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ZAPORIZHZHIA STATE MEDICAL AND PHARMACEUTICAL UNIVERSITY
Department of Internal Diseases 2

CHRONIC CORONARY SYNDROMES: RECOMMENDATIONS FOR DIAGNOSIS AND MANAGEMENT

Guide for practical classes of 5th year students specialty "Medicine"

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Approved by the meeting of the Central methodical committee of Zaporizhzhia State Medical and Pharmaceutical University and it is recommended for the use in educational process for foreign students. (Protocol no __ "__" ___ ____ 2023)

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The guide was developed for students of 5th courses of medical faculties to help learn internal medicine. It contains recommendations for the diagnosis and management of chronic coronary syndromes, in accordance with the work program in the discipline of "Internal Medicine" for Specialties "Medicine" and "Pediatrics"..

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CONTENT

Index of acronyms.

ABI - Ankle-brachial index

ACE - Angiotensin-converting enzyme

ACS - Acute coronary syndrome(s)

AF - Atrial fibrillation

ARB - Angiotensin receptor blocker

BB - beta-blocker

BMI - Body mass index

BP - Blood pressure

CABG - Coronary artery bypass grafting

CAD - Coronary artery disease

CCB - Calcium channel blocker

CCS - Chronic coronary syndrome(s)

CFR - Coronary flow reserve

CHD - Coronary heart disease

CKD - Chronic kidney disease

CMR - Cardiac magnetic resonance

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

FFR - Fractional flow reserve

GFR - Glomerular filtration rate

HbA1c - Glycated haemoglobin

HF - Heart failure

ICA - Invasive coronary angiography

IMT - Intima-media thickness

LAD - Left anterior descending

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

PAD - Peripheral artery disease

PCI - Percutaneous coronary intervention

PCSK9 - Proprotein convertase subtilisin-kexin type 9

PET - Positron emission tomography

PTP - Pre-test probability

RAS - Renin-angiotensin system

RCT - Randomized clinical trial

SCORE - Systematic COronary Risk Evaluation

Foreword

The task force is addressed to students of 5th course of medical university for helping to study of some parts of internal medicine in field of clinical cardiology.

The study of chronic coronary syndromes is a component of the typical and working programs in the discipline "Internal Medicine" in the 5th year of higher medical education in the specialty "Medicine".

Coronary artery disease (CAD) is a pathological process characterized by the accumulation of atherosclerotic plaques in the arteries of the epicardium. This process can be modified by lifestyle changes, pharmacological therapies, and invasive interventions aimed at achieving disease stabilization or regression. The disease can have a long, stable period, but it can also become unstable at any time, usually due to an acute atherothrombotic event caused by plaque rupture or erosion. The dynamic nature of the CAD process leads to various clinical manifestations that can be conveniently classified as acute coronary syndromes (ACS) or chronic coronary syndromes (CCS). We will review the recommendations for the management of patients with CCS.

New/revised concepts in these guidelines:

- The guidelines have been revised to focus on CVD rather than stable CAD.

- This change emphasizes the fact that the clinical presentation of CAD can be categorized as either ACS or CCS. CAD is a dynamic process of atherosclerotic plaque accumulation and functional changes in the coronary circulation that can be modified by lifestyle, pharmacological therapy, and revascularization, leading to disease stabilization or regression.

- The current CCS guidelines identify six clinical scenarios that are most commonly encountered in patients.

- The pre-test probability (PTB) of CAD based on age, gender, and symptom pattern has undergone significant changes. In addition, a new wording "Clinical likelihood of CAD" was introduced, which also uses various risk factors for CAD as modifiers of the PTV. The use of different diagnostic tests in different patient groups to exclude or confirm CAD was updated.

- The recommendations emphasize the crucial role of lifestyle modification and other preventive measures in reducing the risk of further cardiovascular complications and mortality.

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;

(II) patients with new onset of heart failure (HF) or left ventricular (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.

All of these manifestations are classified as CCS, but have different risks for future cardiovascular events (e.g., death or myocardial infarction (MI)), and the risk may change over time. The risk may increase as a result of poorly controlled cardiovascular risk factors, suboptimal lifestyle modifications and/or drug therapy, or unsuccessful revascularization. In addition, the risk may be reduced by appropriate secondary prevention and successful revascularization. The development of ACS can acutely destabilize each of these clinical scenarios. Thus, CCS is defined by different evolutionary phases of coronary artery disease, except in situations where acute coronary thrombosis dominates the clinical manifestations (i.e., ACS).

Recommendations are categorized by class and level of evidence.

Categories of recommendations

Class I - evidence and/or consensus of experts that a given diagnostic method or treatment is appropriate and effective.

Class II - there is conflicting evidence and/or disagreement among experts about the usefulness/effectiveness of a diagnostic or treatment method:

IIa - the evidence and/or expert opinion on the benefit and effectiveness prevails;

IIb - the benefit and effectiveness are insufficiently supported by evidence and/or expert opinion.

Class III - there is evidence and/or consensus among experts that a given diagnostic method or treatment is not useful and effective, and in some cases may be harmful.

Levels of evidence for recommendations

A - recommendations are based on the results of at least 2 randomized clinical trials;

B - recommendations are based on the results of one randomized clinical trial and/or a meta-analysis of non-randomized trials;

C - recommendations are based on the general opinion of experts and/or the results of small studies, retrospective studies and registries.

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

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 Table 1. 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.

After these steps, appropriate therapies are to be initiated, which include lifestyle management, medical therapy, and revascularization when indicated.

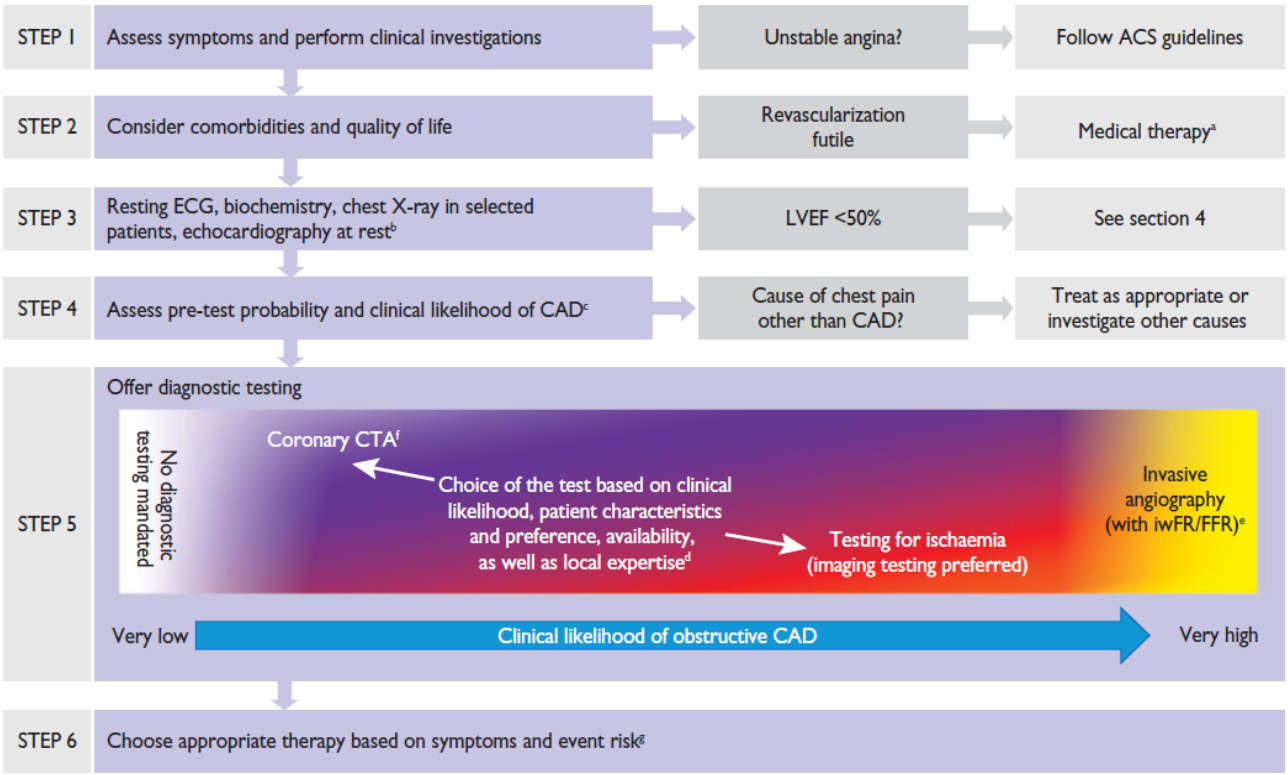
Step 1: Symptoms and signs.

A careful history is the cornerstone of angina diagnosis. A high degree of diagnostic confidence can be achieved on the basis of history alone, although physical examination and objective tests are often necessary to confirm the diagnosis, rule out alternative diagnoses, and assess the severity of the underlying disease. The history should include any manifestations of cardiovascular disease (CVD) and risk factors (i.e., family history of CVD, dyslipidemia, diabetes, hypertension, smoking, and other factors).

The characteristics of discomfort associated with myocardial ischemia (angina) can be divided into four categories: localization, nature, duration, and relationship to

physical activity and other aggravating or weakening factors. Discomfort caused by myocardial ischemia is usually localized in the chest, near the sternum, but can 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 or heaviness; sometimes as a squeezing, constricting, or burning pain. It may be helpful to ask the patient about the presence of "discomfort" as many do not feel "pain" or "pressure" in the chest. Shortness of breath can accompany angina, and chest discomfort can also be accompanied by less specific symptoms such as fatigue or fainting, nausea, burning, anxiety, or fear of death. Shortness of breath may be the sole symptom of CHD, and it can be difficult to differentiate from shortness of breath caused by other conditions.

Table 1. 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. aIf the diagnosis of CAD is uncertain, establishing a diagnosis using non-invasive functional imaging for myocardial ischaemia before treatment may be reasonable. bMay 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. cConsider exercise ECG to assess symptoms, arrhythmias, exercise tolerance, BP response, and event risk in selected patients. dAbility to exercise, individual test-related risks, and likelihood of obtaining diagnostic test result. eHigh 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. fFunctional imaging for myocardial ischaemia if coronary CTA has shown CAD of uncertain grade or is non-diagnostic. gConsider also angina without obstructive disease in the epicardial coronary arteries.

The duration of the discomfort is short - <10 minutes in most cases, and often a few minutes or less, and chest pain lasting for several seconds is unlikely to be associated with CAD. An important characteristic is the association with exercise. Symptoms are classically manifested or aggravated by increased exertion - for example, walking downhill or against the wind, or in cold weather - and quickly disappear within a few minutes when these causative factors decrease. Exacerbation of symptoms after a heavy meal or after waking up in the morning are classic features of angina pectoris. Paradoxically, angina can be reduced by physical activity (walk-through angina) or with a second load (warm-up for angina). Sublingual nitrates quickly relieve angina. Symptoms are not related to breathing or position. The threshold of angina and symptoms can vary significantly from day to day and even on the same day.

The classification, although subjective, is practical and has proven value in determining the likelihood of obstructive CAD. Studies published since 2015 have reported that most patients suspected of having CAD have atypical or non-anginal chest pain, with less than 10 to 15% having typical angina. The Canadian Cardiovascular Society classification is still widely used as a system for assessing angina to quantify the threshold at which symptoms occur in relation to physical activity (Table 2).

Table 2. 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.

A physical examination of a patient with suspected CAD is important to assess for anemia, hypertension, heart valve disease, hypertrophic cardiomyopathy, or arrhythmia. It is also recommended that practitioners calculate body mass index (BMI) and look for evidence of non-coronary vascular disease that may be asymptomatic [includes palpation of the peripheral pulse and auscultation of the carotid and femoral arteries 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 cutting pain, which makes CAD more unlikely. You should also try to reproduce the symptoms with palpation and test the effect of sublingual nitroglycerin to classify the symptoms. The definitions of typical and atypical angina are summarized in 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.

Stable or unstable angina.

Unstable angina can be manifested by the following symptoms: (i) as angina pectoris, i.e., characteristic pain and location that occurs at rest and lasts for a long time (>20 minutes); (ii) new-onset angina (2 months), transition from moderate to severe angina (Canadian Heart Association scale - grade II or III); or (iii) unstable angina, i.e., pre-existing angina that progressively increases in severity and intensity over a short period of time. Management of angina that meets these criteria is addressed in the ESC guidelines for the management of ACS. New angina is generally considered unstable angina; however, if angina occurs for the first time with heavy exertion and resolves at rest, the suspected condition falls within the definition of CCS rather than unstable angina. Patients with unstable angina defined as low risk are advised to use the diagnostic and prognostic algorithms presented in these guidelines after the period of instability subsides. 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 elevated troponin levels. Under these conditions, a noninvasive diagnostic strategy is recommended before deciding on an invasive strategy. Given the above definition, stable and unstable angina may overlap, and many patients with CAD go through a period of unstable angina.

Difference between symptoms caused by epicardial artery stenosis and microvascular/vasospastic disease

The distinction between symptoms caused by epicardial artery stenosis and symptoms caused by microvascular or vasospastic disease cannot be made with sufficient certainty. Relying on an ischemia test or coronary anatomy imaging is often unavoidable to exclude obstructive CAD, which may not be present in symptomatic patients. This section of the guidelines discusses the diagnostic analysis of microvascular or vasospastic disease.

