in previous Guidelines,[88,284] the AUGUSTUS trial (An Open-label, 2×2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention) showed, firstly, that apixaban 5 mg b.i.d. (i.e. the licensed dose for thromboprophylaxis in AF) was associated with significantly less major or clinically relevant non-major bleeding than VKA; and, secondly, that aspirin, compared with placebo, was associated with significantly more bleeding, with the safest combination being apixaban and placebo in addition to $P2Y_{12}$ inhibitor (predominantly clopidogrel).[301] However, there were numerically, but not statistically significantly, more stent thrombosis events with placebo than with aspirin, and the trial was not powered to assess differences in these events between groups.[301] Consequently, when concerns about thrombotic risk prevail over concerns about bleeding risk, ≥1 month of triple therapy [oral anticoagulant (OAC), aspirin, and clopidogrel] is recommended to cover the period when the risk of stent thrombosis is presumed to exceed the risk of bleeding.[300,301] There is currently limited evidence to support the use of OACs with ticagrelor or prasugrel as dual therapy after PCI as an alternative to triple therapy.[300,301]

3.3.2.3.2 Long-term combination therapy in patients with atrial fibrillation or another indication for anticoagulation. OAC monotherapy is generally recommended 6–12 months after PCI in patients with AF, as there is a lack of specific data supporting long-term treatment with an OAC and a single antiplatelet agent; however, in highly selected cases with high ischaemic risk, dual therapy with an OAC and aspirin or clopidogrel may be considered.[300]

3.3.2.4 Proton pump inhibitors

Proton pump inhibitors reduce the risk of gastrointestinal bleeding in patients treated with antiplatelet drugs and may be a useful adjunctive treatment for improving safety.[275] Long-term proton pump inhibitor use is associated with hypomagnesaemia, but the role of monitoring serum magnesium levels is uncertain. Proton pump inhibitors that inhibit *CYP2C19*, particularly omeprazole and esomeprazole, may reduce the pharmacodynamic response to clopidogrel. Although this has not been shown to affect the risk of ischaemic events or stent thrombosis, co-administration of omeprazole or esomeprazole with clopidogrel is generally not recommended.

3.3.2.5 Cardiac surgery and antithrombotic therapy

Aspirin should normally be continued in patients with CCS undergoing elective cardiac surgery, and other antithrombotic drugs stopped at intervals according to their duration of action and

indication (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 dose and renal function). Reloading of aspirin after CABG surgery may improve graft patency.[302] The role of DAPT or dual therapy with aspirin and rivaroxaban after CABG surgery is uncertain as large prospective studies are lacking. However, RCT results have suggested higher graft patency rates with DAPT compared with aspirin monotherapy.[284,303,304]

3.3.2.6 Non-cardiac surgery and antithrombotic therapy

Non-cardiac surgery is associated with an increased risk of MI. Following PCI, whenever possible, it is recommended to postpone elective surgery until the recommended course of DAPT has been completed. Usually, this will mean delaying surgery until 6 months after PCI, but surgery between 3–6 months may be considered by a multidisciplinary team, including an interventional cardiologist, if clinically indicated. In most types of surgery, aspirin should be continued as the benefit outweighs the bleeding risk, but this may not be appropriate for procedures associated with extremely high bleeding risk (intracranial procedures, transurethral prostatectomy, intraocular procedures, etc.).[284] The COMPASS study included CCS patients with a history of peripheral revascularization procedures, and demonstrated benefits of aspirin and rivaroxaban 2.5 mg b.i.d. compared with aspirin alone, including reductions in major adverse limb events and mortality, suggesting the need to risk-stratify patients after non-cardiac vascular surgery for atherosclerotic disease.[305,306]

Recommendations for event prevention I

Recommendations	Class[a]	Level[b]
Antithrombotic therapy in patients with CCS and in sinus rhythm		
Aspirin 75–100 mg daily is recommended in patients with a previous MI or revascularization.[270]	I	A
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in patients with aspirin intolerance.[273]	I	B
Clopidogrel 75 mg daily may be considered in preference to aspirin in symptomatic or asymptomatic patients, with either PAD or a history of ischaemic stroke or transient ischaemic attack.[273]	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
Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a **high risk** of ischaemic events[c] and without high bleeding risk[d] (see *Table 9* for options).[289,296,297,307]	IIa	A
Adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a **moderately increased risk** of ischaemic events[e] and without high bleeding risk[d] (see *Table 9* for options).[289,296,297,307]	IIb	A
Antithrombotic therapy post-PCI in patients with CCS and in sinus rhythm		
Aspirin 75–100 mg daily is recommended following stenting.[284]	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 duration (1–3 months) is indicated due to risk or the occurrence of life-threatening bleeding.[284]	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.[284]	IIa	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.[284]	IIb	C
Prasugrel or ticagrelor may be considered, at least as initial therapy, in specific high-risk situations of elective stenting (e.g. suboptimal stent deployment or other procedural characteristics associated with high risk of stent thrombosis, complex left main stem, or multivessel stenting) or if DAPT cannot be used because of aspirin intolerance.	IIb	C
Antithrombotic therapy in patients with CCS and AF		
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC,[f] a NOAC is recommended in preference to a VKA.[299–301,308–311]	I	A
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[g] ≥2 in males and ≥3 in females.[299]	I	A

Continued

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[g] of 1 in males and 2 in females.[299]	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[c] who do not have a high bleeding risk.[d] [295,297,299]	IIb	B
Antithrombotic therapy in post-PCI patients with AF or another indication for an OAC		
It is recommended that peri-procedural aspirin and clopidogrel are administered to patients undergoing coronary stent implantation.	I	C
In patients who are eligible for a NOAC, it is recommended that a NOAC (apixaban 5 mg b.i.d., dabigatran 150 mg b.i.d., edoxaban 60 mg o.d., or rivaroxaban 20 mg o.d.)[f] is used in preference to a VKA in combination with antiplatelet therapy.[300,301,308,310,311]	I	A
When rivaroxaban is used and concerns about high bleeding risk[d] prevail over concerns about stent thrombosis[h] or ischaemic stroke,[g] rivaroxaban 15 mg o.d. should be considered in preference to rivaroxaban 20 mg o.d. for the duration of concomitant single or dual antiplatelet therapy.[300,301,308,310]	IIa	B
When dabigatran is used and concerns about high bleeding risk[d] prevail over concerns about stent thrombosis[h] or ischaemic stroke,[g] dabigatran 110 mg b.i.d. should be considered in preference to dabigatran 150 mg b.i.d. for the duration of concomitant single or dual antiplatelet therapy.[300,301,308]	IIa	B
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[h] is low, or if concerns about bleeding risk prevail over concerns about the risk of stent thrombosis,[h] irrespective of the type of stent used.[301,308–310]	IIa	B
Triple therapy with aspirin, clopidogrel, and an OAC for ≥1 month should be considered when the risk of stent thrombosis[h] 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
In patients with an indication for a VKA in combination with aspirin and/or clopidogrel, the dose intensity of the VKA should be carefully regulated with a target international normalized ratio in the range of 2.0–2.5 and with time in therapeutic range >70%.[300,301,308–310]	IIa	B
Dual therapy with an OAC and either ticagrelor or prasugrel may be considered as an alternative to triple therapy with an OAC, aspirin, and clopidogrel in patients with a moderate or high risk of stent thrombosis,[h] irrespective of the type of stent used.	IIb	C
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and an OAC.	III	C
Use of proton pump inhibitors		
Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or OAC monotherapy who are at high risk of gastrointestinal bleeding.[284]	I	A

AF = atrial fibrillation; b.i.d. = bis in die (twice a day); CAD = coronary artery disease; CCS = chronic coronary syndromes; CHA_2DS_2-VASc = Cardiac failure, Hypertension, Age ≥75 [Doubled], Diabetes, Stroke [Doubled] – Vascular disease, Age 65–74 and Sex category [Female]; CKD = chronic kidney disease; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; HF = heart failure; MI = myocardial infarction; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; o.d. = omni die (once a day); PAD = peripheral artery disease; PCI = percutaneous coronary intervention; VKA = vitamin K antagonist.

[a]Class of recommendation.

[b]Level of evidence.

[c]Diffuse multivessel CAD with at least one of the following: diabetes mellitus requiring medication, recurrent MI, PAD, or CKD with eGFR 15–59 mL/min/1.73 m^2.

[d]Prior history of intracerebral haemorrhage or ischaemic stroke, history of other intracranial pathology, recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, or renal failure requiring dialysis or with eGFR <15 mL/min/1.73 m^2.

[e]At least one of the following: multivessel/diffuse CAD, diabetes mellitus requiring medication, recurrent MI, PAD, HF, or CKD with eGFR 15–59 mL/min/1.73 m^2.

[f]See summary of product characteristics for reduced doses or contraindications for each NOAC in patients with CKD, body weight <60 kg, age >75–80 years, and/or drug interactions.

[g]Congestive HF, hypertension, age ≥75 years (2 points), diabetes, prior stroke/transient ischaemic attack/embolus (2 points), vascular disease (CAD on imaging or angiography,[312] prior MI, PAD, or aortic plaque), age 65–74 years, and female sex.

[h]Risk of stent thrombosis encompasses (i) the risk of thrombosis occurring and (ii) the risk of death should stent thrombosis occur, both of which relate to anatomical, procedural, and clinical characteristics. Risk factors for CCS patients include stenting of left main stem, proximal LAD, or last remaining patent artery; suboptimal stent deployment; stent length >60 mm; diabetes mellitus; CKD; bifurcation with two stents implanted; treatment of chronic total occlusion; and previous stent thrombosis on adequate antithrombotic therapy.

Table 9 Treatment options for dual antithrombotic therapy in combination with aspirin 75 – 100 mg daily in patients who have a high[a] or moderate[b] risk of ischaemic events, and do not have a high bleeding risk[c]

Drug option	Dose	Indication	Additional cautions	References
Clopidogrel	75 mg o.d.	Post-MI in patients who have tolerated DAPT for 1 year		289,290
Prasugrel	10 mg o.d or 5 mg o.d.; if body weight <60 kg or age >75 years	Post-PCI for MI in patients who have tolerated DAPT for 1 year	Age >75 years	289,290,313
Rivaroxaban	2.5 mg b.i.d.	Post-MI >1 year or multivessel CAD	Creatinine clearance 15 - 29 mL/min	297
Ticagrelor	60 mg b.i.d.	Post-MI in patients who have tolerated DAPT for 1 year		291–293,307,314

Treatment options are presented in alphabetical order.
b.i.d. = bis in die (twice a day); CAD = coronary artery disease; CKD = chronic kidney disease; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; HF = heart failure; MI = myocardial infarction; o.d. = omni die (once a day); PAD = peripheral artery disease; PCI = percutaneous coronary intervention.
[a]High risk of ischaemic events is defined as diffuse multivessel CAD with at least one of the following: diabetes mellitus requiring medication, recurrent MI, PAD, or CKD with eGFR 15 - 59 mL/min/1.73 m^2.
[b]Moderately increased risk of ischaemic events is defined as at least one of the following: multivessel/diffuse CAD, diabetes mellitus requiring medication, recurrent MI, PAD, HF, or CKD with eGFR 15 - 59 mL/min/1.73 m^2.
[c]High bleeding risk is defined as history of intracerebral haemorrhage or ischaemic stroke, history of other intracranial pathology, recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, or renal failure requiring dialysis or with eGFR <15 mL/min/1.73 m^2.

3.3.3 Statins and other lipid-lowering drugs

Dyslipidaemia should be managed according to lipid guidelines with pharmacological and lifestyle intervention.[315] Patients with established CAD are regarded as being at very high risk for cardiovascular events and statin treatment must be considered, irrespective of LDL-C levels. The goal of treatment is to lower LDL-C by at least 50% from baseline and to <1.4 mmol/L (<55 mg/dL) although a lower target LDL-C of <1.0 mmol/L (<40 mg/dL) may be considered in patients who have experience a second vascular event within 2 years, not necessarily of the same type as the first event, whilst taking maximally tolerated statin-based therapy. When this level cannot be achieved, the addition of ezetimibe has been demonstrated to decrease cholesterol and cardiovascular events in post-ACS patients, and in those with diabetes,[316] with no further effect on mortality.[317] In addition to exercise, diet, and weight control, which should be recommended to all patients, dietary supplements including phytosterols may lower LDL-C to a lesser extent, but have not been shown to improve clinical outcomes.[318] These are also used in patients with intolerance to statins who constitute a group at higher risk for cardiovascular events.[319] Trials published since 2015 have demonstrated that proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors (evolocumab[320] and alirocumab[321–323]) are very effective at reducing cholesterol, lowering LDL-C in a stable fashion to ≤1.3 mmol/L (50 mg/dL). In outcomes trials, these agents have demonstrated a reduction of cardiovascular and mainly ischaemic events, with little or no impact on mortality.[324] Very low levels of cholesterol are well tolerated and associated with fewer events,[325] but the high cost of PCSK9 inhibitors, unaffordable for many health systems,[326] and their unknown long-term safety have limited their use to date. Low-density lipoprotein apheresis and new therapies such as mipomersen and lomitapide need further research.

