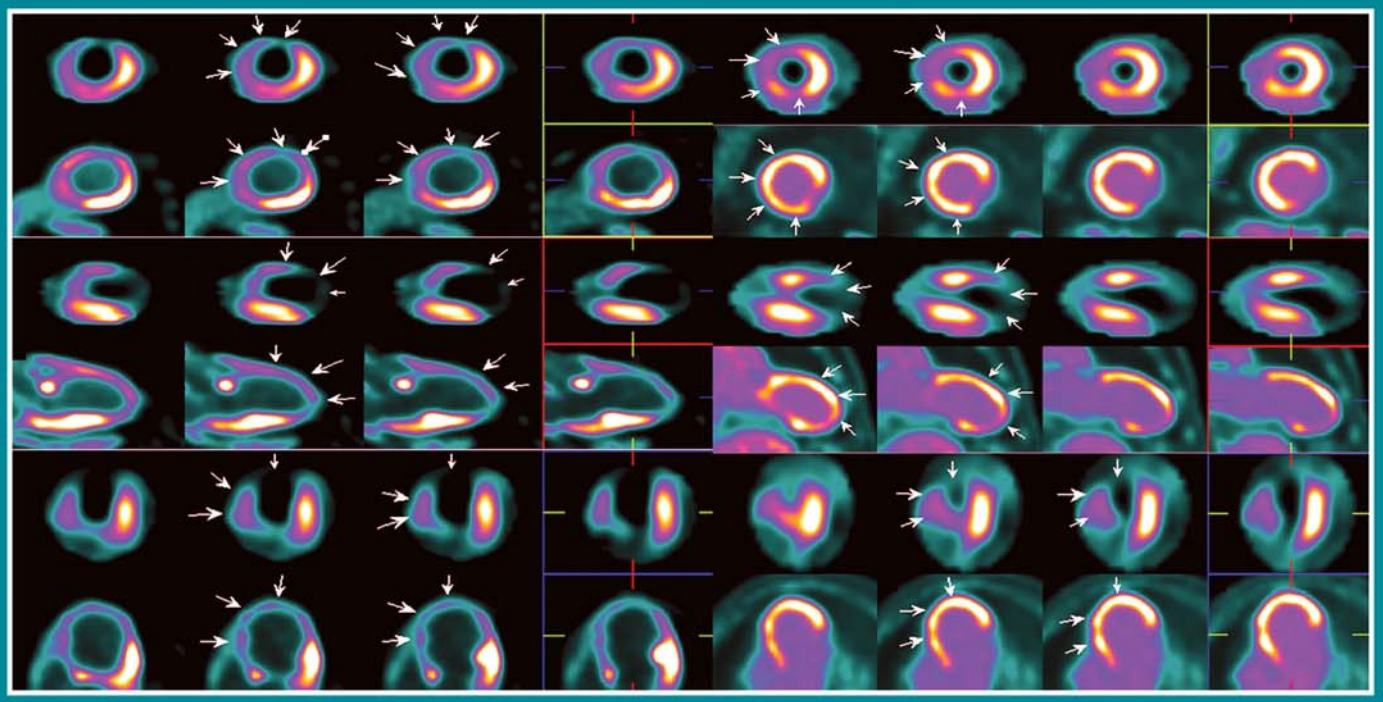
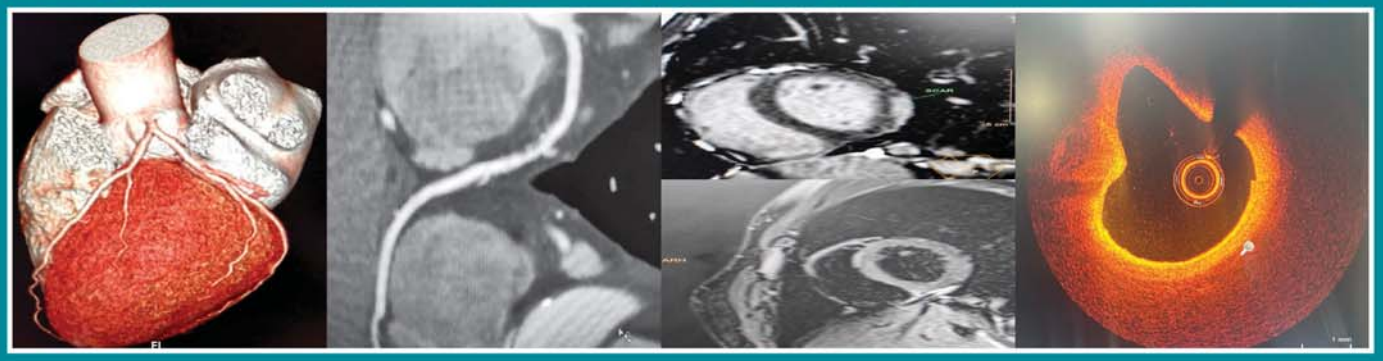
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Cardiac Imaging Update 2025