Step 2: Comorbidities and other causes of symptoms

Before considering any testing, the patient's overall health, comorbidities, and quality of life should be assessed. If revascularization is unlikely to be a viable option, further testing may be kept to a clinically indicated minimum and appropriate

therapy, which may include antianginal drug trials, should be instituted even if the diagnosis of CAD has not been fully demonstrated. Noninvasive functional imaging for ischemia may be an option if the diagnosis needs to be verified.

If the pain is not obviously angina, other diagnostic tests may be indicated to identify gastrointestinal, pulmonary, or musculoskeletal causes of chest pain. However, these patients should also be evaluated based on risk factors, such as SCORE (Systematic Coronary Risk Evaluation)

Step 3: Basic testing.

Basic (first) testing in patients with suspected coronary artery disease includes standard laboratory biochemical testing, resting ECG, possible outpatient ECG monitoring, and, in some patients, chest X-ray. Such testing can be performed on an outpatient basis.

Biochemical tests.

Laboratory tests are used to identify possible causes of ischemia, establish cardiovascular risk factors, comorbidities, and determine prognosis. Hemoglobin is part of a complete blood count and, when there is clinical suspicion of thyroid dysfunction, thyroid hormone levels provide information about possible causes of ischemia. Fasting plasma glucose and glycated hemoglobin (HbA1c) should be measured in every patient with suspected coronary artery disease. If both are inconclusive, an additional oral glucose tolerance test is recommended. Knowledge of glucose metabolism is important because of the well-established association between diabetes and adverse cardiovascular outcomes. Patients with diabetes should be managed according to specific guidelines. The lipid profile, including total cholesterol, high-density lipoprotein, low-density lipoprotein (LDL), and triglycerides, should also be evaluated in any patient with suspected CHD to establish the patient's risk profile and determine the need for treatment. Fasting measurements are recommended to characterize severe dyslipidemia or to monitor high triglyceridemia.

Peripheral arterial disease (PAD) and renal dysfunction increase the likelihood of developing CAD and negatively affect prognosis. Therefore, baseline renal

function should be assessed by estimating glomerular filtration rate (GFR). It may also be appropriate to measure uric acid levels, as hyperuricemia is a common comorbidity and may also affect renal function.

If there is clinical suspicion of unstable CAD, biochemical markers of myocardial damage 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. If high-sensitivity tests are used, low troponin levels can be detected in many patients with stable angina. Elevated troponin levels are associated with adverse outcomes, and small studies have shown a possible added value in the diagnosis of CAD, but larger trials are needed to test the utility of systematic evaluation in patients suspected of having CAD.

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

Recommendations
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]
The following blood tests are recommended in all patients:
• Full blood count (including haemoglobin);[30]
• Creatinine measurement and estimation of renal function;[31,32]
• A lipid profile (including LDL-C).[33,34]
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]
Assessment of thyroid function is recommended in case of clinical suspicion of thyroid disorders.

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

Resting electrocardiogram and ambulatory monitoring.

For almost a century, the paradigm for diagnosing myocardial ischemia has been based on the detection of repolarization abnormalities, mainly in the form of ST-segment depressions. Thus, the resting ECG remains an indispensable component of the initial evaluation of a patient with chest pain. There are two scenarios for clinical evaluation: (i) a patient without symptoms of chest pain or discomfort, and (ii) a patient with prolonged symptoms of angina.

The latter situation is much more common and is often recorded by resting ECG. However, even in the absence of repolarization abnormalities, the ECG may demonstrate indirect signs of CAD, such as signs of previous MI (pathological waves) or conduction abnormalities [mainly left bundle branch block (LBBB) and atrioventricular conduction abnormalities]. Atrial fibrillation (AF) is a common finding in patients with chest pain. Segment depression during supraventricular tachyarrhythmia is not a predictable symptom of CAD.

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

Ambulatory ECG monitoring can reveal evidence of silent myocardial ischemia in patients with CAD, but rarely adds relevant diagnostic or prognostic information that cannot be obtained by stress testing. Most importantly, therapeutic strategies aimed at silent ischemia detected by ambulatory monitoring have not demonstrated clear prognostic benefits.

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.

Echocardiography and magnetic resonance imaging at rest.

Echocardiography will provide important information about the heart function and anatomy. LV ejection fraction (LVEF) is often normal in patients with CCS. Decreased LV function and/or regional wall motion abnormalities may increase the suspicion of ischemic myocardial injury, and the pattern of LV dysfunction after theoretical coronary artery distribution is typical in patients with previous MI. Detection of wall motion abnormalities can be difficult by visual assessment, and detection of early systolic prolongation, reduced systolic shortening, or post-systolic shortening by strain imaging may be useful in patients with normal LV function but clinical suspicion of CAD. It has been reported that a decrease in LV diastolic function is an early sign of ischemic myocardial dysfunction and may also indicate a microvascular disorder.

Echocardiography is an important clinical tool for excluding alternative causes of chest pain and helps to diagnose concomitant heart disease, such as heart valve

disease, HF, and most cardiomyopathies, but it is important to remember that these diseases often coexist with CAD. The use of an echocardiographic contrast agent can be useful in patients with poor acoustic windows.

Cardiac magnetic resonance (CMR) may be considered in patients with suspected coronary artery disease when echocardiography (with contrast) is inconclusive. CMR will provide useful information about cardiac anatomy and systolic cardiac function, similar to echocardiography, in patients who have no contraindications to CMR. CMR can assess global and regional function, and the use of late gadolinium elevation can reveal a typical pattern of myocardial scarring in patients who have already had an MI.

Assessment of LV function is important for all patients for risk stratification and should therefore be performed in all symptomatic patients with suspected CAD.

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.

Chest X-ray.

Chest X-rays are often used in the evaluation of patients with chest pain. However, it does not provide specific information for diagnosis or event risk stratification in CCS. The test can sometimes be useful in evaluating patients with suspected HF. A chest X-ray can also be useful in patients with pulmonary problems that often accompany CHF or to rule out another cause of chest pain in atypical symptoms.

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.

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

The effectiveness of available methods of diagnosing obstructive CAD (i.e., the probability that a patient has the disease if the test is abnormal and the probability that the patient does not have the disease if the test is normal) depends on the prevalence of the disease in the population and thus on the probability that a given patient will actually have CAD. Diagnostic testing is most useful when the probability is intermediate. When the probability is high, a large number of patients need to be studied to identify a few patients who do not have the disease, and a negative test result can rarely rule out obstructive CAD (i.e., the negative predictive value is low). When the probability is low, a negative test can rule out disease, but the

lower the probability, the higher the likelihood of a false positive (i.e., a positive test in the absence of obstructive CAD). Thus, in patients at the extreme end of the probability range, it is advisable to refrain from diagnostic testing and assume that the patient does or does not have obstructive CAD.

The application of the new PTPs (Table 4) has important implications for the referral of patients for diagnostic testing. If diagnostic testing was postponed in patients with a new PTP <15%, this would lead to a significant increase in the proportion of patients for whom diagnostic testing was not recommended, as more patients would be classified as having a PTP <15%. In data from the PROMISE trial (Prospective Multicenter Imaging Study for the Evaluation of Chest Pain), 50% of patients previously classified as intermediate probability of obstructive CAD were reclassified as having a PTP <15% according to the new PTP. According to the results of the pooled analysis, 57% of all patients were classified as PTP <15%. Studies have shown that the outcomes of patients classified with the new PTP <15% are good (annualized risk of cardiovascular death or MI <1%). Consequently, routine testing can be postponed in patients with PTP <15%, thus reducing unnecessary procedures and costs.

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 considered to have such a low probability of disease that diagnostic testing should only be performed for compelling reasons. The introduction of the new PTPs also indicates that patients should not routinely be referred directly for invasive evaluation unless clinical and other data indicate a high probability of obstructive CAD.

Table 4. 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 of contemporary data

	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%

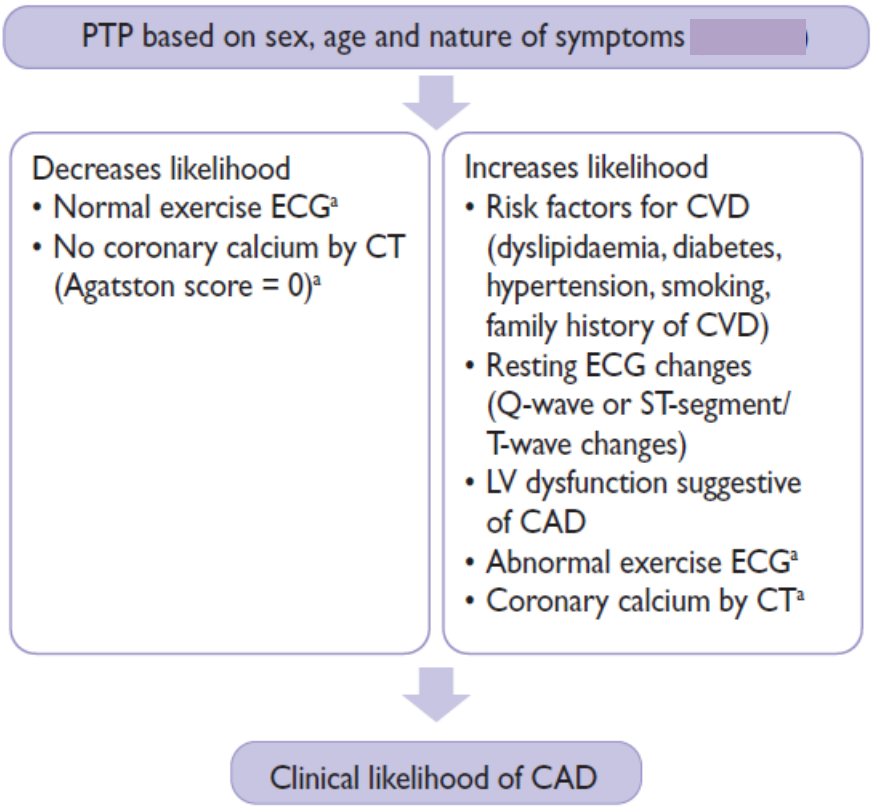
CAD = coronary artery disease; PTP = pre-test probability.

a In addition to the classic Diamond and Forrester classes, patients with dyspnoea only or dyspnoea as the primary symptom are included.

Areas highlighted in dark green indicate groups where noninvasive testing is most beneficial (PTP > 15%). Areas highlighted in light green indicate groups with a pretest CAD probability of 5-15%, where diagnostic testing may be considered after assessing the overall clinical probability based on the PPP modifiers.

Clinical models that include information on CVD risk factors, ECG changes, or coronary calcification have improved the identification of patients with obstructive CAD compared to age, gender, and symptoms. Therefore, the presence of CVD risk factors (such as family history of CVD, dyslipidemia, diabetes, hypertension, smoking, and other factors) that increase the probability of CAD can be used as modifiers of PTV estimate. If there are possible ECG Q-wave, ST-segment, or T-wave changes, LV dysfunction suggestive of ischemia, and exercise ECG findings, as well as information on coronary calcification, an improved assessment of PTP of obstructive CAD can be used. However, it should be noted that coronary calcification imaging does not exclude coronary stenosis caused by non-calcified atherosclerotic lesions, and the presence of coronary calcification is a weak predictor of obstructive CAD. Although the optimal use of these factors to improve the estimation of PTP has not yet been established, they should be considered in addition to PTP based on sex, age, and symptom presentation to determine the overall clinical likelihood of obstructive CAD. 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.

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.

Step 5: Selecting appropriate testing

In patients who do not perform revascularization due to comorbidities, the diagnosis of CAD can be made clinically and only medical therapy is required. If the diagnosis of CAD is inaccurate, it may be advisable to establish the diagnosis using noninvasive functional imaging of myocardial ischemia before starting treatment.

In a patient with a high likelihood of developing CAD, symptoms that do not respond to medical therapy or typical angina with low exercise, and an initial clinical evaluation (including an echocardiogram and, in selected patients, a stress ECG) that indicates a high risk, it is appropriate to proceed directly to invasive coronary angiography (ICA) without further diagnostic testing. In such circumstances, the indication for revascularization should be based on appropriate invasive confirmation of the hemodynamic significance of the stenosis.

For other patients in whom CAD cannot be excluded by clinical assessment alone, noninvasive diagnostic tests are recommended to establish the diagnosis and assess event risk. Current guidelines recommend either noninvasive functional coronary imaging or anatomic imaging, using coronary CT angiography (CTA) as the initial test for the diagnosis of CAD.

Functional non-invasive tests.

Functional non-invasive tests for the diagnosis of coronary artery disease are designed to detect myocardial ischemia through ECG changes, wall motion abnormalities using stress CMR or stress echocardiography, or perfusion changes using single-photon emission CT (SPECT), positron emission tomography (PET), contrast echocardiography of the myocardium, or contrast CMR. Ischemia can be triggered by exercise or pharmacological stressors, or by increased myocardial work and oxygen demand, or by heterogeneity of myocardial perfusion due to vasodilation. Noninvasive functional examinations are associated with a high accuracy of detecting coronary stenosis that restricts blood flow compared with invasive functional examinations [fractional flow reserve (FFR)]. However, lower-grade coronary atherosclerosis not associated with ischemia remains undetectable by functional testing, and, in the case of negative functional testing results, patients are subject to risk factor modification based on commonly used risk scales and guidelines.

Anatomical non-invasive evaluation.