For patients undergoing PCI, high-dose atorvastatin has been shown to reduce the frequency of peri-procedural events in both statin-naïve patients and patients receiving chronic statin therapy.[327]

3.3.4 Reninangiotensinaldosterone system blockers

ACE inhibitors can reduce mortality, MI, stroke, and HF among patients with LV dysfunction,[328–330] previous vascular disease,[331–333] and high-risk diabetes.[334] It is recommended that ACE inhibitors [or angiotensin receptor blockers (ARBs) in cases of intolerance] be considered for the treatment of patients with CCS with coexisting hypertension, LVEF ≤40%, diabetes, or CKD, unless contraindicated (e.g. severe renal impairment, hyperkalaemia, etc.). However, not all trials have demonstrated that ACE inhibitors reduce all-cause death, cardiovascular death, non-fatal MI, stroke, or HF in patients with atherosclerosis and without impaired LV function.[331,332,335] A meta-analysis, including 24 trials and 61 961 patients, documented that, in CCS patients without HF, renin-angiotensin system (RAS) inhibitors reduced cardiovascular events and death only when compared with placebo, but not when compared with active controls.[336] Hence, ACE inhibitor therapy in CCS patients without HF or high cardiovascular risk is not generally recommended, unless required to meet BP targets.

Neprilysin is an endogenous enzyme that degrades vasoactive peptides such as bradykinin and natriuretic peptides. Pharmacological inhibition of neprilysin raises the levels of these peptides, enhancing diuresis, natriuresis, myocardial relaxation, and antiremodelling, and reducing renin and aldosterone secretion. The first in class is LCZ696, which combines valsartan and sacubitril (neprilysin inhibitor) in a single pill. In patients with HF (LVEF ≤35%) who remain symptomatic despite optimal treatment with an ACE inhibitor, a beta-blocker, and a mineralocorticoid receptor antagonist (MRA), sacubitril/valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients.[337]

Aldosterone blockade with spironolactone or eplerenone is recommended for use in post-MI patients who are already receiving therapeutic doses of an ACE inhibitor and a beta-blocker, have an LVEF ≤35%, and have either diabetes or HF.[338,339] Caution should be exercised when MRAs are used in patients with impaired renal function [estimated GFR (eGFR) <45 mL/min/1.73 m^2] and in those with serum potassium levels ≥5.0 mmol/L.[340]

Recommendations for event prevention II

Lipid-lowering drugs	Class[a]	Level[b]
Statins are recommended in all patients with CCS.[c] [341,342]	I	A
If a patient's goal[c] is not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.[317,320]	I	B
For patients at very high risk who do not achieve their goal[c] on a maximum tolerated dose of statin and ezetimibe, combination with a PCSK9 inhibitor is recommended.[320,323]	I	A
ACE inhibitors		
ACE inhibitors (or ARBs) are recommended if a patient has other conditions (e.g. heart failure, hypertension, or diabetes).[328–330]	I	A
ACE inhibitors should be considered in CCS patients at very high risk of cardiovascular events.[331,332,335,336]	IIa	A
Other drugs		
Beta-blockers are recommended in patients with LV dysfunction or systolic HF.[211,212,214]	I	A
In patients with a previous STEMI, long-term oral treatment with a beta-blocker should be considered.[213,220–222,225,343]	IIa	B

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CCS = chronic coronary syndrome; HF = heart failure; LV = left ventricular; PCSK9 = proprotein convertase subtilisin-kexin type 9; STEMI = ST-elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]The treatment goals are shown in the European Society of Cardiology/European Atherosclerosis Society Guidelines for the management of dyslipidaemias.[315]

3.3.5 Hormone replacement therapy

The results from large randomized trials have shown that hormone replacement therapy provides no prognostic benefit and increases the risk of CVD in women aged >60 years.[344]

3.4 Revascularization

In patients with CCS, optimal medical therapy is key for reducing symptoms, halting the progression of atherosclerosis, and preventing atherothrombotic events. Myocardial revascularization plays a central role in the management of CCS on top of medical treatment, but always as an adjunct to medical therapy without supplanting it. The two objectives of revascularization are symptom relief in patients with angina and/or improvement of prognosis.

Previous Guidelines support indications for revascularization mainly in patients with CCS who receive Guideline-recommended optimal medical therapy and continue to be symptomatic, and/or in whom revascularization may ameliorate prognosis.[88] These recommendations suggested that revascularization in patients with angina and significant stenosis was often a second-line therapy after medical therapy had been unsuccessful. However, angina is associated with impaired quality of life, reduced physical endurance, mental depression, and recurrent hospitalizations and office visits, with impaired clinical outcomes.[345,346]

Revascularization by PCI or CABG may effectively relieve angina, reduce the use of antianginal drugs, and improve exercise capacity and quality of life compared with a strategy of medical therapy alone. In the 5 year follow-up of the FAME 2 (Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2) trial, revascularization improved quality of life, and reduced the use of antianginal drugs and associated side effects.[347] The ORBITA (Objective Randomised Blinded Investigation with optimal medical Therapy or Angioplasty in stable angina) study, entailing a sham procedure in the control group, found no significant improvement in exercise capacity with PCI.[262] The study highlights a significant placebo component to the clinical effects, and alerts us to the pitfalls of interpreting endpoints subject to bias in the absence of sham control and blinding. However, the ORBITA results cannot inform Guidelines due to the limited trial size, short-term observation time until crossover, and insufficient power to assess clinical endpoints.

Revascularization by either PCI or CABG also aims to effectively eliminate myocardial ischaemia and its adverse clinical manifestations among patients with significant coronary stenosis, and to reduce the risk of major acute cardiovascular events including MI and cardiovascular death. Numerous meta-analyses comparing a strategy of PCI with initial medical therapy among patients with CCS have found no[348,349] or a modest[104,350,351] benefit, in terms of survival or MI for an invasive strategy. In this regard, previous Guidelines identified specific subgroups of patients (based on the anatomy of the coronary tree, LV function, risk factors, etc.) in whom revascularization may improve prognosis, indicating that in other groups it may not.[88]

A meta-analysis by Windecker *et al.* reported an incremental reduction of death and MI by revascularization vs. medical therapy only in CCS patients when revascularization was performed with CABG or new-generation drug-eluting stents (DES), as opposed to balloon angioplasty, bare-metal stents, or early DES.[351] Data reported in 2018 indicate a potentially broader prognostic impact of revascularization strategies. The 5 year follow-up of the FAME 2 trial confirmed a sustained clinical benefit in patients treated with PCI specifically targeting the ischaemia-producing stenoses (i.e. FFR <0.80) plus optimal medical therapy vs. optimal medical therapy alone in terms of a significantly lower rate of urgent revascularization (hazard ratio 0.27, 95% CI 0.18–0.41), and a lower rate of spontaneous MI (hazard ratio 0.62, 95% CI 0.39–0.99).[347] In contrast to some of the earlier meta-analyses, this signal was confirmed in a patient-level meta-analysis including 2400 subjects, all of whom underwent invasive physiological guidance, showing a significant reduction in cardiac death and MI after a median follow-up of 33 months with FFR-guided

PCI vs. medical therapy (hazard ratio 0.74, 95% CI 0.56–0.989; *P*=0.041).[352] Together, these new data support a less restrictive indication for revascularization in CCS, in addition to specific anatomy [e.g. left main (LM)] or extended ischaemia (>10%), when PCI is restricted to angiographic stenoses on large vessels causing a significant intracoronary pressure gradient. *Figure 9* summarizes a practical approach to the indications of revascularization in CCS according to the presence or absence of symptoms, and documentation of non-invasive ischaemia. However, the individual risk-benefit ratio should always be evaluated and revascularization considered only if its expected benefit outweighs its potential risk. Also, the aspect of shared decision-making is key, with full information given to the patient about the anticipated advantages and disadvantages of the two strategies, including the DAPT-related bleeding risks in cases of revascularization by PCI. For the discussion of the best choice between revascularization modalities—PCI or CABG—for individual patients, we refer readers to the 2018 ESC myocardial revascularization Guidelines.[88]

4 Patients with new onset of heart failure or reduced left ventricular function

CAD is the most common cause of HF in Europe, and most of the trial evidence supporting management recommendations is based on

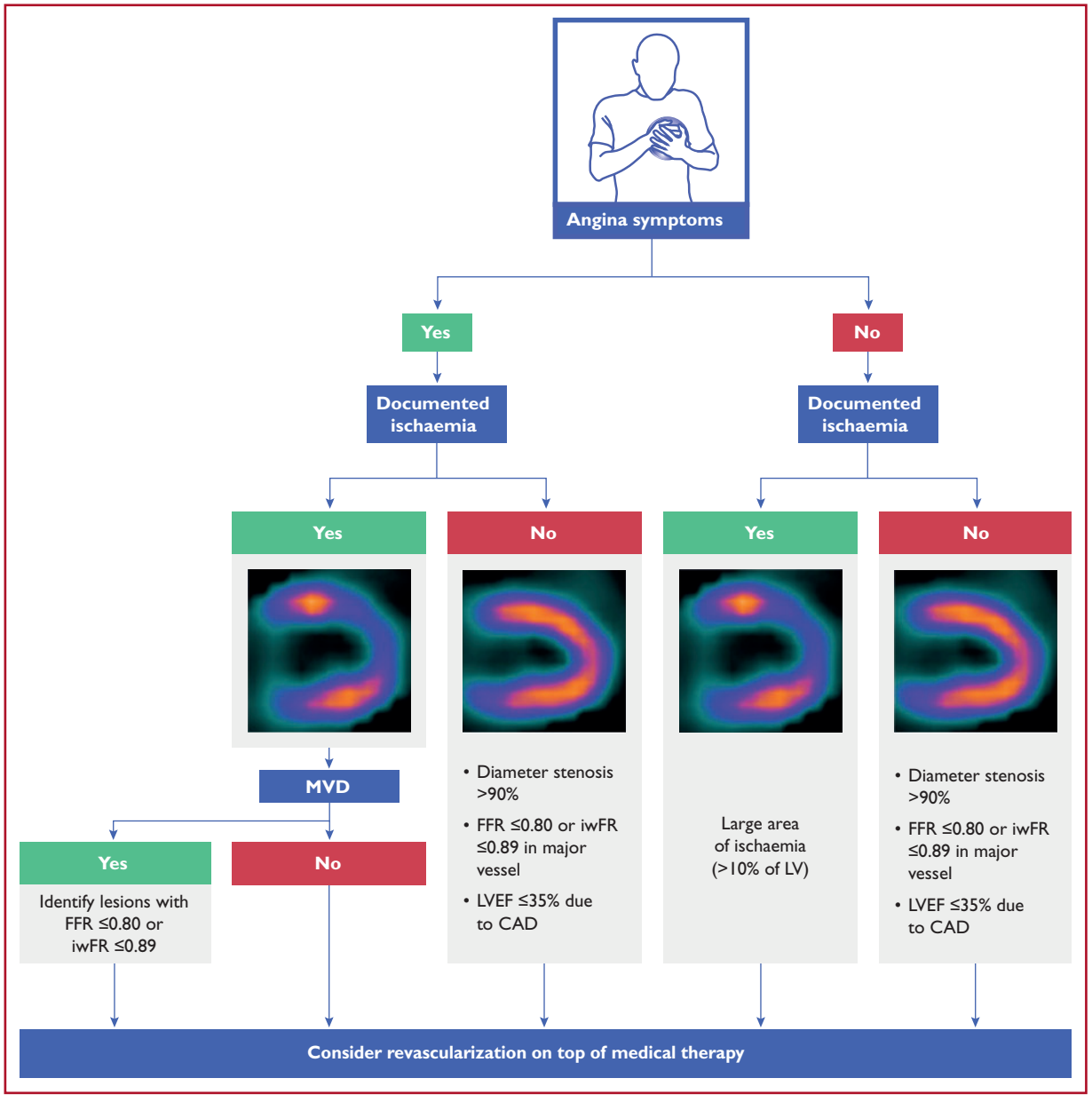

Figure 9 Decision tree for patients undergoing invasive coronary angiography. Decisions for revascularization by percutaneous coronary intervention or coronary artery bypass grafting are based on clinical presentation (symptoms present or absent), and prior documentation of ischaemia (present or absent). In the absence of prior documentation of ischaemia, indications for revascularization depend on invasive evaluation of stenosis severity or prognostic indications. Patients with no symptoms and ischaemia include candidates for transcatheter aortic valve implantation, valve, and other surgery. CAD = coronary artery disease; FFR = fractional flow reserve; iwFR = instantaneous wave-free ratio; LV = left ventricle; LVEF = left ventricular ejection fraction; MVD = multivessel disease.

research conducted in patients with ischaemic cardiomyopathy. The pathophysiology results in systolic dysfunction due to myocardial injury and ischaemia, and most patients with symptomatic HF have reduced ejection fraction (<40%), although patients with CCS may also have symptomatic HF and a preserved ejection fraction (≥50%). Patients with symptomatic HF should be managed clinically according to the 2016 ESC heart failure Guidelines.[340]

History should include the assessment of symptoms suggestive of HF, especially exercise intolerance and dyspnoea on exertion. All major past events related to CAD including MI and revascularization procedures are recorded, as well as all major cardiovascular comorbidity requiring treatment such as AF, hypertension, or valvular dysfunction, and non-cardiovascular comorbidity such as CKD, diabetes, anaemia, or cancer. Current medical therapy, adherence, and tolerance should be reviewed.