GN Mahapatra • PC Manoria • Diwakar Jain

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CHAPTER 13

Chronic Coronary Syndrome: Diagnosis and Management

Monotosh Panja, Arindam Pande, Madhumanti Panja

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INTRODUCTION

The term "stable coronary artery disease" has been updated to "chronic coronary syndrome" (CCS), reflecting a more accurate classification of CAD, which now encompasses two primary clinical presentations: Acute coronary syndrome (ACS) and CCS. CAD is a dynamic disease process characterized by atherosclerotic plaque formation, rupture, and erosion, which can be influenced by lifestyle modifications, pharmacological therapies, and revascularization. These interventions promote plaque stabilization or regression, thereby slowing or preventing disease progression.

Chronic coronary syndrome represents an updated conceptual framework encompassing various clinical manifestations stemming from chronic structural and/or functional abnormalities in the coronary arteries and microvasculature. These pathological changes create a predisposition for transient myocardial hypoperfusion (ischemia) due to demand-supply imbalance, typically—though not exclusively—triggered by physical exertion, emotional stress, or other physiological stressors. Clinical presentations may include angina pectoris, atypical chest discomfort, dyspnea, or remain entirely asymptomatic. While often clinically stable for extended periods, CCS reflects an inherently progressive disease process that carries the constant risk of acute destabilization manifesting as ACS. Importantly, this nomenclature distinguishes between the underlying coronary pathology and its clinical manifestations.

DIAGNOSIS OF CHRONIC CORONARY SYNDROME

Coronary artery disease primarily results from atherosclerotic plaque accumulation in the major epicardial coronary arteries, leading to progressive luminal obstruction. The hallmark symptom of angina pectoris occurs when this obstruction creates an imbalance between myocardial oxygen demand and supply, resulting in transient myocardial ischemia. This pathophysiological mechanism underlies both CCSs and acute coronary events.

Patients typically report substernal chest discomfort characterized by pressure or heaviness, often radiating to the jaw, shoulder, back, or arm, with episodes lasting several minutes. This symptomatology demonstrates classic provocation by physical exertion, emotional stress, cold exposure, or heavy meals, and typically resolves with rest or sublingual nitroglycerin within 2–5 minutes. Some patients may present with anginal equivalents, including epigastric discomfort, exertional dyspnea, unexplained fatigue, or presyncope. Based on symptom characteristics, presentations are clinically categorized as:

1. Typical angina (meeting all classic features)
2. Atypical angina (partial symptom correspondence), or
3. Noncardiac chest pain (lacking ischemic features)

The different clinical scenarios in patients with suspected or established CCS are:

- Patients with suspected CAD and "stable" anginal symptoms, and/or dyspnea
- Patients with new onset of heart failure (HF) or left ventricular (LV) dysfunction and suspected CAD
- Asymptomatic and symptomatic patients with stabilized symptoms <1 year after an ACS, or patients with recent revascularization
- Asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization[1]
- Patients with angina and suspected vasospastic or microvascular disease, and
- Asymptomatic subjects in whom CAD is detected at screening.