Anatomical noninvasive evaluation by visualizing the lumen and wall of the coronary artery with an intravenous contrast agent can be performed with coronary computed tomographic angiography (CTA), which provides high accuracy in detecting obstructive coronary stenoses identified by invasive coronary angiography, as both tests are based on anatomy. However, stenoses estimated at 50-90% on visual inspection are not necessarily functionally significant, i.e., they do not always cause myocardial ischemia. Therefore, either noninvasive or invasive functional testing is recommended for further angiographic evaluation of stenosis detected by coronary

CTA or invasive angiography, unless very high-grade stenosis (>90% in diameter) is detected by invasive angiography. The presence or absence of obstructive coronary atherosclerosis on coronary CTA provides prognostic information and can be used to guide preventive therapy. Randomized, prospective clinical trials have demonstrated that diagnostic testing with coronary CTA is associated with clinical outcomes similar to those of functional imaging in patients with suspected coronary artery disease. In patients with extensive coronary artery disease, coronary CTA was not inferior to invasive coronary angiography for decision-making and determining revascularization targets.

The role of exercise ECG.

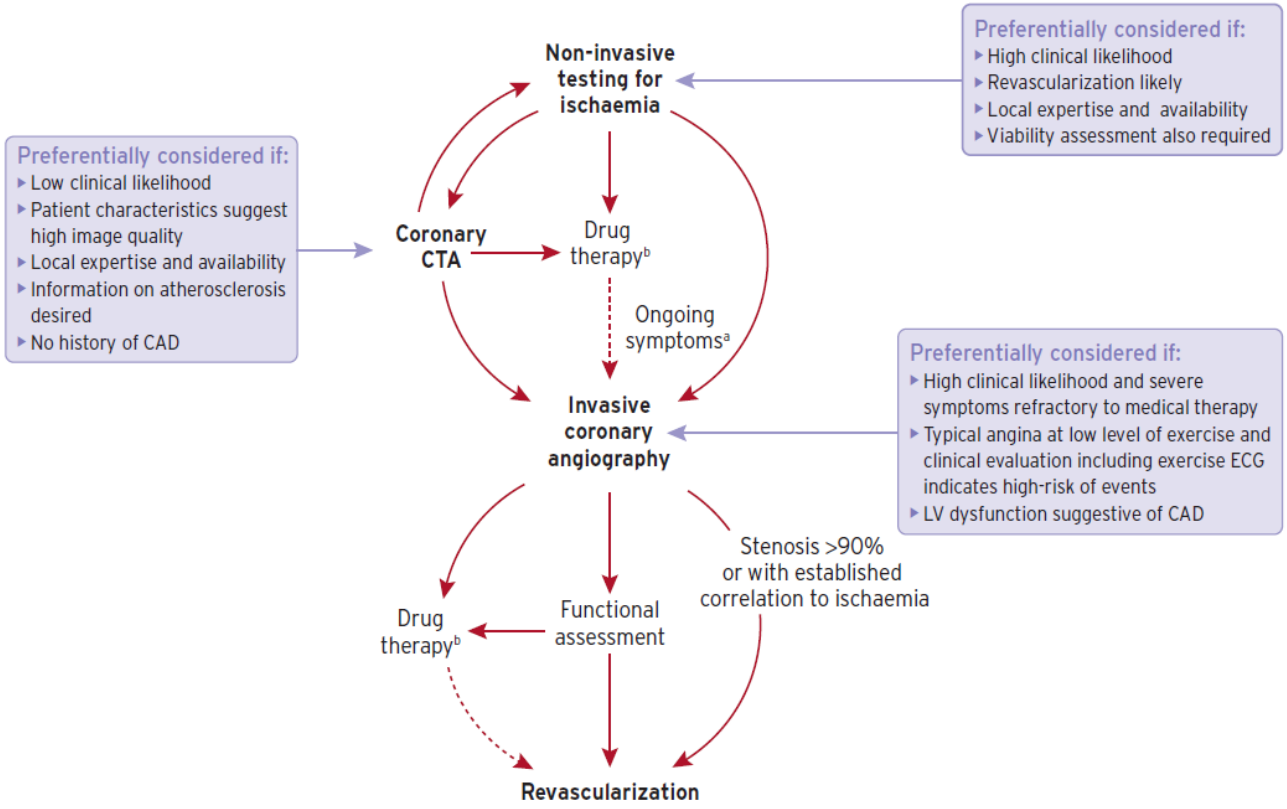
Exercise ECG has lower diagnostic performance than imaging tests and has limited power to exclude or confirm CAD. Since the publication of the previous version of these guidelines, RCTs have compared the effects of diagnostic strategies on clinical outcomes. These studies have shown that the addition of coronary CTA or functional imaging clarifies the diagnosis, guides preventive therapy and interventions, and potentially reduces the risk of MI compared with exercise ECG. Some, but not all, registry studies have also shown similar benefits for the use of a visual diagnostic test in patients treated in daily clinical practice. Therefore, this guideline recommends the use of an imaging diagnostic test instead of a exercise ECG as the initial test for the diagnosis of CAD.

The exercise ECG can be considered as an alternative to diagnosing CAD when imaging tests are not available, bearing in mind the risk of false negative and false positive test results. The exercise ECG has no diagnostic value for patients with ECG abnormalities that interfere with the interpretation of ST-segment changes during stress (i.e., LBBB, Wolff-Parkinson-White syndrome, ST-segment depression >0.1 mV on resting ECG). The exercise ECG provides additional clinically useful information. Therefore, the use of exercise ECG may be considered in selected patients to complement clinical assessment.

Selection of diagnostic tests.

Functional or anatomical tests can be used to establish the diagnosis of coronary artery disease. A summary of the main diagnostic pathways is shown in the scheme below. Information about the anatomical structure and ischemia is required to make a decision about revascularization.

Main diagnostic pathways in symptomatic patients with suspected obstructive coronary artery disease.



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.
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.

The impact of clinical likelihood on the choice of a diagnostic test.

Each noninvasive diagnostic test has a certain range of clinical likelihood of CAD, where the benefit of its use is maximized. Given the clinical likelihood of CAD and the likelihood ratio of a particular test, it is possible to estimate the post-test probability of CAD after performing such a test. Using this approach, the optimal

clinical probability ranges for each test can be estimated, where they can reclassify patients from low to high post-test probability of CAD.

Computed tomographic coronary angiography is the preferred test in patients with a lower clinical likelihood of CAD, no prior diagnosis of CAD, and characteristics associated with a high likelihood of good image quality. It detects subclinical coronary atherosclerosis, but can also accurately exclude both anatomically and functionally significant CAD. It has higher accuracy values when the examinations are subject to low clinical probability. To date, trials evaluating outcomes after coronary CTA have mainly included patients with low clinical likelihood.

Functional assessment of ischemia (noninvasive or invasive) is required in most patients before a decision on revascularization can be made. Thus, functional noninvasive testing may be preferred in patients in the higher clinical probability range if revascularization is possible or if the patient has been previously diagnosed with CAD.

In addition to diagnostic accuracy and clinical confidence, the choice of noninvasive test depends on other patient characteristics, local expertise, and test availability.

Invasive testing.

For diagnostic purposes, invasive coronary angiography (ICA) is only necessary for patients with suspected coronary artery disease in cases of inconclusive noninvasive testing. However, ICA may be indicated if noninvasive assessment suggests a high risk of an event to determine revascularization options.

In a patient with a high clinical likelihood of CVD and symptoms unresponsive to medical therapy or with typical angina with low exercise, and initial clinical assessment indicates a high risk of an event, early ICA without prior noninvasive risk stratification may be useful to identify lesions that are potentially amenable to revascularization. Invasive functional assessment should complement ICA, especially

in patients with coronary stenoses of 50-90%, given the frequent discrepancies between angiographic and hemodynamic severity of coronary stenoses.

It has been shown that systematic integration of ICA leads to a change in management strategies in 30-50% of patients. The methods used to perform ICA have improved significantly, leading to a decrease in the incidence of complications. This is especially true for ICA performed through the radial artery. The main complication associated with conventional femoral artery catheterization is bleeding requiring blood transfusion. ICA should not be performed in patients with angina who refuse invasive procedures, prefer to avoid revascularization, are not candidates for percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), or who are not expected to improve their functional status or quality of life.

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

Recommendations
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]
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.
Functional imaging for myocardial ischaemia is recommended if coronary CTA has shown CAD of uncertain functional significance or is not diagnostic.[4,55,73]
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]
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]
Coronary CTA should be considered as an alternative to invasive angiography if another non-invasive test is equivocal or non-diagnostic.
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.
Coronary calcium detection by CT is not recommended to identify individuals with obstructive CAD.

CAD = coronary artery disease; CT = computed tomography; CTA = computed tomography angiography.
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
Exercise ECG is recommended for the assessment of exercise tolerance, symptoms, arrhythmias, BP response, and event risk in selected patients.[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]
Exercise ECG may be considered in patients on treatment to evaluate control of symptoms and ischaemia.
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.

BP = blood pressure; CAD = coronary artery disease; ECG = electrocardiogram.
c When this information will have an impact on diagnostic strategy or management.

Step 6: Assessment of event risk

Event risk assessment is recommended in every patient with suspected or newly diagnosed coronary artery disease, as it has a major impact on the decision regarding therapy. The process of risk stratification is used to identify patients at high risk of events who will benefit from revascularization beyond symptom reduction. Event risk stratification is usually based on the scores used to make the diagnosis of coronary artery disease. All patients should undergo cardiovascular event risk stratification using clinical assessment, assessment of LV function by resting echocardiography, and, in most cases, noninvasive assessment of ischemia or coronary anatomy. Although the diagnostic value of the exercise ECG is limited, the occurrence of ST-segment depression at low exercise combined with symptoms of exertion (angina or dyspnea), poor exercise capacity, complex ventricular tachycardia or arrhythmias, and abnormal blood pressure responses are markers of high risk of cardiac mortality. Patients with typical angina and LV systolic dysfunction in a pattern suggestive of coronary artery disease also have a high risk of cardiac mortality. Invasive coronary angiography for risk stratification is only required in a selected subset of patients, and additional ejection fraction may be required for event risk stratification, if necessary.

Definition of risk levels.

In patients with established CCS, the risk of annual cardiac mortality is used to describe the risk of events. As in the previous version of the guidelines, high risk of events is defined as a cardiac mortality rate of >3% per year, and low risk is defined as a cardiac mortality rate of <1% per year.

The definition of high risk of complications based on the results of diagnostic examinations in symptomatic patients or patients with diagnosed CCS is shown in Table 5.

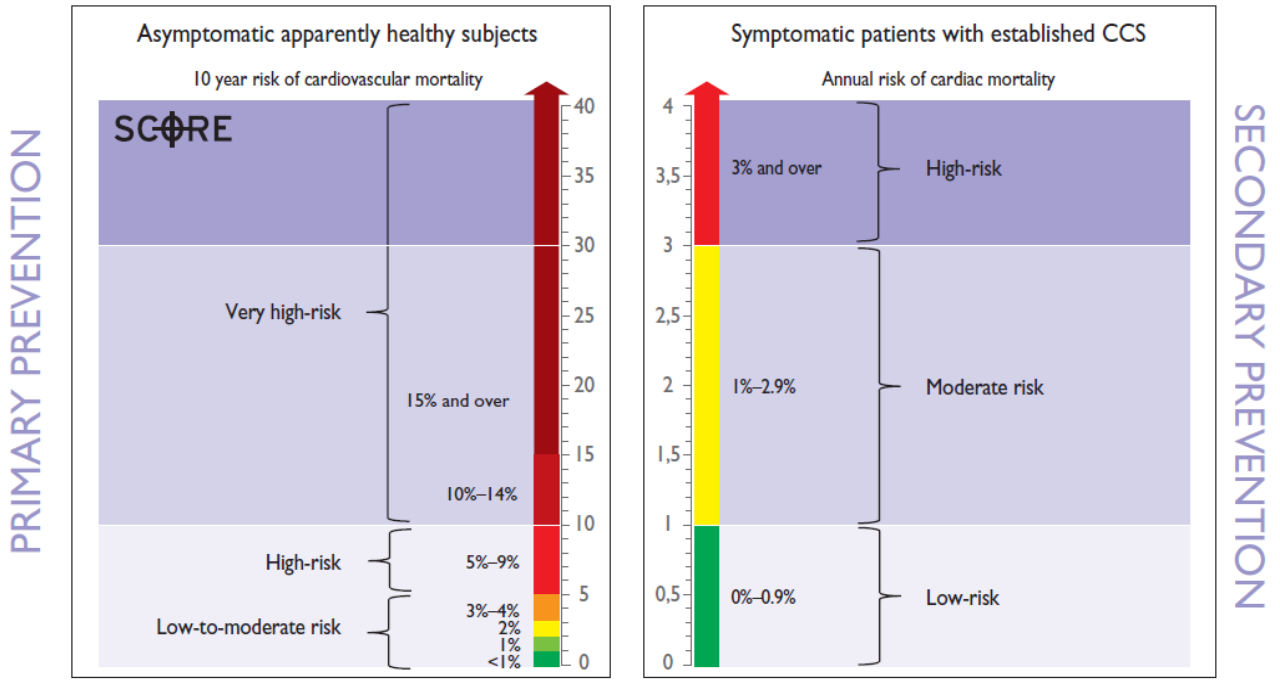
Table 5. Definitions of high event risk for different test modalities in patients with established chronic coronary syndromes.

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.

Notably, the risk level differs from the SCORE-based risk score in asymptomatic individuals without diabetes who are subjectively healthy. The SCORE scale determines 10-year cardiovascular mortality in asymptomatic individuals. The differences in these risk assessment tools and scales are illustrated in the scheme below. The results of different examination methods corresponding to a high risk of complications are presented in Table 5. For all non-invasive examinations presented in Table 5, normal examination results are associated with a low risk of complications.