Physical examination should assess the nutritional status of patients, and estimate biological age and cognitive ability. Recorded physical signs include heart rate, heart rhythm, supine BP, murmurs suggestive of aortic stenosis or mitral insufficiency, signs of pulmonary congestion with basal rales or pleural effusion, signs of systemic congestion with dependant oedema, hepatomegaly, and elevated jugular venous pressure.

A *routine ECG* provides information on heart rate and rhythm, extrasystole, signs of ischaemia, pathological Q waves, hypertrophy, conduction abnormalities, and bundle branch block.

Imaging should include an echocardiographic examination with Doppler to evaluate evidence of ischaemic cardiomyopathy with HF with reduced ejection fraction, HF with mid-range ejection fraction, or HF with preserved ejection fraction, focal/diffuse LV or right ventricular systolic dysfunction, evidence of diastolic dysfunction, hypertrophy, chamber volumes, valvular function, and evidence of pulmonary hypertension. Chest X-ray can detect signs of pulmonary congestion, interstitial oedema, infiltration, or pleural effusion. If not known, coronary angiography (or coronary CTA) should be performed to establish the presence and extent of CAD, and evaluate the potential for revascularization.[52,53]

Laboratory investigations should measure natriuretic peptide levels to rule-out the diagnosis of suspected HF. When present, the severity of HF can be assessed.[25,49] Renal function along with serum electrolytes should be measured routinely to detect the development of renal insufficiency, hyponatraemia, or hyperkalaemia, especially at the initiation and during up-titration of pharmacological therapy.

The *management* of patients with symptomatic HF requires adequate diuretic therapy, preferably with a loop diuretic, to relieve signs and symptoms of pulmonary and systemic congestion. Inhibitors of both the RAS system (ACE inhibitors, ARBs, angiotensin receptor-neprilysin inhibitor) and the adrenergic nervous system (beta-blockers) are indicated in all symptomatic patients with HF.[340] In patients with persistent symptoms, an MRA is also indicated. Up-titration of these drugs should be gradual to avoid symptomatic systolic hypotension, renal insufficiency, or hyperkalaemia.

Patients who remain symptomatic, with LV systolic dysfunction and evidence of ventricular dysrhythmia or bundle branch block, may be eligible for a device [cardiac resynchronization therapy (CRT)/implantable cardioverter-defibrillator]. Such devices may provide symptomatic relief, reduce morbidity, and improve survival.[353–356] Patients with HF may decompensate rapidly following the onset of atrial or ventricular dysrhythmia, and should be treated according to current Guidelines. Patients with HF, and haemodynamically significant aortic stenosis or mitral insufficiency, may require percutaneous or surgical intervention.

Myocardial revascularization should be considered in eligible patients with HF based on their symptoms, coronary anatomy, and risk profile. Successful revascularization in patients with HF due to ischaemic cardiomyopathy may improve LV dysfunction and prognosis by reducing ischaemia to viable, hibernating myocardium. If available, cooperation with a multidisciplinary HF team is strongly advised.[348,357,358]

General recommendations for the management of patients with chronic coronary syndromes and symptomatic heart failure due to ischaemic cardiomyopathy and left ventricular systolic dysfunction

Recommendations for drug therapy	Class[a]	Level[b]
Diuretic therapy is recommended in symptomatic patients with signs of pulmonary or systemic congestion to relieve HF symptoms.[359,360]	I	B
Beta-blockers are recommended as essential components of treatment due to their efficacy in both relieving angina, and reducing morbidity and mortality in HF.[214,361–367]	I	A
ACE inhibitor therapy is recommended in patients with symptomatic HF or asymptomatic LV dysfunction following MI, to improve symptoms and reduce morbidity and mortality.[333,368]	I	A
An ARB is recommended as an alternative in patients who do not tolerate ACE inhibition, or an angiotensin receptor-neprilysin inhibitor in patients with persistent symptoms despite optimal medical therapy.[337,369]	I	B
An MRA is recommended in patients who remain symptomatic despite adequate treatment with an ACE inhibitor and beta-blocker, to reduce morbidity and mortality.[360,370]	I	A
A short-acting oral or transcutaneous nitrate should be considered (effective antianginal treatment, safe in HF).[371]	IIa	A
Ivabradine should be considered in patients with sinus rhythm, an LVEF ≤35% and a resting heart rate >70 b.p.m. who remain symptomatic despite adequate treatment with a beta-blocker, ACE inhibitor, and MRA, to reduce morbidity and mortality.[238,372,373]	IIa	B
Amlodipine may be considered for relief of angina in patients with HF who do not tolerate beta-blockers, and is considered safe in HF.[374,375]	IIb	B

Continued

For devices, comorbidities, and revascularization		
In patients with HF and bradycardia with high-degree atrioventricular block who require pacing, a CRT with a pacemaker rather than right ventricular pacing is recommended.[353]	I	A
An implantable cardioverter-defibrillator is recommended in patients with documented ventricular dysrhythmia causing haemodynamic instability (secondary prevention), as well as in patients with symptomatic HF and an LVEF ≤35%, to reduce the risk of sudden death and all-cause mortality.[354,376–382]	I	A
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 ms and LBBB QRS morphology, and with LVEF ≤35%, despite optimal medical therapy to improve symptoms, and reduce morbidity and mortality.[355,356,383–392]	I	A
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration 130 - 149 ms and LBBB QRS morphology, and with LVEF ≤35%, despite optimal medical therapy to improve symptoms, and reduce morbidity and mortality.[355,356,383–392]	I	B
Comprehensive risk profiling and multidisciplinary management, including treatment of major comorbidities such as hypertension, hyperlipidaemia, diabetes, anaemia, and obesity, as well as smoking cessation and lifestyle modification, are recommended.[393–396]	I	A
Myocardial revascularization is recommended when angina persists despite treatment with antianginal drugs.[348,357,397]	I	A

ACE inhibitor = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; b.p.m. = beats per minute; CCS = chronic coronary syndromes; CRT = cardiac resynchronization therapy; HF = heart failure; LBBB = left bundle branch block; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist.
[a]Class of recommendation.
[b]Level of evidence.

5 Patients with a long-standing diagnosis of chronic coronary syndromes

In patients with a long-standing diagnosis of CCS, lifelong treatment and surveillance are required (*Figure 10*). The clinical course of patients with CCS may be benign over the course of time. However, patients with CCS may develop a variety of cardiovascular complications or undergo therapeutic measures, some directly related to the underlying CAD, and some having therapeutic or prognostic interactions with the underlying disease. Risk for complications may occur in an otherwise asymptomatic patient, and thus the assessment of risk status applies to symptomatic and asymptomatic patients.

Periodic assessment of the patient's individual risk may be considered (*Figure 10*). Scores that apply clinical parameters have been shown to predict outcomes among patients with CCS. Moreover, if the clinical parameters are complemented by biomarkers, such a risk score may be even more accurate. In 2017, a biomarker-based risk model to predict cardiovascular mortality in patients with CCS was developed and externally validated.[398]

5.1 Patients with stabilized symptoms <1 year after an acute coronary syndrome or patients with recent revascularization

After revascularization and/or after stabilized ACS (<1 year), patients should be monitored more vigilantly, because they are at greater risk for complications and because they are subject to changes in pharmacological treatment.[45] Thus, we recommend at least two visits in the first year of follow-up. In a patient who had LV systolic dysfunction before the revascularization procedure or after the ACS, a reassessment of LV function must be considered 8–12 weeks after the intervention. Cardiac function may have improved, owing to mechanisms such as recovery from myocardial stunning or hibernation, which may be reversed by revascularization.[52,53] Conversely, cardiac function may have deteriorated given other concomitant CVD (e.g. valvular disease, infection or inflammation, arrhythmia, etc.). In such cases, these other damaging factors need to be identified and treated. Likewise, non-invasive assessment of myocardial ischaemia may be considered after revascularization to rule-out residual ischaemia or to document the residual ischaemia as reference for subsequent assessments over time.

5.2 Patients >1 year after initial diagnosis or revascularization

To assess a patient's risk, an annual evaluation by a cardiovascular practitioner (cardiologist, general physician, or nurse) is warranted, even if the patient is asymptomatic. It is recommended that the annual evaluation should assess the patient's overall clinical status and medication compliance, as well as the risk profile (as reflected by risk scores). Laboratory tests—which include a lipid profile, renal function, a complete blood count, and possibly biomarkers—should be performed every 2 years.[45] A patient with a worsening risk score over time may warrant more intense therapy or diagnostic measures, although risk score-guided therapy has not yet been proved to ameliorate outcomes.

A 12 lead ECG should be a part of every such visit to delineate heart rate and heart rhythm, to detect changes suggestive of silent ischaemia/infarction, and to discern abnormalities in the specific electrocardiographic segments (e.g. PR, QRS, and QT intervals). It may be beneficial to assess LV function (diastolic and systolic), valvular status, and cardiac dimensions in apparently asymptomatic patients every 3–5 years.[52,53] In cases of unexplained reduction in systolic LV function, especially if regional, imaging of coronary artery anatomy is recommended. Likewise, it may be beneficial to assess non-invasively for silent ischaemia in an apparently asymptomatic patient every 3–5

years, preferably applying stress imaging. Coronary CTA should not be used for follow-up of patients with established CAD given its strength on morphological insight, but lack of functional information related to ischaemia. However, coronary CTA may be used for unique cases, such as delineation of patency of coronary artery bypass grafts.

The lipid profile and glycaemia status should be reassessed periodically to determine efficacy of treatment and, in patients without diabetes, to detect new development of diabetes. There is no evidence to support recommendations for the frequency of reassessment of these risk factors, but consensus suggests annual evaluation.

Elevated inflammatory markers, particularly of high-sensitivity C-reactive protein, have also been associated with an increased event risk in patients with and without CAD in multiple studies,[25] although the robustness of the association has been questioned because of reporting and publication bias.[399] In addition, von Willebrand factor, interleukin-6, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) have identified as been predictors of outcome.[25] Other

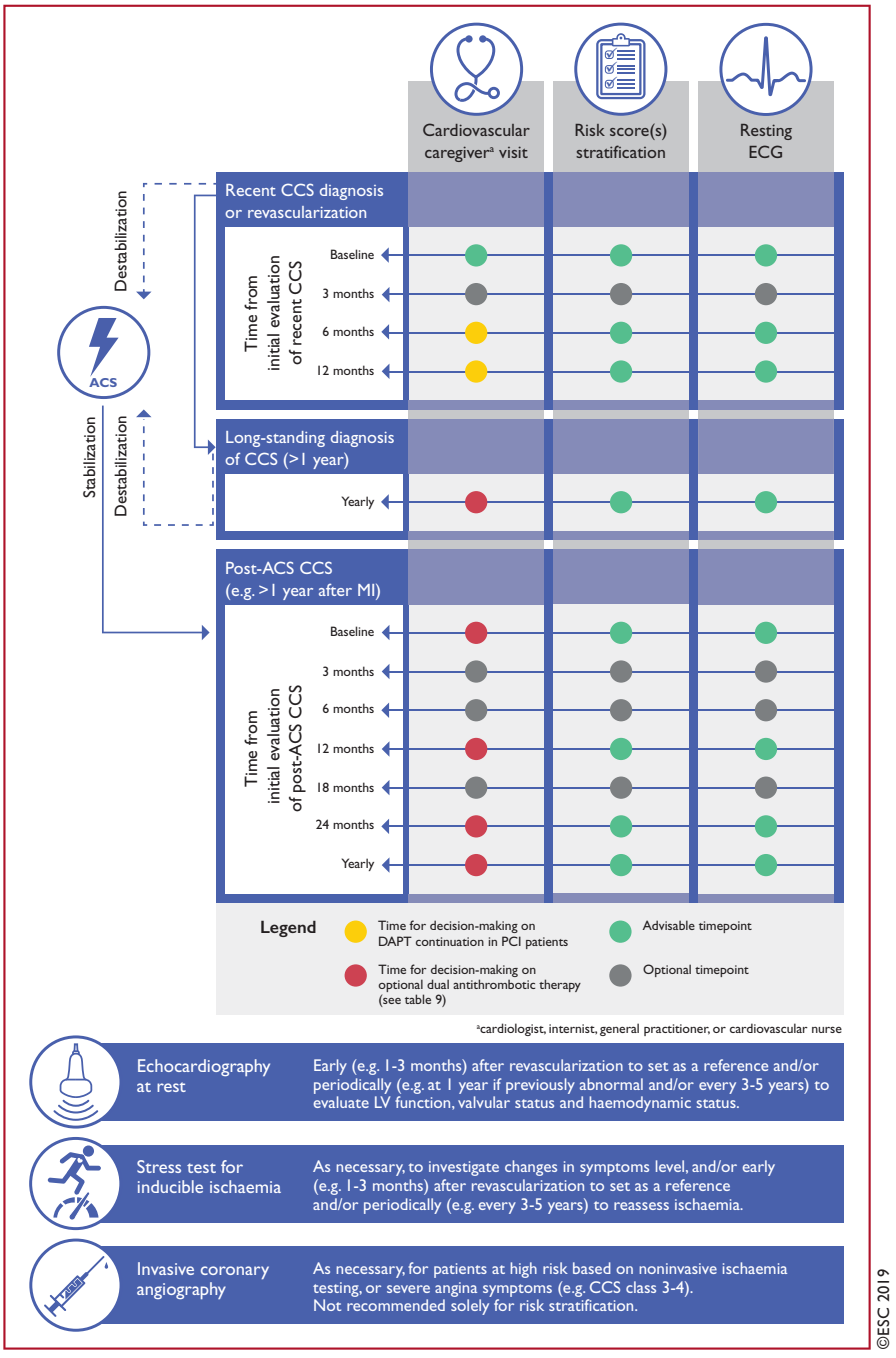

Figure 10 Proposed algorithm according to patient types commonly observed at chronic coronary syndrome outpatient clinics. The frequency of follow-up may be subject to variation based on clinical judgement. ACS = acute coronary syndromes; CCS = chronic coronary syndromes; DAPT = dual antiplatelet therapy; ECG = electrocardiogram; LV = left ventricular; MI = myocardial infarction; PCI = percutaneous coronary intervention. [a]Cardiologist, internist, general practitioner, or cardiovascular nurse.

readily available biomarkers shown to predict prognosis in patients with CCS include heart rate, haemoglobin, and white cell count.[400] Scores based on aggregated biomarkers may have greater success than individual biomarkers. A multiple biomarker score combining high-sensitivity C-reactive protein, heat shock protein 70, and fibrin degradation products significantly improved C-statistics and the net reclassification index compared with a basic model using clinical data.[401] Similar results were reported for a combination of high-sensitivity cardiac troponin T, NT-proBNP, and LDL-C.[398] In several studies, genetic risk scores have been shown to improve risk prediction above traditional risk factors in general population samples[402,403] and to predict recurrent events in populations with known CCS.[404–407] Although there is additional prognostic value in using several individual and aggregated biomarkers, there is currently no evidence that routine use leads to improved care. Nevertheless, these measurements may have a role in selected patients (e.g. when testing for haemostatic abnormalities in those with previous MI without conventional risk factors or a strong family history of CAD).

Patients with unequivocal symptoms suggestive of ACS should be expeditiously referred for evaluation, applying current Guidelines for diagnosis and management. Among patients with more equivocal symptoms, stress imaging is recommended[408] and, if not available and the ECG is amenable to identification of ischaemia, exercise stress electrocardiography can be used as an alternative. In patients with severe angina and a high-risk clinical profile, direct referral for ICA is recommended, provided that *ad hoc* physiological assessment of haemodynamic stenosis significance is readily available in the catheterization laboratory [e.g. instantaneous wave-free ratio (iwFR) or FFR]. Likewise, ICA is recommended for patients with evidence of significant ischaemia obtained by non-invasive testing.

6 Angina without obstructive disease in the epicardial coronary arteries

In clinical practice, a marked discrepancy between findings regarding coronary anatomy, the presence of symptoms, and the results of non-invasive tests frequently occurs.[13] These patients deserve attention, as angina and non-obstructive disease are associated with an increased risk of adverse clinical events.[14] Low diagnostic yield of ICA can be explained by the presence of: (i) stenoses with mild or moderate angiographic severity, or diffuse coronary narrowing, with underestimated functional significance identified by ICA; (ii) disorders affecting the microcirculatory domain that escape the resolution of angiographic techniques; and (iii) dynamic stenoses of epicardial vessels caused by coronary spasm or intramyocardial bridges that are not evident during CTA or ICA. Intracoronary pressure measurements are useful in circumventing the first of these scenarios. For diagnostic workup, patients with angina and/or myocardial ischaemia showing coronary stenoses with non-ischaemic FFR or iwFR values may also be labelled as having non-obstructive epicardial disease.

The presence of clear-cut anginal symptoms and abnormal non-invasive tests in patients with non-obstructed epicardial vessels should lead to the suspicion of a non-obstructive cause of ischaemia. Quite often, and mainly as a result of persistence of symptoms, patients with angina and no obstructive disease undergo multiple diagnostic tests, including repeated coronary CTA or ICA, that contribute to increased healthcare costs.[409] Because diagnostic pathways to investigate microcirculatory or vasomotor coronary disorders are often not implemented, a final diagnosis supported by objective

Recommendations for patients with a long-standing diagnosis of chronic coronary syndromes

Recommendations for asymptomatic patients	Class[a]	Level[b]
A periodic visit to a cardiovascular healthcare professional is recommended to reassess any potential change in the risk status of patients, entailing clinical evaluation of lifestyle-modification measures, adherence to targets of cardiovascular risk factors, and the development of comorbidities that may affect treatments and outcomes.	I	C
In patients with mild or no symptoms receiving medical treatment in whom non-invasive risk stratification indicates a high risk, and for whom revascularization is considered for improvement of prognosis, invasive coronary angiography (with FFR when necessary) is recommended.	I	C
Coronary CTA is not recommended as a routine follow-up test for patients with established CAD.	III	C
Invasive coronary angiography is not recommended solely for risk stratification.	III	C
Symptomatic patients		
Reassessment of CAD status is recommended in patients with deteriorating LV systolic function that cannot be attributed to a reversible cause (e.g. long-standing tachycardia or myocarditis).	I	C
Risk stratification is recommended in patients with new or worsening symptom levels, preferably using stress imaging or, alternatively, exercise stress ECG.[408]	I	B
It is recommended to expeditiously refer patients with significant worsening of symptoms for evaluation.	I	C
Invasive coronary angiography (with FFR/iwFR when necessary) is recommended for risk stratification in patients with severe CAD, particularly if the symptoms are refractory to medical treatment or if they have a high-risk clinical profile.	I	C

CAD = coronary artery disease; CTA = computed tomography angiography; ECG = electrocardiogram; FFR = fractional flow reserve; iwFR = instantaneous wave-free ratio; LV = left ventricular.
[a]Class of recommendation.
[b]Level of evidence.

evidence is seldom reached. Owing to this, patient dismay and depression are not rare in this clinical population.[410,411] Of note, the use of a structured, systematic approach to explore microcirculatory and vasomotor disorders in patients with non-obstructive CAD, as delineated below, has been shown to increase diagnostic yield.[412,413] Furthermore, an RCT, which reported in 2018, found that in patients with non-obstructive coronary disease, tailored treatment guided by the results of intracoronary testing [coronary flow reserve (CFR), microcirculatory resistance, and acetylcholine testing] resulted in a significant reduction of anginal symptoms, compared with conventional, non-guided medical treatment.[414]

6.1 Microvascular angina

Patients with microvascular angina typically have exercise-related angina, evidence of ischaemia in non-invasive tests, and either no stenoses or mild-to-moderate stenoses (40–60%), revealed by ICA or CTA, that are deemed functionally non-relevant.[415] Given the similarity of angina symptoms, a microvascular origin of angina is typically suspected, after excluding obstructive epicardial coronary stenoses, during diagnostic workup of patients with suspected myocardial ischaemia. Regional LV wall motion abnormalities rarely develop during exercise or stress in patients with microvascular angina.[412,416] Some patients may also have a mixed pattern of angina, with occasional episodes at rest, particularly associated with exposure to cold.

Secondary microvascular angina, in the absence of epicardial obstruction, may result from cardiac or systemic conditions, including those that cause LV hypertrophy (such as hypertrophic cardiomyopathy, aortic stenosis, and hypertensive heart disease) or inflammation (such as myocarditis or vasculitis).[417]

6.1.1 Risk stratification

The presence of microcirculatory dysfunction in patients with CCS entails a worse prognosis than originally thought, probably because most recent evidence has been based on follow-up of patients in whom abnormalities in the microcirculation have been objectively documented with invasive or non-invasive techniques.[418–423]

Microcirculatory dysfunction precedes the development of epicardial lesions, particularly in women,[419] and is associated with impaired outcomes. Among patients with diabetes undergoing diagnostic workup, those without obstructive epicardial disease but with an abnormal CFR have similarly poor long-term prognosis as those with obstructive epicardial disease.[421] In patients with non-significant coronary stenoses by FFR, the presence of abnormal CFR is associated with an excess of events in the long-term,[418,422,423] particularly when the index of microcirculatory resistance (IMR) is also abnormal.[422]

6.1.2 Diagnosis

The possibility of a microcirculatory origin of angina should be considered in patients with clear-cut angina, abnormal non-invasive functional tests, and coronary vessels that are either normal or have mild stenosis deemed functionally non-significant on ICA or CTA. One of the challenges in performing a comprehensive assessment of microvascular function is testing the two main mechanisms of dysfunction separately: impaired microcirculatory conductance and arteriolar dysregulation.[424–426] Yet, outlining which of these two pathways is affected is critically relevant in setting medical treatment to relieve patient symptoms.[414]

Impaired microcirculatory conductance can be diagnosed by measuring CFR or minimal microcirculatory resistance (the inverse of conductance). CFR can be measured non-invasively with transthoracic Doppler echocardiography [by imaging left anterior descending (LAD) flow],[427] magnetic resonance imaging (myocardial perfusion index),[428–430] or PET.[431] Microcirculatory resistance can be measured in the catheterization laboratory by combining intracoronary pressure with thermodilution-based data (to calculate the IMR) or Doppler flow velocity (to calculate hyperaemic microvascular resistance or HMR).[432,433] Both intracoronary thermodilution and Doppler allow the calculation of CFR. For decision-making purposes, values of IMR ≥25 units or CFR <2.0 are indicative of abnormal microcirculatory function.[414] Both CFR and IMR are typically measured while using intravenous vasodilators, such as adenosine or regadenoson.

In contrast, the diagnosis of *arteriolar dysregulation* requires the assessment of endothelial function in the coronary microcirculation by selective intracoronary acetylcholine infusion (see *section 6.5*). In the presence of dysfunctional vascular endothelium or abnormal function of smooth muscle cells, acetylcholine (an endothelium-dependent vasodilator that also acts directly on smooth muscle cells) triggers paradoxical arteriolar vasoconstriction.[434] Thus, in patients with microvascular angina and arteriolar dysregulation, acetylcholine challenge is likely to trigger microvascular spasm. This arteriolar response to acetylcholine causes anginal symptoms with or without concomitant ischaemic ECG changes, and a decrease in coronary blood flow velocity if concomitant Doppler measurements are performed. Peripheral pulse tonometry during reactive hyperaemia may also reveal abnormal systemic endothelial function in patients with angina and non-obstructive CAD.[435]

6.1.3 Treatment

Treatment of microvascular angina should address the dominant mechanism of microcirculatory dysfunction. In patients with abnormal CFR <2.0 or IMR ≥25 units, and a negative acetylcholine provocation test, beta-blockers, ACE inhibitors, and statins, along with lifestyle changes and weight loss, are indicated.[436,437] Patients developing ECG changes and angina in response to acetylcholine testing but without severe epicardial vasoconstriction (all suggestive of microvascular spasm) may be treated like vasospastic angina patients. The effectiveness of a tailored treatment strategy was investigated in the CorMiCa trial, which randomized 151 patients to a stratified medical treatment (based on the results of CFR, IMR, and acetylcholine testing) vs. a standard-care group (including a sham interventional diagnostic procedure). At 1 year, there was a significant difference in angina scores favouring patients assigned to the stratified medical treatment arm.[414]

Investigations in patients with suspected coronary microvascular angina

Recommendations	Class[a]	Level[b]
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.[412,413]	IIa	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.[412,438–440]	IIb	B
Transthoracic Doppler of the LAD, CMR, and PET may be considered for non-invasive assessment of CFR.[430–432,441]	IIb	B

CFR = coronary flow reserve; CMR = cardiac magnetic resonance; ECG = electrocardiogram; FFR = fractional flow reserve; iwFR = instantaneous wave-free ratio; LAD = left anterior descending; PET = positron emission tomography.
[a]Class of recommendation.
[b]Level of evidence.