Comparison of risk assessments in asymptomatic apparently healthy subjects (primary prevention) and patients with established chronic coronary syndromes (secondary prevention).



CCS = chronic coronary syndromes; SCORE = Systematic COronary Risk Evaluation.
Note that in asymptomatic subjects (left panel), SCORE estimates 10 year cardiovascular mortality, while in symptomatic patients (right panel), annual cardiac mortality is estimated.

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.

Lifestyle modification.

The general principles of managing patients with CCS are aimed at alleviating symptoms and improving prognosis through the use of appropriate medications and interventions, as well as controlling risk factors, including lifestyle. Optimal drug therapy in the COURAGE (Clinical Outcomes of Revascularization and Active Drug Evaluation) trial combined medication adherence promotion, lifestyle counseling, and support for lifestyle risk factors, all of which were delivered by nurses who specialize in these areas. Achieving optimal patient management can be best accomplished by a multidisciplinary team that can provide individualized and flexible support to patients.

Lifestyle modification and risk factor control.

Implementation of a healthy lifestyle reduces the risk of further cardiovascular events and mortality and is complementary to appropriate secondary prevention therapy. Lifestyle recommendations and interventions are described in more detail in the ESC guidelines for CVD prevention in clinical practice and are available elsewhere. Lifestyle factors are important, and adherence to healthy habits (including smoking cessation, recommended physical activity, healthy eating, and maintaining a healthy weight) significantly reduces the risk of future cardiovascular complications and death, even when controlled for evidence-based secondary prevention therapies and procedures.

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.

Smoking.

Smoking cessation improves the prognosis of patients with CCS, including a 36% reduction in mortality for those who quit. Interventions to promote smoking cessation include brief advice, counseling, and pharmacologic therapy, including nicotine replacement. Patients should also avoid secondhand smoke.

All forms of nicotine replacement therapy, bupropion, and varenicline are more effective than control in promoting smoking cessation than do quitting, and a combination of behavioral and pharmacological approaches is effective and highly recommended. Nicotine replacement therapy was associated with minor events, such as arrhythmia and angina, and bupropion had a protective effect against major adverse cardiovascular events.

Although previous systematic reviews have found very limited and conflicting evidence that e-cigarettes (primarily first-generation devices) are useful for improving smoking cessation compared to placebo or nicotine replacement therapy, a recent large clinical trial found that e-cigarettes are more effective than nicotine replacement therapy in smoking cessation.

In clinical encounters with smokers, clinicians should follow the "Five" rule: ask about smoking, advise to quit, assess readiness to quit, assist in quitting (pharmacological support and referral to behavioral counseling), and arrange for follow-up.

Diet and alcohol.

An unhealthy diet is a leading factor in the development of coronary artery disease and its progression, and changes in the structure of a healthy diet in patients with CCS have led to a decrease in mortality and cardiovascular events.

A Mediterranean diet high in fruits, vegetables, legumes, fiber, polyunsaturated fats, nuts, and fish is used, avoiding or limiting refined carbohydrates, red meat, dairy products, and saturated fats. Although light to moderate alcohol consumption (1-2 drinks per day) does not increase the risk of MI, levels of >100 g per week were associated with higher mortality in a large meta-analysis of individual data. An

analysis of the Global Burden of Disease 1990-2016 concluded that with zero alcohol consumption, the risk of death and disability was minimal.

Weight management.

In a population-based study, the risk of CVD, as well as cardiovascular morbidity and mortality, was higher in overweight or obese individuals compared to those with a normal BMI (20-25 kg/m2). Obesity was associated with a shorter life expectancy, and overweight was associated with the development of CVD at an earlier age. Waist circumference is a marker of central obesity and is strongly associated with the development of CVD and diabetes. Recommended waist circumference: <94 cm for men (<90 cm for South Asian and Asian men) and <80 cm for women.

In individuals with CAD, intentional weight loss is associated with a significantly lower risk of adverse clinical outcomes. Although there have been many arguments about the relative benefits of low-fat and low-carbohydrate diets, Gardner et al. found similar weight loss and benefits in patients randomized to a healthy low-fat or low-carbohydrate diet. This finding was independent of patients' genotypic patterns and baseline insulin secretion. For weight management, a healthy, low-calorie diet is recommended to achieve and maintain a healthy weight (BMI <25 kg/m2). Increased physical activity is also recommended.

Physical activity.

Exercise is referred to as a "poly-pill" because of its multiple beneficial effects on cardiovascular risk factors and cardiovascular physiology. Each increase in peak oxygen consumption by 1 ml/kg/min is associated with a 14-17% reduction in the risk of cardiovascular and total death in women and men.

Recommendations for physical activity for patients with CCS are 30-60 minutes of moderate-intensity aerobic activity >5 days a week. Even irregular physical activity in leisure time reduces the risk of mortality among previously sedentary patients, and increased activity is associated with lower cardiovascular mortality.

Resistance exercise supports muscle mass, strength, and function, and with aerobic activity has benefits for insulin sensitivity and lipid and blood pressure control.

Cardiac rehabilitation.

Exercise-based cardiac rehabilitation has been consistently shown to be effective in reducing cardiovascular mortality and hospitalization compared to no exercise control in patients with CAD, and this benefit continues in the modern era. It is important that the benefits of cardiac rehabilitation occur across diagnostic categories.

Psychosocial factors.

Patients with heart disease have twice the risk of mood and anxiety disorders compared to people without heart disease. Psychosocial stress, depression, and anxiety are associated with worse outcomes and make it difficult for patients to make positive lifestyle changes or adhere to a therapeutic regimen.

The ESC guidelines recommend assessing psychosocial risk factors. Clinical trials have shown that psychological and pharmacological interventions have beneficial effects on depression, anxiety disorders, and stress, with some evidence of reduced cardiac mortality and events compared to placebo.

Environmental factors.

Polluted air is considered one of the 10 leading risk factors for global mortality. Exposure to air pollution increases the risk of developing MI, as well as hospitalization and death from heart failure, stroke, and arrhythmias. Patients with CCS should avoid heavily polluted regions. Air purifiers with high-efficiency particulate air ("HEPA") filters reduce indoor pollution, and wearing N95 respiratory masks in heavily polluted areas has protective properties. Environmental noise also increases the risk of CVD. Policies and regulations that reduce air and noise pollution in the environment should be supported, and patients should be informed of these risks.

Sexual activity.

Patients with CCS often worry about the cardiovascular risk associated with sexual activity and/or experience sexual dysfunction. The risk of provoking sudden death or acute MI is very low, especially when sexual activity is performed with a stable partner in a familiar environment without stress, or without excessive food or alcohol consumption beforehand. Although sexual activity temporarily increases the risk of MI, it is responsible for <1% of acute MI and <1-1.7% of sudden deaths during sexual activity. The energy expenditure during sexual activity is usually low to moderate (3-5 metabolic equivalents) and climbing two flights of stairs is often used as an equivalent activity in terms of energy expenditure. Regular physical activity reduces the risk of adverse events during sexual activity. Sexual dysfunction in patients with CCS includes decreased libido and sexual activity and a high prevalence of erectile dysfunction. Sexual dysfunction can be caused by underlying vascular conditions, psychosocial factors, specific medications, the number of medications, and changes in relationships. Thiazide diuretics and beta-blockers (except nebivolol) can negatively affect erectile function, but studies published since 2011 have not found a consistent association between most modern cardiovascular drugs and erectile dysfunction. Phosphodiesterase-5 inhibitors for the treatment of erectile dysfunction are generally safe for patients with CCS, but should not be used in patients taking nitrates.

Adherence and sustainability.

Adherence to lifestyle changes and medication is a challenge. A systematic review of epidemiologic studies showed that a significant number of patients do not adhere to their prescribed cardiovascular medications, and 9% of cardiovascular complications in Europe are associated with nonadherence to treatment. In older men with coronary heart disease, better adherence to treatment recommendations has a positive effect on clinical outcomes, regardless of other conditions. Polypharmacy

plays a negative role in treatment adherence, and the complexity of treatment regimens is associated with non-adherence and a higher incidence of hospitalization.

When prescribing medications, preference should be given to those with the highest level of evidence and those with a wider range of beneficial effects. Simplifying treatment regimens can help (and there is some evidence of the benefits of cognitive education strategies, electronic feedback monitoring, and support from nurses who specialize in these issues). Review of prescribed medications by primary care providers can be useful in patients with multiple pathologies, to reduce the risk of adverse interactions and to simplify treatment regimens.

Influenza vaccination.

Annual influenza vaccination can improve the prevention of acute MI in patients with CCS, change the prognosis of HF, and reduce cardiovascular mortality in adults aged ≥ 65 years. Therefore, annual influenza vaccination is recommended for patients with CAD, especially in the elderly.

Pharmacological management.

The goals of pharmacologic treatment of patients with CCS are to reduce the symptoms of angina and exercise-induced ischemia and to prevent cardiovascular events.

Immediate relief of angina symptoms or prevention of symptoms in circumstances that may cause angina is usually obtained with fast-acting nitroglycerin preparations. Antiischemic drugs, lifestyle changes, regular exercise, patient education, and revascularization all play a role in minimizing or eliminating symptoms over the long term (long-term prevention).

Prevention of cardiovascular events targets MI and cardiac death related to CAD and focuses on reducing the incidence of acute thrombotic events and the development of ventricular dysfunction.

Anti-ischaemic drugs

General strategy.

Optimal treatment can be defined as treatment that satisfactorily controls symptoms and prevents cardiac events associated with CCS with maximum patient adherence and minimal adverse events. However, there is no universal definition of optimal treatment in patients with CCS, and drug therapy should be adapted to the characteristics and preferences of each patient. Initial medical therapy usually consists of one or two antiischemic drugs, if necessary, plus drugs for secondary prevention of CVD. The initial choice of antiischemic drugs depends on the expected tolerance associated with the patient's individual profile and comorbidities, potential drug interactions with concomitant therapy, patient preferences after notification of possible side effects, and availability of medications. It remains unclear whether combination therapy with two antianginal drugs [e.g., a beta-blocker (BB) and a calcium channel blocker (CCB)] is more effective than monotherapy with any class of antianginal drug in reducing clinical events.

BBs or CCB are recommended as first-line treatment, although no RCTs to date have compared this strategy with an alternative strategy using initial administration of other antiischemic drugs or a combination of beta-blockers and CCBs. The results of a network analysis of 46 trials and 71 treatment comparisons supported the initial combination of BB and CCB. The same meta-analysis suggests that several additional second-line antianginal drugs (long-acting nitrates, ranolazine, trimetazidine, and ivabradine) may be useful in combination with BB or CCB as first-line therapy, until data on nicorandil were available. Regardless of the initial strategy, the response to initial antiplatelet therapy should be reassessed 2 to 4 weeks after treatment initiation.

Antiischemic drugs have been shown to be beneficial against symptoms associated with myocardial ischemia, but they do not prevent cardiovascular complications in most patients with CCS.

Nitrates.

Short-acting nitrates for acute effort angina.

Sublingual and aerosolized nitroglycerin preparations provide immediate relief of angina. The spray works faster than sublingual nitroglycerin. When symptoms of angina appear, the patient should rest in a sitting position (standing provokes syncope, and lying down increases venous return and preload) and take nitroglycerin (0.3-0.6 mg tablet sublingually and not swallowed, or 0.4 mg spray on the tongue - do not swallow or inhale) every 5 minutes until the pain disappears, or a maximum of 1.2 mg is taken within 15 minutes. During this period, if angina persists, you should immediately consult a doctor. Nitroglycerin can be administered for prophylaxis before exercise, which is known to provoke angina. Isosorbide dinitrate (5 mg sublingually) has a somewhat slower onset of action than nitroglycerin due to hepatic conversion to mononitrate. The effect of isosorbide dinitrate can last <1 hour if the drug is taken sublingually or lasts for several hours if the drug is taken orally.

Long-acting nitrates for angina prophylaxis.

Long-acting nitrate drugs (e.g., nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate) should be considered as second-line therapy for the relief of angina 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 are few data comparing nitrates with BBs or BCCs from which to draw clear conclusions about their relative efficacy. When taken for a long period of time, long-acting nitrates provoke tolerance with loss of efficacy, which requires the administration of a reduced dose of nitrates or a nitrate-free interval of 10-14 hours. Nitroglycerin can be administered orally or transdermally via a slow-release system. The bioavailability of isosorbide dinitrate is subject to interindividual variability in hepatic conversion and is generally lower than that of isosorbide mononitrate (its active metabolite), which has 100% bioavailability. Dose titration is important in all formulations to obtain maximum symptom control at the tolerated dose. Discontinuation should be short and abrupt to avoid an increase in angina. The most common side effects are hypotension, headache, and facial flushing.

Contraindications include hypertrophic obstructive cardiomyopathy, severe aortic valve stenosis, and concomitant use of phosphodiesterase inhibitors (e.g., sildenafil, tadalafil, or vardenafil) or riociguat.

Beta-blockers (BB).

The dose of BB should be adjusted to limit the heart rate to 55-60 beats per minute at rest. Discontinuation should be limited and not abrupt. BBs can be combined with dihydropyridine (DHD) CCBs to reduce DHD-induced tachycardia, but with an uncertain increase in clinical value. The beta-blocker is cautiously combined with verapamil or diltiazem because of the potential for worsening of HF, excessive bradycardia, and/or atrioventricular block. Combination of BB with nitrate attenuates the reflex tachycardia of nitrate. The main side effects of BB are fatigue, depression, bradycardia, heart block, bronchospasm, peripheral vasoconstriction, postural hypotension, impotence, and masking of hypoglycemia symptoms.

In certain patients with recent MI and in those with chronic HF with reduced ejection fraction, BBs are associated with significant reductions in mortality and/or cardiovascular events, but the protective benefit in patients with CAD without prior MI or HF is less well established and there is a lack of placebo-controlled trials. 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 percutaneous coronary intervention (PCI), the use of BBs at discharge was not associated with any reduction in cardiovascular morbidity or mortality at 30 days and three years of follow-up. However, in patients with previous MI who underwent coronary artery bypass grafting (CABG), BBs were associated with a lower risk of long-term mortality and adverse cardiovascular events. Other observational studies and meta-analyses question the benefit of long-term beta-blocker therapy (>1 year) in patients with previous MI.

Calcium channel blockers.

While CCBs improve symptoms and reduce myocardial ischemia, they have not been shown to reduce major morbidity or mortality in patients with CCS.

Non-dihydropyridine agents (calcium channel blockers that lower the heart rate).

Verapamil. Verapamil has a wide range of approved indications, including all types of angina (exertional, vasospastic and unstable), supraventricular tachycardia and hypertension. Indirect evidence suggests good safety, but with risks of heart block, bradycardia, and HF. Compared to metoprolol, the antianginal activity was similar. Compared with atenolol in hypertension with CAD, verapamil is associated with fewer cases of diabetes, fewer angina attacks, and less psychological depression. BB in combination with verapamil is not recommended (due to the risk of heart block).

Diltiazem. Diltiazem, with its low side effects, has advantages over verapamil in the treatment of angina pectoris. Like verapamil, it acts through peripheral vasodilation, reducing exercise-induced coronary narrowing, a modest negative inotropic effect, and sinus node inhibition. There were no results of studies comparing diltiazem and verapamil.

In some selected patients, non-DHP CCBs can be combined with beta-blockers for the treatment of angina. However, in such cases, they should be used under close monitoring of patients' tolerance to excessive bradycardia or signs of HF. The use of non-DHP CCBs in patients with LV dysfunction is not recommended.

Dihydropyridine agents

Long-acting nifedipine. This medication is a powerful arterial vasodilator that has several serious side effects. Long-acting nifedipine has been particularly well tested in patients with hypertension and angina when added to BB. In the large placebo-controlled ACTION trial, the addition of long-acting nifedipine [60 mg once daily] to conventional angina treatment did not affect the survival of major cardiovascular events. Long-acting nifedipine proved to be safe and reduced the need for coronary angiography and cardiovascular interventions. There are few relative contraindications to nifedipine (severe aortic stenosis, hypertrophic obstructive

cardiomyopathy, or HF), and cautious combination with BB is usually possible and desirable. Vasodilating side effects include headache and swelling of the feet.

Amlodipine. The very long half-life of amlodipine and its good tolerability make it an effective antianginal and antihypertensive agent, which distinguishes it from drugs that are taken two or three times a day. There are few side effects, mainly swelling of the feet. In patients with CCS and normal blood pressure (75% of those taking a beta-blocker), amlodipine 10 mg/day reduces coronary revascularization and hospitalization for angina during a 24-month trial. Exercise-induced ischemia is more effectively reduced by amlodipine, 5 mg titrated to 10 mg/day, than by BB atenolol, 50 mg/day, and their combination is even better. However, the combination of a beta-blocker and a CCB is often not used, even in some studies reporting "optimally treated" stable angina pectoris.

Ivabradine.

Ivabradine has been reported to be non-inferior to atenolol or amlodipine in the treatment of angina and ischemia in patients with CCS. The addition of ivabradine 7.5 mg 2 p/d to atenolol therapy provided better control of heart rate and anginal symptoms. In 10,917 patients with limited pre-existing angina who were enrolled in the BEAUTIFUL mortality assessment, ivabradine did not reduce cardiovascular mortality in patients with MI or HF. In 2014, the European Medicines Agency issued recommendations to reduce the risk of bradycardia and placed ivabradine under additional monitoring. Taken together, these results support the use of ivabradine as a second-line drug in patients with CCS.

Nicorandil.

Nicorandil is a nitrate derivative of nicotinamide with antianginal effects similar to those of nitrates or beta-blockers. Side effects include nausea, vomiting, and potentially severe oral, intestinal, and mucosal ulcers. In the placebo-controlled IONA (Impact Of Nicorandil in Angina) trial (n = 5126), nicorandil significantly reduced mortality from coronary artery disease (CAD), non-fatal MI, or unplanned

hospital admission for suspected angina symptoms in patients with CCS, but there were no results in mortality from CAD or non-fatal MI. These results support the use of nicorandil as a second-line drug in patients with CCS.

Ranolazine.

Ranolazine is a selective inhibitor of late inward sodium flux. Side effects include dizziness, nausea, and constipation. In addition, ranolazine prolongs the QT and should therefore be used with caution in patients with QT prolongation or on QT prolonging drugs.

In a relatively large subgroup of patients with chronic angina (n = 3565), a significant reduction in recurrent ischemia, worsening of angina, and increased antianginal therapy was observed. In another placebo-controlled study of patients with diabetes and coronary artery disease receiving one or two antianginal drugs, ranolazine reduced angina and sublingual nitroglycerin use with good tolerability.

These findings support the use of ranolazine as a second-line treatment in patients with refractory angina despite the use of common antianginal agents such as BB, CCB, and/or long-acting nitrates. Conversely, there is a lack of evidence to support the use of ranolazine in patients with CAD after PCI with incomplete revascularization.

Trimetazidine.

Trimetazidine appears to have a hemodynamically neutral side effect profile. Trimetazidine (35 mg dose) has been added to BB (atenolol) for the improvement of angina pectoris, as reviewed by the European Medicines Agency in June 2012. It remains contraindicated in Parkinson's disease and movement disorders such as tremor (shaking), muscle stiffness, gait disturbances, and restless legs syndrome. A meta-analysis in 2014, mostly Chinese, studies consisting of 1628 patients showed that treatment with trimetazidine in addition to other antianginal drugs was associated with fewer average weekly angina attacks, less weekly nitroglycerin use, longer time to 1 mm ST depression, more total work, and longer exercise duration at peak

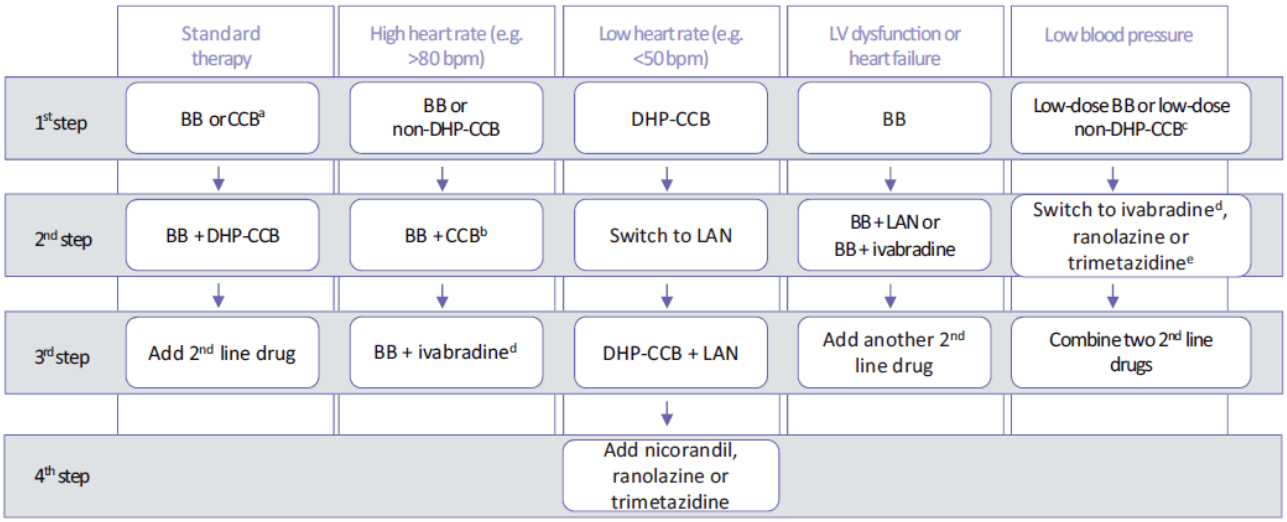
exercise than treatment with other antianginal drugs for stable angina. These findings support the use of trimetazidine as a second-line treatment in patients with CCS whose symptoms are not adequately controlled by other antianginal drugs or who are intolerant to them.

Allopurinol.

In 2010, a randomized crossover study of 65 patients with coronary artery disease showed that allopurinol at a dose of 600 mg per day increased the time to ST-segment depression and angina. A review study of 29,298 incident allopurinol use episodes found an association of allopurinol use with a reduced risk of MI in the elderly, especially when used for >2 years. However, the role of allopurinol in reducing clinical events in CVD remains unclear.

A stepwise strategy for anti-ischemic drug therapy in CCS is proposed, depending on certain basic patient characteristics (Table 6). Incomplete responses or poor tolerance at each step justify moving on 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.

Table 6.Suggested stepwise strategy for long term anti-ischaemic drug therapy in patients with chronic coronary syndromes and specific baseline characteristics.



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.

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.

Patients with low blood pressure.

Patients with low blood pressure are recommended to be prescribed antianginal drugs in very low doses, preferably using drugs that have no or limited effect on blood pressure. Low-dose beta-blockers or low-dose non-DHP CCBs can be tested first under careful monitoring of tolerance. Ivabradine (in patients with sinus rhythm), ranolazine, or trimetazidine can also be used.

Patients with low heart rate.

An increase in heart rate is linearly correlated with cardiovascular events, and the benefit of reducing heart rate as a treatment goal in subgroups of patients with CCS has been demonstrated with various drugs. However, in patients with underlying bradycardia (e.g., heart rate <60/min), heart rate lowering drugs (beta-blockers, ivabradine, and heart rate lowering CCBs) should be avoided or used with caution and, if necessary, started at very low doses. Preferably, antianginal drugs should be administered without lowering the heart rate.

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.

Event prevention

Antiplatelet drugs.

Platelet activation and aggregation is the driving force for coronary thrombosis, which is the basis for the use of antiplatelet drugs in patients with CCS due to the favorable balance between the prevention of ischemic events and an increased risk of bleeding. Dual antiplatelet therapy ("DAPT") with aspirin and an oral P2Y12 inhibitor is the basis of antithrombotic therapy after MI and/or PCI (Table 7).

Table 7. 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
Clopidogrel	75 mg o.d.	Post-MI in patients who have tolerated DAPT for 1 year	
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
Rivaroxaban	2.5 mg b.i.d.	Post-MI >1 year or multivessel CAD	Creatinine clearance 15 - 29 mL/min
Ticagrelor	60 mg b.i.d.	Post-MI in patients who have tolerated DAPT for 1 year	

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 m2.

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 m2.

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 m2.

Low-dose aspirin.

Aspirin works by irreversibly inhibiting platelet cyclooxygenase-1 and thus thromboxane production, which is usually completed with chronic dosing >75 mg/day. The gastrointestinal side effects of aspirin increase with higher doses, and current experience supports a daily dose of 75-100 mg for the prevention of ischemic complications in patients with CAD, with or without a history of MI. Since aspirin's inhibition of cyclooxygenase-1 is stable and predictable in patients who adhere to the prescribed treatment, there is no need to analyze platelet function to monitor individual response. Although other nonselective NSAIDs, such as ibuprofen, reversibly inhibit cyclooxygenase-1, their adverse effects on cardiovascular risk suggest that they cannot be recommended as an alternative treatment for patients with aspirin intolerance.

Oral P2Y12 inhibitors.

P2Y12 inhibitors block the platelet receptor P2Y12, which plays a key role in platelet activation and increased arterial thrombosis. Clopidogrel and prasugrel are

thienopyridine prodrugs that irreversibly block P2Y12 through active metabolites. Ticagrelor is a reversibly binding P2Y12 inhibitor that does not require metabolic activation.

The CAPRIE trial showed an overall non-significant benefit of clopidogrel compared to aspirin with a similar safety profile for the prevention of cardiovascular events in patients with previous MI and stroke. Despite its lower antiplatelet efficacy, clopidogrel demonstrated efficacy compared to ticagrelor. Clopidogrel is limited by variable pharmacodynamic effects associated with variable efficiency of its conversion to the active metabolite, partly related to variants of loss of function of the CYP2C19 gene, which leads to insufficient efficacy in some patients. Drugs that inhibit CYP2C19, such as omeprazole, may reduce the response to clopidogrel.

Prasugrel has a faster, more predictable and, on average, greater antiplatelet effect than clopidogrel. Prasugrel is more effective than clopidogrel in aspirin-treated patients who have had PCI, but not in patients with ACS. Prasugrel is associated with a higher incidence of nonfatal and fatal bleeding than clopidogrel in patients with ACS who have undergone PCI, resulting in apparent harm in patients with a history of ischemic stroke and no apparent benefit in those aged >75 years or <60 kg.

Ticagrelor has the most predictable and consistently high level of P2Y12 inhibition during maintenance therapy in adherent patients, and has a faster onset and also faster and more predictable compensation of action compared to clopidogrel. Ticagrelor with a loading dose of 180 mg followed by 90 mg 2 bw/d achieved a greater reduction in ischemic events compared with clopidogrel in patients treated with aspirin, regardless of revascularization strategy, at the expense of a greater number of fatal bleeds. Ticagrelor at doses of 90 or 60 mg 2 bw/day reduced the 3-year composite incidence of MI, stroke, or cardiovascular death compared with placebo in stable patients treated with aspirin. The equivalent efficacy and similar safety of the two doses of ticagrelor was attributed to similar levels of platelet inhibition. Ticagrelor may cause dyspnea, which is often temporary, often mild and tolerable, but occasionally requires switching to thienopyridine. Ticagrelor is

metabolized via CYP3A and therefore should not be used with strong CYP3A inhibitors or inducers.