6.2 Vasospastic angina

Vasospastic angina should be suspected in patients with anginal symptoms occurring predominantly at rest, with maintained effort tolerance. The likelihood of vasospastic angina increases when attacks follow a circadian pattern, with more episodes at night and in the early morning hours. Patients are frequently younger and have fewer cardiovascular risk factors than patients with effort angina, except for cigarette smoking.[442] Coronary vasospasm should be also suspected in patients with patent coronary stents and persistent angina.[443,444]

6.2.1 Diagnosis

The diagnosis of vasospastic angina is based on detecting transient ischaemic ST-segment changes during an angina attack (usually at rest). Patients with Prinzmetal angina represent a special subset in whom resting angina is accompanied by transient ST-segment elevation.[442,445] These ECG changes correlate with proximal vessel occlusion and diffuse, distal subocclusive narrowing of epicardial vessels. As most attacks of vasospastic angina are self-limiting, documentation of these ECG changes is challenging. Ambulatory ECG monitoring, preferably with 12 lead recording, may be helpful in patients in whom vasospastic angina is suspected. The occurrence of ST-segment shifts at normal heart rate supports the likelihood of myocardial ischaemia caused by spasm. Extended Holter monitoring (for >1 week) may be required for successful documentation of transient ST-segment changes in these patients. Ambulatory ECG monitoring may also be used to assess the results of medical therapy in controlling the frequency of vasospastic events.

In patients with suspected vasospastic angina and documented ECG changes, CTA or ICA is indicated to rule-out the presence of fixed coronary stenosis. Angiographic documentation of coronary spasm requires the use of a provocation test in the catheterization laboratory. Given the low sensitivity of hyperventilation and the cold pressor test, intracoronary administration of acetylcholine or ergonovine during ICA are the preferred provocation tests.[442] Both pharmacological agents are safe, provided that they are selectively infused into the left or right coronary artery, and that triggered spasm is readily controlled with intracoronary nitrates. A low percentage of patients may develop ventricular tachycardia/ventricular fibrillation or bradyarrhythmias during the provocation test (3.2 and 2.7%, respectively), similar to that reported during spontaneous spasm attacks (7%).[446] Intravenous administration of ergonovine for non-invasive tests should be discouraged due to the risk of triggering prolonged spasm in multiple vessels, which may be very difficult to manage and can be fatal.[447]

A provocation test for coronary spasm is considered positive when it triggers: (i) anginal symptoms, (ii) ischaemic ECG changes, and (iii) severe vasoconstriction of the epicardial vessel. Should the test fail in triggering all three components, it should be considered equivocal.[442] The development of angina in response to acetylcholine injections in the absence of angiographically evident spasm, with or without accompanying ST-segment changes, may indicate microvascular spasm and is seen frequently in patients presenting with microvascular angina.[445]

6.2.2 Treatment

In patients with epicardial or microcirculatory vasomotor disorders, CCBs and long-acting nitrates constitute the treatment of choice, in addition to the control of cardiovascular risk factors and lifestyle changes.[437,445] Nifedipine has been shown to be effective in reducing coronary spasm associated with stent implantation.[444]

Recommendations for investigations in patients with suspected vasospastic angina

Recommendations	Class[a]	Level[b]
An ECG is recommended during angina if possible.	I	C
Invasive angiography or coronary CTA is recommended in patients with characteristic episodic resting angina and ST-segment changes, which resolve with nitrates and/or calcium antagonists, to determine the extent of underlying coronary disease.	I	C
Ambulatory ST-segment monitoring should be considered to identify ST-segment deviation in the absence of increased heart rate.	IIa	C
An intracoronary provocation test should be considered to identify coronary spasm in patients with normal findings or non-obstructive lesions on coronary arteriography and a clinical picture of coronary spasm, to diagnose the site and mode of spasm.[412,414,438–440]	IIa	B

CTA = computed tomography angiography; ECG = electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.

7 Screening for coronary artery disease in asymptomatic subjects

In an effort to lower the high burden of coronary deaths in asymptomatic adults, numerous measurements of risk factors and risk markers, as well as stress tests, are often performed as screening investigations. The 2016 European Guidelines on CVD prevention in clinical practice have focused on these issues in detail.[15] These recommendations have been adapted for the purpose of these Guidelines.

In general, the use of risk-estimation systems such as SCORE is recommended (see also *Figure 6*). Subjects with a family history of premature CAD should be screened for familial hypercholesterolaemia. Coronary calcium score, ankle-brachial index, and carotid ultrasound for plaque detection may provide useful information about the atherosclerotic risk in selected patients, but routine use of biomarkers or other imaging tests for CAD are not recommended. The new biomarkers have incremental predictive value over classical ones,[448] but the net reclassification improvement is still only modest (7–18%) compared, for example, with the coronary calcium score, which has a net reclassification improvement of 66%.[449]

Only subjects at high event risk should be considered for further non-invasive or invasive testing. There are no data on how to manage asymptomatic subjects who receive testing and have a positive test result beyond the recommendations listed in these Guidelines. However, the principles of risk stratification, as described above for symptomatic patients, also apply to these individuals.[450] It is important to remember that data demonstrating improved prognosis following appropriate management based on new biomarkers are still lacking.

It is important to note that patients with cancer and undergoing cancer treatment, or chronic inflammatory diseases such as inflammatory bowel diseases, rheumatoid arthritis, and systemic lupus erythematosus, may deserve more intensive risk screening, counselling, and management.[451–454]

Persons whose occupations involve public safety (e.g. airline pilots, or lorry or bus drivers), or who are professional or high-profile athletes, commonly undergo periodic testing for the assessment of exercise capacity and evaluation of possible heart disease, including CAD. Although there are insufficient data to justify this approach, these evaluations may be done for medicolegal reasons. The threshold for performing an imaging test in such persons may be lower than in the average patient. Otherwise, the same considerations as discussed above for other asymptomatic persons apply to these individuals.

Recommendations for screening for coronary artery disease in asymptomatic subjects

Recommendations	Class[a]	Level[b]
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
Assessment of family history of premature CVD (defined as a fatal or non-fatal CVD event, or/and established diagnosis of CVD in first-degree male relatives before 55 years of age or female relatives before 65 years of age) is recommended as part of cardiovascular risk assessment.	I	C
It is recommended that all individuals aged <50 years with a family history of premature CVD in a first-degree relative (<55 years of age in men or <65 years of age in women) or familial hypercholesterolaemia are screened using a validated clinical score.[455,456]	I	B
Assessment of coronary artery calcium score with computed tomography may be considered as a risk modifier[c] in the cardiovascular risk assessment of asymptomatic subjects.[449,457]	IIb	B
Atherosclerotic plaque detection by carotid artery ultrasound may be considered as a risk modifier[c] in the cardiovascular risk assessment of asymptomatic subjects.[458]	IIb	B
ABI may be considered as a risk modifier[c] in cardiovascular risk assessment.[459]	IIb	B
In high-risk asymptomatic adults (with diabetes, a strong family history of CAD, or when previous risk-assessment tests suggest a high risk of CAD), functional imaging or coronary CTA may be considered for cardiovascular risk assessment.	IIb	C
In asymptomatic adults (including sedentary adults considering starting a vigorous exercise programme), an exercise ECG may be considered for cardiovascular risk assessment, particularly when attention is paid to non-ECG markers such as exercise capacity.	IIb	C
Carotid ultrasound IMT for cardiovascular risk assessment is not recommended.[460]	III	A
In low-risk non-diabetic asymptomatic adults, coronary CTA or functional imaging for ischaemia are not indicated for further diagnostic assessment.	III	C
Routine assessment of circulating biomarkers is not recommended for cardiovascular risk stratification.[448,449,461,462]	III	B

ABI = ankle-brachial index; CAD = coronary artery disease; CKD = chronic kidney disease; CTA = computed tomography angiography; CVD = cardiovascular disease; ECG = electrocardiogram; IMT = intima-media thickness; SCORE = Systematic COronary Risk Evaluation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reclassifies patients better into low- or high-risk groups.

8 Chronic coronary syndromes in specific circumstances

8.1 Cardiovascular comorbidities

8.1.1 Hypertension

Hypertension is the most prevalent cardiovascular risk factor and is closely associated with CCS. Thresholds for the definition of hypertension are provided in *Table 10*. BP lowering can significantly reduce major cardiovascular risk, including CHD. Meta-analysis suggests that for every 10 mmHg reduction in systolic BP, CAD can be reduced by 17%.[463] More intensive BP targets (office BP <130 mmHg) have been associated with favourable outcomes and are endorsed by the 2018 ESC/ESH Guidelines for the management of arterial hypertension.[464] It is recommended treat hypertensive patients with CCS are treated to office targets of 130/80 mmHg, because an increased systolic BP of ≥140 mmHg and diastolic BP of ≥80 mmHg, but also a systolic BP of <120 mmHg and diastolic BP of <70 mmHg, are associated with increased risk[465,466] (*Table 10*). Whether the J-curve phenomenon exists in patients with revascularized CAD remains uncertain. In hypertensive patients with CHD, beta-blockers and RAS blockers may improve post-MI outcomes.[467] In patients with symptomatic angina, beta-blockers and calcium antagonists are the preferred components of the drug-treatment strategy. The combination of ACE inhibitors and ARBs is not recommended for the treatment of hypertension because of increased renal adverse events without beneficially influencing outcome.[468,469]

Table 10 Blood pressure thresholds for the definition of hypertension with different types of blood pressure measurement[470–472]

Category	Systolic BP (mmHg)		Diastolic BP (mmHg)
Office BP	≥140	and/or	≥90
≥80 years of age	≥160	and/or	≥90
Ambulatory BP			
Daytime (or awake)	≥135	and/or	≥85
Night-time (or asleep)	≥120	and/or	≥70
24 h	≥130	and/or	≥80
Home BP	≥135	and/or	≥85

BP = blood pressure.

Recommendations for hypertension treatment in chronic coronary syndromes

Recommendations	Class[a]	Level[b]
It is recommended that office BP is controlled to target values: systolic BP 120 - 130 mmHg in general and systolic BP 130 - 140 mmHg in older patients (aged >65 years).[463–467,470–472]	I	A
In hypertensive patients with a recent MI, beta-blockers and RAS blockers are recommended.[467]	I	A
In patients with symptomatic angina, beta-blockers and/or CCBs are recommended.[467]	I	A
The combination of ACE inhibitors and ARBs is not recommended.[468,469]	III	A

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; RAS = renin-angiotensin system.
[a]Class of recommendation.
[b]Level of evidence.

8.1.2 Valvular heart disease (including planned transcatheter aortic valve implantation)

Coronary angiography for the assessment of CAD is recommended before valve surgery or when percutaneous valvular intervention is planned, to determine if revascularization is required. Coronary CTA may be considered in patients with low risk for CAD, or in patients in whom conventional ICA is technically not feasible or associated with increased risk. The combination of PCI and transcatheter aortic valve implantation appears feasible and safe, but more data are needed before definite recommendations can be provided.[473,474] The routine use of stress testing to detect CAD associated with severe symptomatic valvular disease is not recommended because of low diagnostic value and potential risk. Symptom-limited stress testing in patients with valvular heart disease appears safe, and may be useful to unmask symptoms in asymptomatic patients or in patients with equivocal symptoms.[475]

Recommendations for valvular disease in chronic coronary syndromes[476]

Recommendations	Class[a]	Level[b]
ICA is recommended before valve surgery and for any of the following: history of CVD, suspected myocardial ischaemia, LV systolic dysfunction, in men >40 years of age and postmenopausal women, or one or more cardiovascular risk factors.	I	C
ICA is recommended in the evaluation of moderate-to-severe functional mitral regurgitation.	I	C
Coronary CTA should be considered as an alternative to coronary angiography before valve intervention in patients with severe valvular heart disease and low probability of CAD.	IIa	C
PCI should be considered in patients undergoing transcatheter aortic valve implantation and coronary artery diameter stenosis >70% in proximal segments.	IIa	C
In severe valvular heart disease, stress testing should not be routinely used to detect CAD because of the low diagnostic yield and potential risks.	III	C

CAD = coronary artery disease; CTA = computed tomography angiography; CVD = cardiovascular disease; ICA = invasive coronary angiography; LV = left ventricular; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.