The optimal timing of initiation of P2Y12 inhibition before coronary angiography and possible PCI in patients with CVD is uncertain, but the increasing use of the radial artery approach and clinical experience has allowed for consideration of prior clopidogrel treatment in patients who are at high risk of requiring PCI. Limited pharmacodynamic studies support the unlicensed use of prasugrel or ticagrelor in stable PCI patients at high risk of stent thrombosis, but the safety/efficacy balance of this approach compared with clopidogrel has not been established.

Duration of dual antiplatelet therapy.

After PCI for stable angina, an optimal balance of efficacy and safety is achieved in most patients after 6 months. Premature discontinuation of the P2Y12 inhibitor is associated with an increased risk of stent thrombosis and is not recommended. However, a shorter duration of DAPT can be considered in patients at high risk of life-threatening bleeding, given the very low risk of stent thrombosis after 13 months. A study of DAPT in patients undergoing PCI showed that extended therapy with clopidogrel or prasugrel beyond 12 months reduces ischemic events and stent thrombosis. A greater benefit from extended clopidogrel or prasugrel was observed in patients treated for MI.

Anticoagulant drugs in sinus rhythm.

Anticoagulant drugs inhibit the action and/or formation of thrombin, which plays a key role in both clotting and platelet activation. Thus, anticoagulants have been shown to reduce the risk of arterial thrombotic events. The higher efficacy and safety of the DAPT, compared with aspirin and anticoagulation, in preventing stent thrombosis led to the abandonment of the latter strategy in favor of the DAPT after PCI. The combination of antiplatelet therapy and standard anticoagulant doses of warfarin or apixaban for secondary prevention after ACS was associated with an

unfavorable balance of efficacy and bleeding. However, recently reported studies have renewed interest in combining lower doses of anticoagulants with antiplatelet therapy.

Low-dose rivaroxaban.

Rivaroxaban is a factor Xa inhibitor that has been studied at a low dose of 2.5 mg 2 bw/d in several patient populations in sinus rhythm. This dose is one quarter of the standard dose used for anticoagulation in patients with AF. In GEMINI-ACS (a study comparing the safety of rivaroxaban versus acetylsalicylic acid in addition to clopidogrel or ticagrelor therapy in ACS), rivaroxaban 2.5 mg 2 bw/d was compared with aspirin in patients receiving a P2Y12 inhibitor who were stable after PCI. The results suggested similar safety of rivaroxaban to aspirin in this setting, but larger studies are needed to substantiate this finding. In addition, the safety of PCI without prior aspirin treatment is unknown.

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. 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).

Combined anticoagulant and antiplatelet therapy after percutaneous coronary intervention in patients with atrial fibrillation or other indications for oral anticoagulation. For periprocedural treatment, it is recommended to avoid interrupting VKA if possible, whereas it is recommended to discontinue NOAC therapy 12-48 hours before PCI, depending on renal function and the specific NOAC

regimen. Radial arterial access is preferred along with intra-procedural unfractionated heparin either at the standard dose (70-100 U/kg) or, in those with uninterrupted VKA, at a lower dose of 30-50 U/kg. Pretreatment with aspirin 75-100 mg per day is recommended, and prasugrel or ticagrelor is preferred to clopidogrel (loading dose 300-600 mg, unless during long-term maintenance therapy). Patients who have received aspirin and clopidogrel after PCI should keep the target international normalized ratio between 2.0 and 2.5. When concern about the risk of thrombosis outweighs concern about the risk of bleeding, it is recommended to overlap the period when the risk of stent thrombosis is assumed to be greater than the risk of bleeding. At present, there is limited evidence to support the use of OAC with ticagrelor or prasugrel as dual therapy after PCI as a substitute for triple therapy.

Long-term combination therapy in patients with atrial fibrillation or other indications for anticoagulation. Monotherapy with OAC 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 OAC and a single antiplatelet agent; however, in very rare cases with high ischemic risk, dual therapy with OAC and aspirin or clopidogrel may be considered.

Proton pump inhibitors.

Proton pump inhibitors reduce the risk of gastrointestinal bleeding in patients receiving antiplatelet drugs and may be a useful adjunct to improve safety. Prolonged use of proton pump inhibitors is associated with hypomagnesemia, but the role of monitoring serum magnesium levels is uncertain. Proton pump inhibitors that inhibit CYP2C19, such as omeprazole and esomeprazole, may reduce the pharmacodynamic response to clopidogrel. Although this has not been shown to affect the risk of ischemic events or stent thrombosis, the co-administration of omeprazole or esomeprazole with clopidogrel is generally not recommended.

Cardiac surgery and antithrombotic therapy.

Aspirin should generally be continued in patients with CCS who have undergone cardiac surgery, and other antithrombotic medications should be discontinued at intervals according to their duration of action and indications (prasugrel stopped >7 days before; clopidogrel >5 days before; ticagrelor >3 days before; and rivaroxaban, apixaban, edoxaban, and dabigatran 12 days before, depending on dose and renal function). Restarting aspirin after CABG surgical therapy may improve graft patency. The role of DAPT or

or dual therapy with aspirin and rivaroxaban after CABG surgical therapy is uncertain, as there is a lack of large prospective studies. However, the results of RCTs suggest higher graft patency rates with DAPT compared to aspirin monotherapy.

Non-cardiac surgery and antithrombotic therapy.

Non-cardiac surgery is associated with an increased risk of MI. After PCI, whenever possible, it is recommended to postpone elective surgery until the recommended course of DAPT is completed. This will usually mean delaying surgery for up to 6 months after PCI, but surgery between 3-6 months may be considered by a multidisciplinary team, including an interventional cardiologist, if clinically indicated. For most types of surgery, aspirin should be continued as the benefit outweighs the risk of bleeding, but this may not be appropriate for procedures associated with an extremely high risk of bleeding (intracranial procedures, transurethral prostatectomy, intraocular procedures, etc.). The COMPASS trial included patients with coronary artery disease who had a history of peripheral revascularization procedures and demonstrated the benefits of aspirin and rivaroxaban 2.5 mg b.i.d. compared with aspirin alone, including a reduction in major adverse events and mortality, suggesting that it is necessary to risk stratifying patients after cardiac vascular surgery for atherosclerotic disease.

Recommendations for event prevention I.

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

AF = atrial fibrillation; b.i.d. = bis in die (twice a day); CAD = coronary artery disease; CCS = chronic coronary syndromes; 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 m2.
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 m2.
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 m2.

Statins and other lipid-lowering drugs.

Patients with established coronary artery disease are considered to be at very high risk of cardiovascular events, and statin treatment should be considered regardless of LDL cholesterol levels. The goal of treatment is to reduce 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 experienced a second vascular event within 2 years, not necessarily of the same type as the first, although on statin therapy. When this level cannot be achieved, the addition of ezetimibe has been shown to reduce cholesterol levels and cardiovascular risk in patients with coronary artery disease and in patients with diabetes, without further impact on mortality. In addition to exercise, diet, and weight control, which

should be recommended for all patients, dietary supplements, including phytosterols, may lower LDL cholesterol to a lesser extent, but have not been shown to improve clinical outcomes. They are also used in patients with statin intolerance, who are at increased risk of cardiovascular events. Trials published since 2015 have demonstrated that proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors (evolocumab and alirocumab) are very effective in lowering cholesterol levels, consistently reducing LDL to <1.3 mmol/L (50 mg/dL). In trials, these agents have demonstrated a reduction in cardiovascular and mainly ischemic events, with little or no effect on mortality. Very low cholesterol levels are well tolerated and associated with fewer events, but the high cost of PCSK9 inhibitors, which are not affordable for many healthcare systems, and their unknown long-term safety have limited their use to date.

Renin-angiotensin-aldosterone system (RAS) blockers.

ACE inhibitors can reduce mortality, MI, and stroke among patients with LV dysfunction, preexisting vascular disease, and high risk of diabetes. It is recommended to consider ACE inhibitors [or angiotensin receptor blockers (ARBs) in cases of intolerance] for the treatment of patients with CCS with concomitant hypertension, LVEF <40%, diabetes, or CHF, unless contraindicated (e.g., severe renal impairment, hyperkalemia, etc.). However, not all trials have shown that ACE inhibitors reduce all-cause mortality, cardiovascular death, fatal MI, stroke, or HF in patients with atherosclerosis and without LV dysfunction. A meta-analysis including 24 trials and 61,961 patients documented that in patients with CAD without HF, renin-angiotensin system inhibitors reduced cardiovascular events and death only compared with placebo, but not compared with active controls. Thus, ACE inhibitor therapy in patients with CCS without HF or high cardiovascular risk is generally not recommended unless it is required to achieve target blood pressure.

Neprilysin is an endogenous enzyme that degrades vasoactive peptides such as bradykinin and natriuretic peptide. Pharmacologic inhibition of neprilysin increases the level of these peptides, enhancing diuresis, natriuresis, myocardial relaxation and

antiremodeling, while decreasing renin and aldosterone secretion. The first in the class is LCZ696, which combines valsartan and sacubitril (a neprilysin inhibitor) in one tablet. In patients with HF (LVEF <35%) who remain symptomatic despite optimal treatment with an ACE inhibitor, beta-blocker, and aldosterone antagonists, sacubitril/valsartan is recommended instead of an ACE inhibitor to further reduce the risk of hospitalization and death in outpatients.

Aldosterone blockade with spironolactone or eplerenone is recommended for patients after MI who are already receiving therapeutic doses of an ACE inhibitor and a beta-blocker, have LVEF <35%, and have diabetes or HF. Caution should be exercised when using aldosterone antagonists in patients with impaired renal function [estimated GFR <45 mL/min/1.73 m2] and in those with a serum potassium level >5.0 mmol/L.

Hormone replacement therapy.

The results of large randomized trials have shown that hormone replacement therapy does not provide prognostic benefit and increases the risk of CVD in women aged >60 years.

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

Revascularization

In patients with CCS, optimal medical therapy is key to reducing symptoms, stopping the progression of atherosclerosis, and preventing atherothrombotic events. Myocardial revascularization plays a central role in the treatment of CCS, in addition to medical treatment, but it is always an adjunct to medical therapy, not replacing it. The two goals of revascularization are symptomatic relief in patients with angina and/or improvement of prognosis.

The current guidelines support the indication for revascularization, mainly in patients with CCS who are receiving guideline-recommended optimal medical therapy and continue to be symptomatic and/or in whom revascularization may improve prognosis. These guidelines indicate that revascularization in patients with angina and significant stenosis has often been a second-line therapy after medical therapy has failed. However, angina is associated with poorer quality of life, decreased physical endurance, mental depression, and recurrent hospitalizations and visits to the hospital with impaired clinical outcomes.

Revascularization with PCI or CABG can effectively relieve angina, reduce the use of antianginal drugs, and improve performance and quality of life compared with a medical therapy strategy. During the 5-year follow-up of the FAME 2 trial, revascularization improved quality of life and reduced the use of antianginal drugs and related side effects.

Revascularization with either PCI or CABG is also aimed at effectively eliminating myocardial ischemia and its adverse clinical manifestations among patients with significant coronary stenosis, as well as reducing the risk of major acute cardiovascular events, including MI and cardiovascular death. Numerous meta-analyses comparing PCI strategy with initial medical therapy among patients with

CAD have found no or little benefit in terms of survival or MI for the invasive strategy. In this regard, previous guidelines have identified specific subgroups of patients (based on coronary anatomy, LV function, risk factors, etc.) in whom revascularization may improve prognosis, indicating that it may not in other groups.

However, the individual risk-benefit ratio should always be assessed, and revascularization should be considered only if the expected benefit outweighs its potential risk. For a discussion of the best choice between PCI or CABG revascularization for individual patients, we refer to the ESC guidelines for myocardial revascularization.

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

Coronary artery disease is the most common cause of HF in Europe, and most of the evidence supporting the guidelines is based on studies conducted in patients with ischemic cardiomyopathy. The majority of patients with symptomatic HF have a reduced ejection fraction (<40%), although patients with CCS can also have symptomatic HF and a preserved ejection fraction (>50%).

Patients with symptomatic HF should be managed according to the ESC Guidelines for Heart Failure.

The history should include an assessment of symptoms suggestive of HF, especially exercise intolerance and dyspnea on exertion. All major past events related to CAD, including MI and revascularization, as well as all major cardiovascular diseases requiring treatment, such as AF, hypertension or valve dysfunction, and non-cardiovascular comorbidity: CKD, diabetes, anemia, or cancer.

The physical examination should assess patients' nutritional status, biological age, and cognitive abilities. Physical signs recorded include heart rate, heart rhythm, supine blood pressure, murmurs suggestive of aortic stenosis or mitral insufficiency, signs of pulmonary congestion with basal rales or pleural effusion, signs of systemic congestion with dependent edema, hepatomegaly, and elevated jugular venous pressure.

A routine ECG provides information on heart rate and rhythm, extrasystoles, signs of ischemia, abnormal Q waves, hypertrophy, conduction disturbances, and bundle branch block.

Imaging should include an echocardiographic examination with Doppler to assess for evidence of ischemic cardiomyopathy in 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. A chest radiograph may show signs of pulmonary congestion, interstitial edema, infiltration, or pleural effusion. If unknown, coronary angiography (or coronary CTA) should be performed

to determine the presence and extent of coronary artery disease and to assess the potential for revascularization.

Laboratory tests should measure the level of natriuretic peptide to exclude the diagnosis of suspected HF. Renal function along with serum electrolytes should be measured regularly to detect the development of renal failure, hyponatremia, or hyperkalemia, especially at the beginning and during titration of pharmacologic therapy.

The treatment of patients with symptomatic HF requires adequate diuretic therapy, preferably with a loop diuretic, to alleviate 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 for all symptomatic patients with HF. In patients with persistent symptoms, CMRI is also indicated.

Patients with persistent symptoms, systolic LV dysfunction, and evidence of ventricular arrhythmia or bundle branch block may be eligible for a pacemaker (cardiac resynchronization therapy/implantable cardioverter-defibrillator). These devices can provide symptomatic relief, reduce morbidity, and improve survival. Patients with HF may decompensate rapidly after the onset of atrial or ventricular arrhythmias and should be treated according to current guidelines. Patients with HF and hemodynamically significant aortic stenosis or mitral insufficiency may require percutaneous or surgical intervention.

Myocardial revascularization should be considered in patients with HF based on their symptoms, coronary anatomy, and risk profile. Successful revascularization in patients with HF due to ischemic cardiomyopathy can improve LV dysfunction and prognosis. When available, collaboration with a multidisciplinary team is highly recommended.

III. Patients with a long-standing diagnosis of chronic coronary syndromes.

Patients with a long-standing diagnosis of CCS require lifelong treatment and monitoring. The clinical course of patients with CCS may be benign for a certain period of time. However, patients with CCS may develop a variety of cardiovascular complications or undergo therapeutic interventions, some directly related to the underlying coronary artery disease, and some with therapeutic or prognostic interaction with the underlying disease.

Periodic assessment of the patient's individual risk may be considered. Scores that use clinical parameters have been shown to predict outcomes among patients with CCS. Moreover, if clinical parameters are complemented by biomarkers, such a risk score can be even more accurate. In 2017, a biomarker-based risk model was developed to predict cardiovascular mortality in patients with CAD.

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 followed more closely because they are at higher risk of complications and because they may undergo changes in pharmacologic treatment. Thus, we recommend at least two visits during the first year of follow-up. In a patient who had LV systolic dysfunction before the revascularization procedure or after ACS, it is necessary to review LV function 8-12 weeks after the intervention. Cardiac function may have improved and, conversely, cardiac function may deteriorate in other concomitant CVD (e.g., valve disease, infection or inflammation, arrhythmia, etc.). In such cases, these other detrimental factors need to be identified and treated. Similarly, noninvasive assessment of myocardial ischemia may be considered after revascularization to rule out residual ischemia or to document residual ischemia as a guide for further assessments over time.

Patients >1 year after initial diagnosis or revascularization

To assess a patient's risk, an annual evaluation by a cardiovascular physician (cardiologist, general practitioner, or nurse practitioner) is warranted even if the disease is asymptomatic. It is recommended that the annual evaluation assesses the patient's overall clinical condition and medication compliance, as well as the risk profile (as reflected by risk scores). Laboratory tests including lipid profile, renal function, complete blood count, and possibly biomarkers should be performed every 2 years. A patient with worsening risk levels over time may require more intensive therapy or diagnostic measures, although risk-based therapy has not yet been shown to improve outcomes.

A 12-lead ECG should be part of every such visit to delineate heart rate and heart rhythm, detect changes suggestive of silent ischemia/infarction, and identify abnormalities in specific electrocardiographic segments (e.g., PR, QRS, and QT intervals). It may be useful to evaluate LV function (diastolic and systolic), valvular status, and heart size in asymptomatic patients every 3-5 years. In cases of unexplained reduction of LV systolic function, especially localized, it is recommended to visualize the anatomy of the coronary artery. Similarly, noninvasive assessment of silent ischemia in an apparently asymptomatic patient every 3-5 years, preferably using stress imaging, may be useful. Coronary CTA should not be used to follow patients with established coronary artery disease, given its strength in the morphologic sense. However, coronary CTA can be used for unique cases, such as delineating the patency of coronary shunts.

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

Elevated levels of inflammatory markers, in particular high-sensitivity C-reactive protein, were also associated with an increased risk of complications in patients with and without CAD. Willebrand factor, interleukin-6, and N-terminal pro-

B-type natriuretic peptide (NTproBNP) were found to be prognostic factors for outcome. Other readily available biomarkers shown to be prognostic in patients with CCS include heart rate, hemoglobin, and white blood cell count. Assessments based on a combination of biomarkers may be more successful than single biomarkers. The multiple biomarker score combining high-sensitivity C-reactive protein, heat shock protein 70, and fibrin degradation products significantly improved the statistics and net reclassification rate compared to the baseline model using clinical data. Similar results have been reported for the combination of high-sensitivity cardiac troponin T, NT-proBNP, and LDL-C. Several studies have shown that genetic risk scores improve risk prediction above traditional risk factors in general population samples and predict recurrent events in populations with known CVD. Although there is additional prognostic value in the use of multiple individual and aggregate biomarkers, there is currently no evidence that routine use leads to improved care. Nevertheless, these measurements may play a role in selected patients.

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 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.

IV. Angina without obstructive disease in the epicardial coronary arteries

In clinical practice, there is often a marked discrepancy between coronary anatomy findings, symptoms, and noninvasive test results. These patients deserve attention because angina and nonobstructive disease are associated with an increased risk of adverse clinical events. The low diagnostic yield of ICA can be explained by the presence of: (I) mild or moderate angiographic stenosis or diffuse coronary narrowing, with reduced functional significance detected by ICA; (II) disorders affecting the microcirculatory level that elude resolution by angiographic techniques; and (III) dynamic epicardial stenosis caused by coronary spasm or intramyocardial communication that is not detected by CTA or ICA. Intracoronary pressure measurements are useful to circumvent the first of these scenarios. For diagnostic purposes, patients with angina and/or myocardial ischemia who demonstrate coronary stenoses with nonischemic FFR or MRC values may also be labeled as having non-obstructive epicardial disease.

The presence of pronounced anginal symptoms and abnormal noninvasive tests in patients with obstructed epicardial vessels should lead to the suspicion of a non-obstructive cause of ischemia. Quite often, and mainly due to persistent symptoms, patients with angina and no obstructive disease undergo multiple diagnostic tests, including repeated coronary CTA or ICA, which contribute to increased healthcare costs. Because diagnostic pathways for microcirculatory or vasomotor coronary disorders are often not implemented, a definitive diagnosis supported by objective evidence is rarely achieved. As a result, patient anxiety and depression are not uncommon in this clinical population. It should be noted that the use of a structured, systematized approach to the study of microcirculatory and vasomotor disorders in patients with non-obstructive coronary artery disease, as described below, has shown an increase in diagnostic yield.

Microvascular angina.

Patients with microvascular angina usually have exercise-related angina and no mild to moderate stenoses (40-60%) detected by ICA or CTA, which are considered

functionally non-relevant. Given the similarity of angina symptoms, microvascular origin of angina is usually suspected after excluding obstructive coronary stenoses of the epicardium during the diagnostic examination of patients with suspected myocardial ischemia. Regional LV wall motion disorders rarely develop during exercise or stress in patients with microvascular angina. Some patients may also have a mixed picture of angina with periodic episodes at rest, especially when exposed to cold.

Secondary microvascular angina in the absence of epicardial obstruction may be the result of cardiac or systemic conditions, including those that cause LV hypertrophy (e.g., hypertrophic cardiomyopathy, aortic stenosis, and hypertension) or inflammation (e.g., myocarditis or vasculitis).

Risk stratification.

The presence of microcirculatory dysfunction in patients with CCS leads to a worse prognosis than originally thought, probably because recent results are based on the observation of patients in whom abnormalities in the microcirculation are objectively documented by invasive or noninvasive methods.

Microcirculatory dysfunction precedes the development of epicardial damage, especially in women, and is associated with poor outcomes. Among diabetic patients undergoing diagnosis, patients who do not have obstructive epicardial disease but have abnormal coronary flow reserve (CFR) have a similarly poor long-term prognosis as patients with obstructive epicardial disease.

Diagnosis.

The possibility of a microcirculatory origin of angina should be considered in patients with pronounced angina, abnormal noninvasive functional tests, and coronary vessels that are normal or have mild stenosis that is considered functionally insignificant by ICA or CTA. One of the challenges in performing a comprehensive functional assessment is testing the two main mechanisms of dysfunction: microcirculatory conduction abnormalities and arteriolar dysregulation. Nevertheless,

delineating which of these two pathways is affected is critical in establishing medical treatment to alleviate the patient's symptoms.

Impaired microcirculatory conduction can be diagnosed by measuring CFR or minimal microcirculatory resistance (reverse conduction). CFR can be measured noninvasively with transthoracic Doppler echocardiography [by visualizing left anterior descending flow], magnetic resonance imaging (myocardial perfusion index), or PET. Microcirculatory resistance can be measured in the catheterization laboratory by combining intracoronary pressure with thermodilution or Doppler flow velocity-based data (to calculate hyperemic microvascular resistance). Both intracoronary thermodilution and Doppler flow velocimetry allow for the calculation of the CFR. For decision-making purposes, a value of the microcirculatory resistance index (IMR) >25 units or a CFR <2.0 indicates a microcirculatory dysfunction. Both CFR and IMR are usually measured with the use of intravenous vasodilators, such as adenosine or regadenoson.

On the contrary, diagnosis of arteriolar dysregulation requires assessment of endothelial function in the coronary microcirculation by selective intracoronary infusion. In the presence of dysfunctional vascular endothelium or smooth muscle cell dysfunction, acetylcholine (an endothelium-dependent vasodilator that also acts directly on smooth muscle cells) triggers paradoxical arteriolar vasoconstriction. Thus, in patients with microvascular angina and arteriolar dysregulation, acetylcholine challenge will provoke microvascular spasm. This arteriolar response to acetylcholine causes angina symptoms with concomitant ischemic ECG changes or a decrease in coronary blood flow velocity if concomitant Doppler measurement is performed. Peripheral pulse tonometry during reactive hyperemia can also detect abnormal endothelial function in patients with angina and CAD.

Treatment.

Treatment of microvascular angina should address the dominant mechanism of microcirculatory dysfunction. In patients with an abnormal CFR <2.0 or IMR >25 units and a negative acetylcholine provocation test, beta-blockers, ACE inhibitors,

and statins are prescribed along with lifestyle changes and weight loss. Patients who have ECG changes and angina in response to acetylcholine testing, but without severe epicardial constriction (all indicative of microvascular spasms), can be treated as patients with vasospastic angina.

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.

Vasospastic angina.

Vasospastic angina should be suspected in patients with angina symptoms that occur mainly at rest, with exercise tolerance. The likelihood of vasospastic angina increases when the attacks follow a circadian pattern, with more episodes at night and in the morning. Patients are often younger and have fewer cardiovascular risk factors than patients with angina, with the exception of cigarette smoking. Coronary vasospasm should also be suspected in patients with patent coronary stents and persistent angina.

Diagnosis.

The diagnosis of vasospastic angina is based on the detection of transient ischemic changes in the ST segment during an angina attack (usually at rest). Patients with Prinzmetal angina represent a special subtype in which rest angina is accompanied by temporary ST-segment elevation. These ECG changes correlate with proximal vascular occlusion and diffuse, distal subocclusive narrowing of epicardial vessels. Since most attacks of vasospastic angina are self-limited, it is difficult to record these changes on the ECG. Ambulatory ECG monitoring, preferably in 12-lead leads, may be useful in patients with suspected vasospastic angina. The occurrence of ST-segment elevation during normal heartbeat supports the possibility of spasm-induced myocardial ischemia. For successful detection of transient ST-segment changes in these patients, extended Holter monitoring (for >1 week) may be required. Ambulatory ECG monitoring can also be used to evaluate the results of drug therapy to control the frequency of vasospastic events.

In patients with suspected vasospastic angina and documented ECG changes, CTA or ICA has been shown to exclude the presence of fixed coronary stenosis. Angiographic documentation of coronary spasm requires the use of a provocative test in the catheterization laboratory. Given the low sensitivity of hyperventilation and the cold pressor test, the preferred provocative test is intracoronary injection of acetylcholine or ergonovine during ICA. Large pharmacologic agents are safe if they are selectively infused into the left or right coronary artery, and the provoked spasm is easily controlled with intracoronary nitrates. During the provocative test, a low percentage of patients may experience ventricular tachycardia/ventricular fibrillation or bradyarrhythmia (3.2 and 2.7%, respectively), similar to that reported in spontaneous spasm (7%). The intravenous administration of ergonovine for noninvasive tests should be cautious because of the risk of provoking prolonged spasm in multiple vessels, which can be difficult to treat and can be fatal. A coronary spasm provocation test is considered positive when it triggers: (I) angina symptoms, (II) ischemic ECG changes, and (III) severe vasoconstriction of the epicardial

vessels. If the test fails to trigger all three components, it should be considered unequivocal. The development of angina in response to acetylcholine injections in the absence of angiographically evident spasm, with or without concomitant ST-segment changes, may indicate microvascular spasm and is often seen in patients with microvascular angina.

Treatment.

In patients with epicardial or microcirculatory vasomotor disorders, CCBs and long-acting nitrates are the drugs of choice, in addition to controlling cardiovascular risk factors and lifestyle changes. Nifedipine has been shown to be effective in reducing coronary spasm associated with stent implantation.

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.