8.1.3 After heart transplantation

The follow-up and assessment of long-term heart transplant survivors requires specific know-how. Transplant CAD is largely an immunological phenomenon, and remains a significant cause of morbidity and mortality.[477] ICA is recommended for the assessment of transplant CAD and should be performed annually for 5 years after transplantation. If there are no significant abnormalities, angiograms can be performed biannually thereafter. Intravascular ultrasound

examinations may be useful in assessing cardiac allograft vasculopathy and plaque stability.[478] Treatment options for CAD in transplant recipients include pharmacotherapy and revascularization. PCI in the transplanted heart has become an established therapy.[479]

8.2 Non-cardiovascular comorbidities

8.2.1 Cancer

Occurrence of CAD in patients with active cancer is increasing[451,452] as a side effect of cancer therapy (i.e. radiotherapy to the thorax/mediastinum, cardiotoxic chemotherapy, or immunotherapies) or a result of extended cancer therapies in elderly individuals. CAD in patients with active cancer is associated with challenges for clinicians as treatment decisions should be the subject of individualized discussions based on life expectancy, additional comorbidities such as thrombocytopenia, increased thrombosis and bleeding propensity, and potential interactions between drugs used in CCS management and antineoplastic drugs. In cancer patients with increased frailty, the least invasive revascularization procedures are recommended. For further information, see the ESC position paper on cancer treatments and cardiovascular toxicity.[480]

Recommendations for active cancer in chronic coronary syndromes

Recommendations	Class[a]	Level[b]
Treatment decisions should be based on life expectancy, additional comorbidities such as thrombocytopenia, increased thrombosis propensity, and potential interactions between drugs used in CCS management and antineoplastic agents.	I	C
If revascularization is indicated in highly symptomatic patients with active cancer and increased frailty, the least invasive procedure is recommended.	I	C

CCS = chronic coronary syndromes.
[a]Class of recommendation.
[b]Level of evidence.

8.2.2 Diabetes mellitus

Diabetes mellitus confers about a two-fold increased risk for CAD[481] and, consequently, control of risk factors is recommended for the prevention of CVD. Systolic BP in patients with diabetes should be targeted to ≤130 mmHg, if tolerated, but not <120 mmHg, and diastolic BP to <80 mmHg, but not <70 mmHg.[482] Initial antihypertension treatment should consist of a combination of a RAS blocker with a CCB or thiazide/thiazide-like diuretic. ACE inhibitors reduce albuminuria, and the appearance or progression of diabetic nephropathy, more effectively than other drug classes.[482] Patients with diabetes and CAD are considered to be at very high risk; consequently, LDL-C should be lowered to <1.8 mmol/L (<70 mg/dL) or reduced by ≥50% if the baseline LCL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).[15] For the majority of patients with diabetes and CAD, a target glycated HbA1c level of <7% (<53 mmol/L) is recommended.[483,484] Large safety studies on new glucose-lowering drugs, namely sodium-glucose co-transporter-2 and glucagon-like peptide-1 receptor agonists, have demonstrated significant reductions in cardiovascular events. Indications for their clinical use are described in the 2019 ESC/European Association for the Study of Diabetes Guidelines on diabetes mellitus, pre-diabetes, and cardiovascular diseases.[16]

A 12 lead ECG is recommended as part of the routine assessment for screening for conduction abnormalities, LV hypertrophy, and arrhythmias. The high prevalence of significant CAD and prohibitively high cardiovascular mortality may suggest the usefulness of routine screening for CAD (with functional imaging testing or coronary CTA) in asymptomatic patients with diabetes, but no data have shown an improvement in outcomes so far. Routine use of CTA in asymptomatic patients with diabetes is therefore not recommended.

Recommendations for diabetes mellitus in chronic coronary syndromes

Recommendations	Class[a]	Level[b]
Risk factor (BP, LDL-C, and HbA1c) control to targets is recommended in patients with CAD and diabetes mellitus.[482–484]	I	A
In asymptomatic patients with diabetes mellitus, a periodic resting ECG is recommended for cardiovascular detection of conduction abnormalities, AF, and silent MI.	I	C
ACE inhibitor treatment is recommended in CCS patients with diabetes for event prevention.[482]	I	B
The sodium-glucose co-transporter 2 inhibitors empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with diabetes and CVD.[c] [485–487]	I	A
A glucagon-like peptide-1 receptor agonist (liraglutide or semaglutide) is recommended in patients with diabetes and CVD.[c] [488–490]	I	A
In asymptomatic adults (age >40 years) with diabetes, functional imaging or coronary CTA may be considered for advanced cardiovascular risk assessment.[491,492]	IIb	B

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; BP = blood pressure; CAD = coronary artery disease; CCS = chronic coronary syndromes; CTA = computed tomography angiography; CVD = cardiovascular disease; ECG = electrocardiogram; HbA1c = glycated haemoglobin; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Treatment algorithm is available in the 2019 European Society of Cardiology/European Association for the Study of Diabetes Guidelines on diabetes mellitus, pre-diabetes, and cardiovascular diseases.[16]

8.2.3 Chronic kidney disease

CAD is highly prevalent in patients with CKD and a growing number of patients undergoing PCI have concomitant CKD.[493] There is a linear increase in the risk of cardiovascular mortality with decreasing GFR.[494] Medical treatment for risk-factor control (lipids, BP, and glucose) can improve outcomes. Special attention during the workup for CKD patients with suspected obstructive CAD should be paid to the fact that angina is less common and silent ischaemia more common.[495] Additionally, non-invasive stress testing shows reduced accuracy in patients with CKD.[496] The use of an iodinated contrast agent should be minimized to prevent further deterioration of renal function. Decisions regarding diagnostic and treatment modalities should be made accordingly. Interestingly, patients with CKD are less likely to receive invasive management for treatment of CAD compared with those without, although benefits of invasive management have been reported.[497] Revascularization options in patients with CKD include CABG and PCI. Meta-analyses suggest that CABG is associated with higher short-term risk of death, stroke, and repeat revascularization, whereas PCI with a new-generation DES is associated with a higher long-term risk of repeat revascularization.[498,499] Data on patients on haemodialysis are very limited, making generalizable treatment recommendations difficult.

Recommendations for chronic kidney disease in chronic coronary syndromes

Recommendations	Class[a]	Level[b]
It is recommended that risk factors are controlled to target values.[500–502]	I	A
It is recommended that special attention is paid to potential dose adjustments of renally excreted drugs used in CCS.	I	C
It is recommended that the use of iodinated contrast agents is minimized in patients with severe CKD and preserved urine production to prevent further deterioration.[503,504]	I	B

CKD = chronic coronary disease; CCS = chronic coronary syndromes.
[a]Class of recommendation.
[b]Level of evidence.

8.2.4 Elderly

Ageing predisposes patients to a high incidence and prevalence of CAD, in both men and women. Elderly patients (age >75 years) have the greatest mortality and morbidity risk attributable to CCS, which is enriched by the high prevalence of comorbidities (e.g. hypertension, diabetes mellitus, CKD, etc.).[505] Although the prevalence of elderly patients with CAD is increasing, this population is usually undertreated, underdiagnosed, and under-represented in clinical trials. Elderly patients often present with atypical symptoms, which may delay proper diagnosis. The treatment of CCS in the elderly 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. It is recommended that radial access is used whenever possible to reduce access-site complications, when choosing an invasive strategy for patient management.[506,507] 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 elderly patients.[508,509]

Recommendations for elderly patients with chronic coronary syndromes

Recommendations	Class[a]	Level[b]
It is recommended that particular attention is paid to side effects of drugs, intolerance, and overdosing in elderly patients.	I	C
The use of DES is recommended in elderly patients.[508,509]	I	A
Radial access is recommended in elderly patients to reduce access-site bleeding complications.[506,507]	I	B
It is recommended that diagnostic and revascularization decisions are based on symptoms, the extent of ischaemia, frailty, life expectancy, and comorbidities.	I	C

DES = drug-eluting stents.
[a]Class of recommendation.
[b]Level of evidence.

8.3 Sex

Making up ≤30% of study populations, women are widely under-represented in cardiovascular studies.[510] This recruitment bias causes an evidence gap, as sex-based randomized controlled studies are lacking, and most data are extracted from meta-analyses and *post hoc* analyses of trials in ACS patients. Differences in symptom presentation, the accuracy of diagnostic tests for CAD, and other factors that lead to differential triage, evaluation, or early treatment of women with myocardial ischaemia compared with men could contribute to their worse outcomes.[511–514] Whether there are true sex-related differences in mortality after myocardial ischaemia, or whether they owing to older age or a higher prevalence of coexisting diseases in women, remains incompletely understood. It has become evident that sex-related mortality differences are particularly apparent in younger patients, typically those aged <60 years.[511,512,515] The reasons for this age-dependent disparity in mortality remain unclear. Women tend to be treated less aggressively than men.[515] However, patient characteristics and treatments do not entirely account for sex differences in outcomes, even after PCI.[512] It is therefore recommended that women who present with signs suggestive of cardiac ischaemia undergo careful investigation, as clinical symptoms might be atypical. The diagnostic accuracy of the exercise ECG is even lower in women than in men, which is in part related to functional impairment, precluding some women from achieving an adequate workload. Stress echocardiography with exercise or dobutamine stress is an accurate, non-invasive technique for the detection of obstructive CAD and risk among women with suspected CCS.[516] Both women and men have experienced improvements in mortality

when new-generation DES were used.[517–519] The mortality reductions were similar among women and men leaving sex disparities in outcomes unchanged.[512] Women have higher complication rates following CABG and may also have higher mortality risk,[520,521] especially in elderly patients. Hormone replacement therapy in postmenopausal women does not reduce the risk of ischaemic myocardial disease (see *section 3.3.5*), and is therefore not recommended for primary and secondary prevention.[344,522,523]

Recommendation for sex issues and chronic coronary syndromes

Recommendation	Class[a]	Level[b]
Hormone replacement therapy is not recommended for risk reduction in post-menopausal women.	III	C

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

8.4 Patients with refractory angina

Refractory angina refers to long-lasting symptoms (for ≥3 months) due to established reversible ischaemia in the presence of obstructive CAD, which cannot be controlled by escalating medical therapy with the use of second- and third-line pharmacological agents, bypass grafting, or stenting including PCI of chronic total coronary occlusion. Incidence is growing with more advanced CAD, multiple comorbidities, and ageing of the population. The quality of life of patients with refractory angina is poor, with frequent hospitalization and a high level of resource utilization. The number of potential treatment options is increasing, but the level of evidence in support of their safety and efficacy varies from non-existent (in the case of transmyocardial laser application) to promising. RCTs with endpoints such as the severity and frequency of angina, as well as quality of life, are obviously needed, along with safety metrics. To confirm treatment efficacy, trials with a sham-controlled design are desirable, a significant placebo effect being part of the therapeutic effect. Patients with refractory angina are best treated in dedicated 'angina clinics' by multidisciplinary teams experienced in selecting the most suitable therapeutic approach in the individual patient based on an accurate diagnosis of the mechanisms of the pain syndrome. Once conventional anti-ischaemic targets have been exhausted (through an increase in nutrient blood flow delivery and/or reduction in oxygen consumption), 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 (*Table 11*).

Both the STARTSTIM and RENEW (Efficacy and Safety of Targeted Intramyocardial Delivery of Auto CD34+ Stem Cells for Improving Exercise Capacity in Subjects With Refractory Angina) trials were underpowered due to premature study termination. Of note, a patient-level pooled analysis of 304 patients included in three double-blind, cell therapy, placebo-controlled trials, among which was the RENEW trial, showed that active treatment with autologous haematopoietic cells had significant effects on exercise time and angina frequency.[528]

Based on positive results from two RCTs in small groups of patients, both enhanced external counterpulsation and the coronary sinus reducer device represent alternative options in patients with refractory angina, which is resistant after having exhausted all options for medical therapy and mechanical revascularization. Controlled coronary sinus narrowing with the implantation of a large stainless-steel device increases coronary sinus pressure, leading to improved perfusion in the LAD territory.

Total reported experience with all novel therapeutic options remains limited, both regarding the number of treated patients and the duration of follow-up. Larger RCTs are required to define the role of each treatment modality for specific subgroups, to decrease non-responder rates and ascertain benefit beyond potential placebo effects.

Table 11 Potential treatment options for refractory angina and summary of trial data

Therapy	Type of therapy	RCT	Type of control group	Number of patients enrolled
External counterpulsation	Enhanced external counterpulsation	MUST[524]	Sham	139
Extracorporeal shockwave	Low-energy extracorporeal shockwave therapy	Not available	Not available	—
Coronary sinus constriction	Reducer device	COSIRA[525]	Sham	104
Neuromodulation	Spinal cord stimulation	STARTSTIM[526]	Not available	68
	Transcutaneous electrical neural stimulation	Not available	Not available	—
	Subcutaneous electrical neural stimulation	Not available	Not available	—
	Sympathectomy	Denby *et al.*[527]	Placebo	65
Gene therapy	Adenovirus fibroblast growth factor 5	Not available	Not available	—
Autologous cell therapy	Mononuclear bone marrow-derived haematopoietic progenitor cells	RENEW[528]	Placebo	112

RCT = randomized clinical trial.

Recommendations for treatment options for refractory angina

Recommendations	Class[a]	Level[b]
Enhanced external counterpulsation may be considered for symptom relief in patients with debilitating angina refractory to optimal medical and revascularization strategies.[524]	IIb	B
A reducer device for coronary sinus constriction may be considered to ameliorate symptoms of debilitating angina refractory to optimal medical and revascularization strategies.[525]	IIb	B
Spinal cord stimulation may be considered to ameliorate symptoms and quality of life in patients with debilitating angina refractory to optimal medical and revascularization strategies.[526]	IIb	B
Transmyocardial revascularization is not recommended in patients with debilitating angina refractory to optimal medical and revascularization strategies.[529]	III	A

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

9 Key messages

(1) Careful evaluation of patient history, including the characterization of anginal symptoms, and evaluation of risk factors and manifestations of CVD, as well as proper physical examination and basic testing, are crucial for the diagnosis and management of CCS.

(2) Unless obstructive CAD can be excluded based on clinical evaluation alone, either non-invasive functional imaging or anatomical imaging using coronary CTA may be used as the initial test to rule-out or establish the diagnosis of CCS.

(3) Selection of the initial non-invasive diagnostic test is based on the PTP, the test's performance in ruling-in or ruling-out obstructive CAD, patient characteristics, local expertise, and the availability of the test.

(4) For revascularization decisions, both anatomy and functional evaluation are to be considered. Either non-invasive or invasive functional evaluation is required for the assessment of myocardial ischaemia associated with angiographic stenosis, unless very high grade (>90% diameter stenosis).

(5) Assessment of risk serves to identify CCS patients at high event risk who are projected to derive prognostic benefit from revascularization. Risk stratification includes the assessment of LV function.

(6) Patients at high event risk should undergo invasive investigation for consideration of revascularization, even if they have mild or no symptoms.

(7) Implementation of healthy lifestyle behaviours decreases the risk of subsequent cardiovascular events and mortality, and is additional to appropriate secondary prevention therapy. Clinicians should advise on and encourage necessary lifestyle changes in every clinical encounter.

(8) Cognitive behavioural interventions such as supporting patients to set realistic goals, self-monitor, plan how to implement changes and deal with difficult situations, set environmental cues, and engage social support are effective interventions for behaviour change.

(9) Multidisciplinary teams can provide patients with support to make healthy lifestyle changes, and address challenging aspects of behaviour and risk.

(10) Anti-ischaemic treatment must be adapted to the individual patient based on comorbidities, co-administered therapies, expected tolerance and adherence, and patient preferences. The choice of anti-ischaemic drugs to treat CCS should be adapted to the patient's heart rate, BP, and LV function.

(11) Beta-blockers and/or CCBs remain the first-line drugs in patients with CCS. Beta-blockers are recommended in patients with LV dysfunction or HF with reduced ejection fraction.

(12) Long-acting nitrates provoke tolerance with loss of efficacy. This requires prescription of a daily nitrate-free or nitrate-low interval of ~10–14 h.

(13) Antithrombotic therapy is a key part of secondary prevention in patients with CCS and warrants careful consideration. Patients with a previous MI, who are at high risk of ischaemic events and low risk of fatal bleeding, should be considered for long-term DAPT with aspirin and either a $P2Y_{12}$ inhibitor or very low-dose rivaroxaban, unless they have an indication for an OAC such as AF.

(14) Statins are recommended in all patients with CCS. ACE inhibitors (or ARBs) are recommended in the presence of HF, diabetes, or hypertension and should be considered in high-risk patients.

(15) Proton pump inhibitors are recommended in patients receiving aspirin or combination antithrombotic therapy who are at high risk of gastrointestinal bleeding.

(16) Efforts should be made to explain to patients the importance of evidence-based prescriptions to increase adherence to treatment, and repeated therapeutic education is essential in every clinical encounter.

(17) Patients with a long-standing diagnosis of CCS should undergo periodic visits to assess potential changes in risk status, adherence to treatment targets, and the development of comorbidities. Repeat stress imaging or ICA with functional testing is recommended in the presence of worsening symptoms and/or increased risk status.

(18) Assessment of myocardial and valvular function and dimensions, as well as a functional test to rule-out significant myocardial silent ischaemia, may be contemplated every 3–5 years in asymptomatic patients with a long-standing diagnosis of CCS.

(19) An assessment of coronary vasomotor function should be considered in patients with non-significant epicardial CAD and objective evidence of ischaemia.

10 Gaps in the evidence

10.1 Diagnosis and assessment

More information on the effects of various risk factors, biomarkers, and comorbidities on the PTP of obstructive CAD is needed. Adequately powered RCTs are needed to compare the effectiveness of different diagnostic strategies, and to evaluate how to best integrate diagnostic tests in patient care in terms of clinical outcomes and the use of healthcare resources.

10.2 Assessment of risk

Studies should address whether an initial invasive strategy, in addition to optimal medical therapy in patients with CCS and inducible ischaemia by non-invasive testing, improves outcomes. Larger trials are needed to verify the utility of systematic assessment of biomarkers in patients with suspected obstructive CAD.

10.3 Lifestyle management

Research regarding the most effective methods to support healthy lifestyle behaviours in brief or very brief clinical encounters, and sustain medication and lifestyle behaviour adherence over time, is needed. The cardiovascular effects of newer e-cigarettes over the long-term remain unknown, as does their effectiveness in smoking cessation.

The relative benefits of high-intensity interval training vs. moderate-intensity exercise in patients with CCS should be further evaluated. The benefits of decreasing sedentary behaviour, and the most appropriate 'dose' and type of physical activity in patients with CCS, are unknown, as are the effectiveness and cost-effectiveness of increasing cardiac rehabilitation participation among patients with CCS.

10.4 Pharmacological management

The need for and duration of beta-blocker therapy following MI to maintain a protective effect on cardiac events in the absence of LV systolic dysfunction are unknown.

In patients with CCS and without a previous MI, it remains to be determined whether current anti-ischaemic drugs improve prognosis.

Whether the initial use of second-line anti-ischaemic therapy (i.e. long-acting nitrates, ranolazine, nicorandil, ivabradine, or trimetazidine) alone or in combination with a first-line drug (i.e. beta-blocker or CCB) is superior to the combination of a beta-blocker with a CCB to control anginal symptoms and myocardial ischaemia in patients with CCS remains to be proven.

The efficacy and safety of aspirin or an alternative antithrombotic therapy in patients with a mild extent of atherosclerotic disease, such as that discovered by coronary CTA, requires further assessment, including the effect on cancer rates as well as cardiovascular events. The optimal long-term antithrombotic therapy, and strategies for individualizing this, in patients at high risk of ischaemic events is uncertain. Consequently, clinical studies comparing the efficacy and safety of aspirin + $P2Y_{12}$ inhibitor with aspirin + factor Xa inhibitor are warranted to determine which subgroups may be preferentially treated with one or other strategy. The potential clinical benefit of ticagrelor monotherapy, while stopping aspirin, remains unproved at present.

The role of biomarkers in stratifying patients' risk of ischaemic events and bleeding requires clarification, including the role of growth differentiation factor-15 in guiding the risk of bleeding with DAPT. It is uncertain what effect novel lipid-lowering strategies will have on the net clinical benefit of DAPT, with similar implications of other strategies such as intensive BP lowering and, potentially in the future, selective anti-inflammatory therapies.

10.5 Revascularization

Further studies, including RCTs, are needed to assess the value of functional vs. anatomical guidance for CABG. The concept of complete revascularization and its effect on prognosis needs to be re-evaluated by prospective comparisons of functional vs. anatomical guidance for stenting on the one hand, and bypass on the other. Of note, none of the RCTs comparing PCI with CABG to date have used combined anatomical and functional guidance for PCI, a strategy that is suggested to significantly improve outcomes of PCI (Syntax II registry).

10.6 Heart failure and left ventricular dysfunction

Most of the evidence from RCTs supporting the recommendations for the use of drugs and devices in patients with chronic heart failure is based on cohorts with stable ischaemic heart disease and reduced LV function. However, patients with CCS requiring acute or chronic mechanical support are largely excluded from clinical trials, and the optimal management of such patients with drugs and devices during episodes of acute decompensation has not been adequately addressed.

10.7 Patients with long-standing diagnosis of chronic coronary syndromes

The incremental value of using risk scores to serially evaluate patients' risks, and more importantly to adjust the intensity of treatment, remains to be determined.

The optimal time intervals for serial visits remain to be determined.

10.8 Angina without obstructive coronary artery disease

Development of safe and efficacious novel pharmacological agents for this indication remains an unmet need.

10.9 Screening in asymptomatic subjects

Further studies on biomarkers and imaging tests for screening of CAD in asymptomatic subjects are needed. Furthermore, there are limited data on how to manage asymptomatic subjects who receive testing and have a positive test result, as evidence demonstrating improved prognosis following appropriate management is still lacking.

10.10 Comorbidities

The role of PCI in patients with aortic stenosis remains undetermined with respect to the indication for coronary revascularization and timing vs. valve intervention. Further information is needed on how to adapt cardiovascular therapies in patients with chronic inflammatory diseases.

10.11 Patients with refractory angina

Larger RCTs and registries are required to define the role of additional treatment modalities for specific subgroups, to decrease non-responder rates and ascertain benefit beyond potential placebo effects.

11 'What to do' and 'what not to do' messages from the Guidelines

Recommendations: 'what to do' and 'what not to do'	Class[a]	Level[b]
Basic biochemistry testing in the initial diagnostic management of patients with suspected CAD		
If evaluation suggests clinical instability or ACS, repeated measurements of troponin, preferably using high-sensitivity or ultrasensitive assays, are recommended to rule-out myocardial injury associated with ACS.	I	A
The following blood tests are recommended in all patients:		
• Full blood count (including haemoglobin);	I	B
• Creatinine measurement and estimation of renal function;	I	A
• A lipid profile (including LDL-C).	I	A
It is recommended that screening for type 2 diabetes mellitus in patients with suspected and established CCS is implemented with HbA1c and fasting plasma glucose measurements, and that an oral glucose tolerance test is added if HbA1c and fasting plasma glucose results are inconclusive.	I	B
Assessment of thyroid function is recommended in cases where there is clinical suspicion of thyroid disorders.	I	C
Resting ECG in the initial diagnostic management of patients with suspected CAD		
A resting 12 lead ECG is recommended in all patients with chest pain without obvious non-cardiac cause.	I	C
A resting 12 lead ECG is recommended in all patients during or immediately after an episode of angina suspected to indicate clinical instability of CAD.	I	C
ST-segment alterations recorded during supraventricular tachyarrhythmias should not be used as evidence of CAD.	III	C
Ambulatory ECG monitoring in the initial diagnostic management of patients with suspected CAD		
Ambulatory ECG monitoring is recommended in patients with chest pain and suspected arrhythmias.	I	C
Ambulatory ECG monitoring should not be used as routine examination in patients with suspected CCS.	III	C
Resting echocardiography and CMR in the initial diagnostic management of patients with suspected CAD		
A resting transthoracic echocardiogram is recommended in all patients for: • Exclusion of alternative causes of angina; • Identification of regional wall motion abnormalities suggestive of CAD; • Measurement of LVEF for risk-stratification purposes; • Evaluation of diastolic function.	I	B
Chest X-ray in the initial diagnostic management of patients with suspected CAD		
Chest X-ray is recommended for patients with an atypical presentation, signs and symptoms of heart failure, or suspicion of pulmonary disease.	I	C
Use of diagnostic imaging tests in the initial diagnostic management of symptomatic patients with suspected CAD		
Non-invasive functional imaging for myocardial ischaemia or coronary CTA is recommended as the initial test for diagnosing CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone.	I	B
It is recommended that selection of the initial non-invasive diagnostic test is done based on the clinical likelihood of CAD and other patient characteristics that influence test performance, local expertise, and the availability of tests.	I	C
Functional imaging for myocardial ischaemia is recommended if coronary CTA has shown CAD of uncertain functional significance or is not diagnostic.	I	B
Invasive angiography is recommended as an alternative test to diagnose CAD in patients with a high clinical likelihood and severe symptoms refractory to medical therapy, or typical angina at a low level of exercise and clinical evaluation that indicates high event risk. Invasive functional assessment must be available and used to evaluate stenoses before revascularization, unless very high grade (>90% diameter stenosis).	I	B