V. Screening for coronary artery disease in asymptomatic subjects

In an effort to reduce the high rate of coronary death in asymptomatic adults, numerous measurements of risk factors and risk markers, as well as stress tests, are often performed as screening tests. The European guidelines for the prevention of CVD in clinical practice have focused on these issues in detail. These recommendations have been adapted for the purposes of the guidelines.

In general, the use of risk assessment systems such as SCORE is recommended. Subjects with a family history of premature CAD should be screened for familial hypercholesterolemia. Coronary calcium scores and carotid sinus ultrasound for plaque detection can provide useful information about atherosclerotic risk in selected patients, but routine use of biomarkers or other imaging tests for CAD is not recommended.

Only subjects at high risk of events should be considered for further noninvasive or invasive testing. There are no data on how to manage asymptomatic patients who receive testing and test positive, beyond the recommendations listed in these guidelines. However, the principles of risk stratification described above for symptomatic patients also apply to these individuals.

It is important to remember that data demonstrating improved prognosis after appropriate management based on new biomarkers are still lacking. It is important to note that patients with cancer undergoing treatment or chronic inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, and systemic lupus erythematosus may deserve more intensive screening, counseling, and treatment.

Individuals whose occupation involves public safety (e.g., airline pilots, truck or bus drivers) or professional or high profile athletes typically undergo periodic testing to assess exercise capacity and evaluate for possible heart disease, including CAD. Although there is insufficient data to support this approach, these assessments may be done for medico-legal reasons. The threshold for imaging testing in these individuals may be lower than in the average patient. Otherwise, the same principles discussed above for other asymptomatic patients 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.

VI. Chronic coronary syndromes in specific circumstances

Hypertension

Hypertension is the most prevalent cardiovascular risk factor and is closely associated with CCS. 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%. 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. 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. 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. 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.

Recommendations for hypertension treatment in chronic coronary syndromes

Рекомендації	Клас[a]	Рівень[b]
Рекомендується підтримувати такі цільові значення робочого BP: систолічний BP 120–130 мм рт. ст. загалом та систолічний BP 130–140 мм рт. ст. у старших пацієнтів (віком > 65 років).[463-467,470-472]	I	A
У пацієнтів з артеріальною гіпертензією, які нещодавно перенесли MI, рекомендується використовувати бета-блокатори та блокатори RAS.[467]	I	A
У пацієнтів з симптоматичною стенокардією рекомендується використовувати бета-блокатори та/або CCB.[467]	I	A
Комбінація інгібіторів ACE та ARB не рекомендується.[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.

Valvular heart disease (including planned transcatheter aortic valve implantation)

Coronary angiography to evaluate CAD is recommended before valve surgery or when percutaneous coronary intervention is planned to determine whether revascularization is needed. Coronary CTA may be considered in patients at low risk of developing CAD or in patients in whom conventional ICA is technically impractical or associated with increased risk. The combination of PCI and transcatheter aortic valve implantation appears to be feasible and safe, but more data are needed to make definitive recommendations. The routine use of stress testing to detect CAD associated with severe symptomatic valve disease is not recommended because of its low diagnostic value and potential risk. Stress testing with limited symptoms in patients with valvular heart disease appears to be safe and may be useful for symptom detection in asymptomatic patients or in patients with questionable symptoms.

Recommendations for valvular disease in chronic coronary syndromes

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.

After heart transplantation

Specific know-how is required for the follow-up and evaluation of long-term heart transplant survivors. Transplantation CAD is largely an immunologic phenomenon and remains an important cause of morbidity and mortality. ICA is recommended for the evaluation of transplantation CAD and should be performed annually for 5 years after transplantation. If there are no significant abnormalities, angiograms can be performed after that and every two years. Intravascular ultrasound may be useful in assessing vasculopathy and plaque stability of the cardiac allograft. Treatment options for CAD in transplant recipients include pharmacotherapy and revascularization. PCI in the transplanted heart has become a proven method of therapy.

Cancer

The occurrence of CAD in patients with active cancer is increasing as a side effect of cancer therapy (i.e., chest/mediastinal radiation therapy, cardiotoxic chemotherapy, or immunotherapy) or as a result of advanced cancer therapy in the elderly. CAD in patients with active cancer is associated with challenges for clinicians, as treatment decisions should be subject to individualized discussions based on life expectancy, additional comorbidities such as thrombocytopenia, increased thrombosis and bleeding tendencies, and possible interactions between drugs used to treat CAD and antineoplastic agents. The least invasive revascularization procedures are recommended in patients with cancer with severe frailty.

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.

Diabetes mellitus

Diabetes mellitus is associated with a two-fold increased risk for CAD and it is recommended to control risk factors for CVD prevention. Systolic blood pressure in patients with diabetes should be targeted at <130 mm Hg, if tolerated, but not <120 mm Hg, and diastolic blood pressure to <80 mm Hg, but not <70 mm Hg. Initial antihypertensive treatment should consist of a combination of an ACE inhibitor with a CCB, or a thiazide/thiazide-like diuretic. ACE inhibitors reduce albuminuria and the onset or progression of diabetic nephropathy more effectively than other classes of drugs. Patients with diabetes and CAD are at very high risk; therefore, LDL-C levels should be lowered to <1.8 mmol/L (<70 mg/dL) or decreased by >50% if the baseline LDL-C level is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL). Most patients with diabetes and CAD are recommended to achieve a target glycated HbA1c level of <7% (<53 mmol/L). Large safety studies on new glucose-lowering drugs, namely sodium-glucose co-transporters-2 and glucagon-like peptide-1 receptor agonists, have demonstrated a significant reduction in cardiovascular events. Indications for their clinical use are described in the 2019 ESC/European Association for the Study of Diabetes 2019 guidelines for diabetes and cardiovascular disease.

A 12-lead ECG is recommended as part of the routine evaluation for conduction abnormalities, LV hypertrophy, and arrhythmias. The high prevalence of significant CAD and excessive cardiovascular mortality may suggest the benefit 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. Therefore, routine use of CTA in asymptomatic diabetics is 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.

Chronic kidney disease

CAD is very common in patients with CKD, and an increasing number of patients who have undergone PCI have concomitant CKD. Medical treatment to control risk factors (lipids, blood pressure, and glucose) can improve outcomes. Non-invasive stress testing shows reduced accuracy in patients with CKD. The use of iodinated contrast media should be minimized to prevent further deterioration of renal function. Decisions regarding diagnosis and treatment should be made accordingly. Interestingly, patients with CKD are less likely to undergo invasive treatment for coronary artery disease compared with patients without CKD, although the benefits of invasive treatment have been reported. Revascularization options for patients with CKD include CABG and PCI. Meta-analyses suggest that CAD is associated with a higher short-term risk of death, stroke, and repeat revascularization, while PCI with a new generation stent is associated with a higher long-term risk of repeat revascularization. Data on hemodialysis patients are very limited, making it difficult to generalize treatment recommendations.

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.

Elderly patients.

Older people have a greater tendency to have a high incidence and prevalence of CAD in both men and women. Elderly patients (aged >75 years) have the highest risk of mortality and morbidity attributable to CCS, which is enriched by the high prevalence of comorbidities (e.g., hypertension, Diabetes mellitus, CKD, etc.). This population is generally under-treated, under-diagnosed, and underrepresented in clinical trials. Elderly patients often present with atypical symptoms, which can delay proper diagnosis. The treatment of CVD in the elderly is complicated by a greater vulnerability to complications for both conservative and invasive strategies, such as bleeding, renal failure, and neurological impairment. We recommend using a radial approach whenever possible to reduce access site complications when choosing an invasive strategy. The use of chemically coated stents, compared to conventional stents, in combination with short-term DAPT is associated with significant safety and efficacy benefits in elderly patients.

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 revas-cularization 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.

Sex.

Making up <30% of the study population, women are widely underrepresented in cardiovascular research. This enrollment bias causes an evidence gap, as there is a lack of randomized controlled trials based on sex, and most data are extracted from meta-analyses and post hoc analyses of trials in patients with ACS. Whether there are true sex differences in mortality after myocardial ischemia or whether they are due to older age or a higher prevalence of comorbidities in women remains unclear. It has become apparent that mortality differences are particularly pronounced in younger patients, usually those aged <60 years. The reasons for this age-related mortality remain unclear. However, patient characteristics and treatment methods do not fully account for sex differences in outcomes, even after PCI. Therefore, it is recommended that women who have signs suggestive of cardiac ischemia undergo a thorough examination, as clinical symptoms may be atypical. The diagnostic accuracy of the ECG is even lower in women than in men, which is partly due to functional impairment that prevents some women from achieving sufficient exercise. Stress echocardiography with exercise or dobutamine stress is an accurate, non-invasive technique for detecting obstructive CAD and risk among women with suspected CCS. Women have a higher rate of complications after CABG and may also have a high risk of mortality, especially in elderly patients. Hormone replacement therapy in postmenopausal women does not reduce the risk of coronary artery disease and is therefore not recommended for primary and secondary prevention.

Patients with refractory angina.

Refractory angina refers to prolonged symptoms (for >3 months) due to established reversible ischemia in the presence of obstructive coronary artery disease that cannot be controlled by escalating medical therapy with second- and third-line pharmacological agents, bypass surgery, or stenting, including PCI for chronic total coronary occlusion. The quality of life of patients with refractory angina is poor, with

frequent hospitalization and high resource utilization. Patients with refractory angina are best treated in specialized "angina clinics" by multidisciplinary teams with experience in selecting the most appropriate therapeutic approach for a particular patient based on the exact diagnosis and mechanism of the pain syndrome. New therapies can be classified by their mechanism of action: collateral growth promotion, transmural blood flow redistribution, and neuromodulation of cardiac pain.

Based on the positive results of 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 that is resistant after exhaustion of all medical therapy and mechanical revascularization. Controlled coronary sinus narrowing with the implantation of a large stainless device increases coronary sinus pressure, which leads to improved perfusion of the left descending coronary artery.

The overall reported experience with all new therapeutic options remains limited, both in terms of the number of patients treated and the duration of follow-up. Larger RCTs are needed to define the role of each treatment modality for specific subgroups, reduce nonresponse, and establish benefit beyond potential placebo effects.

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.

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 andmanagement 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 ruleout 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 treatmentmust 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 P2Y12 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.

Quiz

1. Which coronary artery is most commonly affected in chronic coronary syndromes?

a) Left main coronary artery

b) Left anterior descending artery

c) Right coronary artery

d) Circumflex artery

e) Posterior descending artery

2. Which of the following laboratory markers is commonly can indicate cardiac muscle damage?

a) Troponin

b) C-reactive protein (CRP)

c) Hemoglobin A1c (HbA1c)

d) Creatinine

e) Thyroid-stimulating hormone (TSH)

3. Which of the following is recommended as a primary prevention strategy for individuals at high risk of developing chronic coronary syndromes?

a) Regular physical exercise

b) Angioplasty

c) Implantable cardioverter-defibrillator (ICD) placement

d) Coronary artery bypass grafting (CABG)

e) Pharmacological stress testing

4. Which of the following is a common symptom of chronic coronary syndromes?

a) Chest pain or discomfort

b) Headache

c) Abdominal cramps

d) Joint stiffness

e) Fatigue

5. What is the leading cause of chronic coronary syndromes?

a) Atherosclerosis

b) Hypertension

c) Diabetes mellitus

d) Chronic obstructive pulmonary disease

e) Congestive heart failure

6. What is one of the primary goals of treatment for chronic coronary syndromes?

a) Relieving symptoms

b) Increasing blood pressure

c) Lowering blood sugar levels

d) Improving lung function

e) Reducing joint inflammation

7. Which of the following lifestyle modifications is recommended for patients with chronic coronary syndromes?

a) Smoking cessation

b) Increased alcohol consumption

c) Sedentary behavior

d) High-sodium diet

e) Irregular sleep patterns

8. Which medication class is commonly used to manage chronic coronary syndromes?

a) Statins

b) Antidepressants

c) Antibiotics

d) Antihistamines

e) Non-steroid anti-inflammatory drugs

9. Which of the following interventions is used to restore blood flow in a blocked coronary artery?

a) Percutaneous coronary intervention (PCI)

b) Spinal tap

c) Endoscopy

d) Colonoscopy

e) Magnetic resonance angiography (MRA)

10. Which of the following medications is commonly prescribed for the management of chronic coronary syndromes?

a) Aspirin

b) Statins

c) Beta-blockers

d) All of the above

e) None of the above

Recommended literature

Basic

1. Internal medicine : textbook for students and interns of higher medical education establishments : in 2 books. Book 1. Diseases of the cardiovaskular and respiratory systems / N. M. Seredyuk [et al.] ; ed. by.: O. Yu. Gubska, I. M. Skrypnyk. - Kyiv : AUS Medicine Publishing, 2020. - 664 p.
2. Davidson's Principles and Practice of Medicine / ed. by.: B. R. Walker [et al.]. - 23rd ed. - India : Elsevier, 2018. - 1417 p.

Additional

1. 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) *European Heart Journal*, https://doi.org/10.1093/eurheartj/ehz425 Published: 31 August 2019
2. 2017 ESC guidelines in review: Comparison of ESC and ACC/AHA guidelines for the diagnosis and management of patients with stable coronary artery disease. J Nucl Cardiol.-2018 Apr;25(2):509-515. doi: 10.1007/s12350-017-1055-0. Epub 2017 Sep 7.
3. 2013 ESC guidelines on the management of stable coronary artery disease. The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. http://eurheartj.oxfordjournals.org/ content/early/2013/ 08/28/eurheartj.eht296