Continued

Coronary CTA is not recommended when extensive coronary calcification, irregular heart rate, significant obesity, inability to cooperate with breath-hold commands, or any other conditions makes good image quality unlikely.	III	C
Coronary calcium detection by computed tomography is not recommended to identify individuals with obstructive CAD.	III	C
Performing exercise ECG in the initial diagnostic management of patients with suspected CAD		
Exercise ECG is recommended for the assessment of exercise tolerance, symptoms, arrhythmias, BP response, and event risk in selected patients.	I	C
Recommendations for risk assessment		
Risk stratification is recommended based on clinical assessment and the result of the diagnostic test initially employed to make a diagnosis of CAD.	I	B
Resting echocardiography is recommended to quantify LV function in all patients with suspected CAD.	I	C
Risk stratification, preferably using stress imaging or coronary CTA (if local expertise and availability permit), or alternatively exercise stress ECG (if significant exercise can be performed and the ECG is amenable to the identification of ischaemic changes), is recommended in patients with suspected or newly diagnosed CAD.	I	B
In symptomatic patients with a high-risk clinical profile, ICA complemented by invasive physiological guidance (FFR) is recommended for cardiovascular risk stratification, particularly if the symptoms are inadequately responding to medical treatment and revascularization is considered for improvement of prognosis.	I	A
In patients with mild or no symptoms, ICA complemented by invasive physiological guidance (FFR/iwFR) is recommended for patients undergoing medical treatment in whom non-invasive risk stratification indicates a high event risk and revascularization is considered for the improvement of prognosis.	I	A
ICA is not recommended solely for risk stratification.	III	C
Recommendations on lifestyle management		
Improvement of lifestyle factors in addition to appropriate pharmacological management is recommended.	I	A
Cognitive behavioural interventions are recommended to help individuals achieve a healthy lifestyle.	I	A
Exercise-based cardiac rehabilitation is recommended as an effective means for patients with CCS to achieve a healthy lifestyle and manage risk factors.	I	A
Involvement of multidisciplinary healthcare professionals (cardiologists, GPs, nurses, dieticians, physiotherapists, psychologists, and pharmacists) is recommended.	I	A
Psychological interventions are recommended to improve symptoms of depression in patients with CCS.	I	B
Annual influenza vaccination is recommended for patients with CCS, especially in the elderly.	I	B
Recommendations on anti-ischaemic drugs in patients with CCS		
General considerations		
Medical treatment of symptomatic patients requires one or more drug(s) for angina/ischaemia relief in association with drug(s) for event prevention.	I	C
It is recommended that patients are educated about the disease, risk factors, and treatment strategy.	I	C
Timely review of the patient's response to medical therapies (e.g. 2–4 weeks after drug initiation) is recommended.	I	C
Angina/ischaemia relief		
Short-acting nitrates are recommended for immediate relief of effort angina.	I	B
First-line treatment is indicated with beta-blockers and/or CCBs to control heart rate and symptoms.	I	A
Nitrates are not recommended in patients with hypertrophic obstructive cardiomyopathy or co-administration of phosphodiesterase inhibitors.	III	B
Recommendations for event prevention		
Antithrombotic therapy in patients with CCS and in sinus rhythm		
Aspirin 75–100 mg daily is recommended in patients with a previous MI or revascularization.	I	A
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in patients with aspirin intolerance.	I	B
Antithrombotic therapy post-PCI in patients with CCS and in sinus rhythm		
Aspirin 75–100 mg daily is recommended following stenting.	I	A
Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg, >5 days, or maintenance therapy) is recommended, in addition to aspirin, for 6 months following coronary stenting, irrespective of stent type, unless a shorter duration (1–3 months) is indicated due to the risk or occurrence of life-threatening bleeding.	I	A
Antithrombotic therapy in patients with CCS and AF		
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
Long-term OAC therapy (a 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

Continued

Antithrombotic therapy in post-PCI patients with AF or another indication for an OAC		
It is recommended that peri-procedural aspirin and clopidogrel are administered to patients undergoing coronary stent implantation.	I	C
In patients who are eligible for a NOAC, it is recommended that a NOAC (apixaban 5 mg b.i.d., dabigatran 150 mg b.i.d., edoxaban 60 mg o.d., or rivaroxaban 20 mg o.d.) is used in preference to a VKA in combination with antiplatelet therapy.	I	A
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and an OAC.	III	C
Use of proton pump inhibitors		
Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or OAC monotherapy who are at high risk of gastrointestinal bleeding.	I	A
Lipid-lowering drugs		
Statins are recommended in all patients with CCS.	I	A
If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.	I	B
For patients at very high risk who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with a PCSK9 inhibitor is recommended.	I	A
ACE inhibitors		
ACE inhibitors (or ARBs) are recommended in the presence of other conditions (e.g. HF, hypertension, or diabetes).	I	A
Other drugs		
Beta-blockers are recommended in patients with LV dysfunction or systolic HF.	I	A
General recommendations for the management of patients with CCS and symptomatic HF due to ischaemic cardiomyopathy and LV systolic dysfunction		
Recommendations for drug therapy		
Diuretic therapy is recommended in symptomatic patients with signs of pulmonary or systemic congestion to relieve HF symptoms.	I	B
Beta-blockers are recommended as an essential component of treatment due to their efficacy in both relieving angina, and reducing morbidity and mortality in HF.	I	A
ACE inhibitor therapy is recommended in patients with symptomatic HF or asymptomatic LV dysfunction following MI, to improve symptoms and reduce morbidity and mortality.	I	A
An ARB is recommended as an alternative in patients who do not tolerate ACE inhibition or an angiotensin receptor-neprilysin inhibitor in patients with persistent symptoms despite optimal medical therapy.	I	B
An MRA is recommended in patients who remain symptomatic despite adequate treatment with an ACE inhibitor and beta-blocker to reduce morbidity and mortality.	I	A
For devices, comorbidities, and revascularization		
In patients with HF and bradycardia with high-degree atrioventricular block who require pacing, a CRT with a pacemaker rather than right ventricular pacing is recommended.	I	A
An implantable cardioverter-defibrillator is recommended in patients with documented ventricular dysrhythmia causing haemodynamic instability (secondary prevention), as well as in patients with symptomatic HF and an LVEF ≤35%, to reduce the risk of sudden death and all-cause mortality.	I	A
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 ms and LBBB QRS morphology, and with LVEF ≤35% despite optimal medical therapy to improve symptoms and reduce morbidity and mortality. [355,356,383–392,353,354,381–390]	I	A
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration 130–149 ms and LBBB QRS morphology, and with LVEF ≤35% despite optimal medical therapy to improve symptoms and reduce morbidity and mortality. [355,356,383–392,353,354,381–390]	I	B
Comprehensive risk profiling and multidisciplinary management, including treatment of major comorbidities such as hypertension, hyperlipidaemia, diabetes, anaemia, and obesity, as well as smoking cessation and lifestyle modification, are recommended.	I	A
Myocardial revascularization is recommended when angina persists despite treatment with antianginal drugs.	I	A
Recommendations for patients with a long-standing diagnosis of CCS		
Asymptomatic patients		
A periodic visit to a cardiovascular healthcare professional is recommended to reassess potential changes in the risk status of patients, entailing clinical evaluation of lifestyle-modification measures, adherence to targets of cardiovascular risk factors, and the development of comorbidities that may affect treatments and outcomes.	I	C

Continued

In patients with mild or no symptoms receiving medical treatment, in whom non-invasive risk stratification indicates a high risk, and for whom revascularization is considered for improvement of prognosis, ICA (with FFR when necessary) is recommended.	I	C
Coronary CTA is not recommended as a routine follow-up test for patients with established CAD.	III	C
ICA is not recommended solely for risk stratification.	III	C
Symptomatic patients		
Reassessment of CAD status is recommended in patients with deteriorating LV systolic function that cannot be attributed to a reversible cause (e.g. long-standing tachycardia or myocarditis).	I	C
Risk stratification is recommended for patients with new or worsening symptom levels, preferably using stress imaging or, alternatively, exercise stress ECG.	I	B
It is recommended that patients with significant worsening of symptoms be expeditiously referred for evaluation.	I	C
ICA (with FFR/iwFR when necessary) is recommended for risk stratification in patients with severe CAD, particularly if the symptoms are refractory to medical treatment or if they have a high-risk clinical profile.	I	C
Investigations in patients with suspected vasospastic angina		
An ECG is recommended during angina if possible.	I	C
Invasive angiography or coronary CTA is recommended in patients with characteristic episodic resting angina and ST-segment changes, which resolve with nitrates and/or calcium antagonists, to determine the extent of underlying coronary disease.	I	C
Screening for CAD in asymptomatic subjects		
Total risk estimation using a risk-estimation system such as SCORE is recommended for asymptomatic adults aged >40 years without evidence of CVD, diabetes, CKD, or familial hypercholesterolaemia.	I	C
Assessment of family history of premature CVD (defined as a fatal or non-fatal CVD event, and/or established diagnosis of CVD in first-degree male relatives before 55 years of age or female relatives before 65 years of age) is recommended as part of cardiovascular risk assessment.	I	C
It is recommended that all individuals aged <50 years with a family history of premature CVD in a first-degree relative (<55 years of age in men, <65 years of age in women) are screened for familial hypercholesterolaemia using a validated clinical score.	I	B
Carotid ultrasound IMT for cardiovascular risk assessment is not recommended.	III	A
In low-risk non-diabetic asymptomatic adults, coronary CTA or functional imaging for ischaemia is not indicated for further diagnostic assessment.	III	C
Routine assessment of circulating biomarkers is not recommendedfor cardiovascular risk stratification.	III	B
Recommendations for hypertension treatment in CCS		
It is recommended that office BP be controlled to target values: systolic BP 120–130 mmHg in general and systolic BP 130–140 mmHg in older patients (aged >65 years).	I	A
In hypertensive patients with a recent MI, beta-blockers and RAS blockers are recommended.	I	A
In patients with symptomatic angina, beta-blockers and/or CCBs are recommended.	I	A
The combination of ACE inhibitors and an ARB is not recommended.	III	A
Recommendations for valvular disease in CCS		
ICA is recommended before valve surgery and any of the following: history of CVD, suspected myocardial ischaemia, LV systolic dysfunction, in men aged >40 years and post-menopausal women, or one or more cardiovascular risk factors.	I	C
ICA is recommended in the evaluation of moderate-to-severe functional mitral regurgitation.	I	C
In severe valvular heart disease, stress testing should not be routinely used to detect CAD because of the low diagnostic yield and potential risks.	III	C
Recommendations for active cancer in CCS		
Treatment decisions should be based on life expectancy, additional comorbidities such as thrombocytopenia, increased thrombosis propensity, and potential interactions between drugs used in CCS management and antineoplastic agents.	I	C
If revascularization is indicated in highly symptomatic patients with active cancer and increased frailty, the least invasive procedure is recommended.	I	C
Recommendations for diabetes mellitus in CCS		
Risk factor (BP, LDL-C, and HbA1c) control to targets is recommended in patients with CAD and diabetes mellitus.	I	A
In asymptomatic patients with diabetes mellitus, a periodic resting ECG is recommended for cardiovascular detection of conduction abnormalities, AF, and silent MI.	I	C

Continued

Treatment with ACE inhibitors is recommended in CCS patients with diabetes for event prevention.	I	B
The sodium-glucose co-transporter 2 inhibitors empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with diabetes and CVD.	I	A
A glucagon-like peptide-1 receptor agonist (liraglutide or semaglutide) is recommended in patients with diabetes and CVD.	I	A
Recommendations for CKD in CCS		
It is recommended that risk factors are controlled to target values.	I	A
It is recommended that special attention be paid to potential dose adjustments of renally excreted drugs used in CCS.	I	C
It is recommended that the use of iodinated contrast agents is minimized in patients with severe CKD and preserved urine production to prevent further deterioration.	I	B
Recommendations for elderly patients with CCS		
It is recommended that particular attention is paid to side effects of drugs, intolerance, and overdosing in elderly patients.	I	C
The use of DES is recommended in elderly patients.	I	A
Radial access is recommended in elderly patients to reduce access-site bleeding complications.	I	B
It is recommended that diagnostic and revascularization decisions are based on symptoms, the extent of ischaemia, frailty, life expectancy, and comorbidities.	I	C
Recommendation for sex issues and CCS		
Hormone replacement therapy is not recommended for risk reduction in post-menopausal women.	III	C
Treatment options in refractory angina		
Transmyocardial revascularization is not recommended in patients with debilitating angina refractory to optimal medical and revascularization strategies.	III	A

ACE = angiotensin-converting enzyme; ACS = acute coronary syndromes; AF = atrial fibrillation; ARB = angiotensin receptor blocker; b.i.d. = bis in die (twice a day); BP = blood pressure; CHA_2DS_2-VASc = Cardiac failure, Hypertension, Age ≥75 [Doubled], Diabetes, Stroke [Doubled] – Vascular disease, Age 65–74 and Sex category [Female]; CAD = coronary artery disease; CCB = calcium channel blocker; CCS = chronic coronary syndromes; CKD = chronic kidney disease; CMR = cardiac magnetic resonance; CRT = cardiac resynchronization therapy; CTA = computed tomography angiography; CVD = cardiovascular disease; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; ECG = electrocardiogram; FFR = fractional flow reserve; GPs = general practitioners; HbA1C = glycated haemoglobin; HF = heart failure; ICA = invasive coronary angiography; IMT = intima-media thickness; iwFR = instantaneous wave-free ratio (instant flow reserve); LBBB = left bundle branch block; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; o.d. = omni die (once a day); PCI = percutaneous coronary intervention; PCSK9 = proprotein convertase subtilisin-kexin type 9; RAS = renin-angiotensin system; VKA = vitamin K antagonist.

[a]Class of recommendation.

[b]Level of evidence.

12 Supplementary data

Supplementary Data with additional Supplementary Tables and Figures complementing the full text—as well as *section 3* on patients with angina and/or dyspnoea, and suspected coronary artery disease—are available on the *European Heart Journal* website and via the ESC website at www.escardio.org/guidelines.

13 Appendix

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