The pretest probability of CAD is based on age, gender, and nature of symptoms which have undergone major revisions in the European Society of Cardiology (ESC)

Guidelines 2024. A new phrase *"Clinical likelihood of CAD"* that utilizes various risk factors of CAD which have also been updated. The application of various diagnostic tests in different patient groups to rule-in or rule-out CAD has been updated.

RECENT GUIDELINES OF CHRONIC CORONARY SYNDROME[2]

Recent guidelines of chronic coronary syndrome are shown in **Table 1**.

TABLE 1: New major recommendations in 2024.

Recommendations	*Class*[a]	*Level*[b]
History taking and risk factor assessment and resting electrocardiogram in individuals with suspected chronic coronary syndrome—Section 3		
In individuals reporting symptoms of suspected myocardial ischemic origin, a detailed assessment of cardiovascular risk factors, medical history, and symptom characteristics (including onset, duration, type, location, triggers, relieving factors, and time of day) is recommended	I	C
Symptoms such as chest pain triggered by emotional stress; dyspnea or dizziness on exertion; pain in the arms, jaw, neck, or upper back; or fatigue should be considered as potential angina equivalents	IIa	B
Basic biochemistry in the initial diagnostic management of individuals with suspected chronic coronary syndrome—Section 3		
Additionally, high-sensitivity C-reactive protein and/or fibrinogen plasma levels should be considered	IIa	B
Likelihood of obstructive atherosclerotic coronary artery disease in the initial diagnostic management of individuals with suspected chronic coronary syndrome—Section 3		
It is recommended to estimate the pretest likelihood of obstructive epicardial CAD using the risk factor-weighted clinical likelihood model	I	B
It is recommended to use additional clinical data (e.g., examination of peripheral arteries, resting ECG, resting echocardiography, presence of vascular calcifications on previously performed imaging tests) to adjust the estimate yielded by the "Risk Factor-weighted Clinical Likelihood" model	I	C
In individuals with a *very low* (≤5%) pretest likelihood of obstructive CAD, deferral of further diagnostic tests should be considered	IIa	B
In individuals with a *low* (>5–15%) pretest likelihood of obstructive CAD, CACS should be considered to reclassify subjects and to identify more individuals with very low (≤5%) CACS-weighted clinical likelihood	IIa	B
In individuals with an initially low (>5–15%) likelihood of obstructive CAD, exercise ECG and detection of atherosclerotic disease in noncoronary arteries may be considered to adjust the pretest likelihood estimate	IIb	C
Ambulatory electrocardiogram in the initial diagnostic management of individuals with suspected chronic coronary syndrome—Section 3		
Ambulatory ECG monitoring should be considered in subjects with suspected vasospastic angina	IIa	B
Noninvasive anatomical imaging tests in the initial diagnostic management of individuals with suspected obstructive coronary artery disease—coronary computed tomography angiography, if available and supported by local expertise—Section 3		
In individuals with suspected CCS and low or moderate (>5–50%) pretest likelihood of obstructive CAD, CCTA is recommended to diagnose obstructive CAD and to estimate the risk of MACE	I	A
Noninvasive tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—stress echocardiography, if available and supported by local expertise—Section 3		
In individuals with suspected CCS and moderate or high (>15–85%) pretest likelihood of obstructive CAD, stress echocardiography is recommended to diagnose myocardial ischemia and to estimate the risk of MACE	I	B
During stress echocardiography, when two or more contiguous myocardial segments are not visualized, it is recommended to use commercially available intravenous ultrasound contrast agents (microbubbles) to improve diagnostic accuracy	I	B
During stress echocardiography, myocardial perfusion using commercially available intravenous ultrasound contrast agents (microbubbles) is recommended to improve diagnostic accuracy and to refine risk stratification beyond wall motion	I	B

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Recommendations	Class[a]	Level[b]
During stress echocardiography, Doppler left anterior descending coronary artery flow reserve may be considered to improve risk stratification beyond wall motion and to assess microvascular function	IIb	B
Noninvasive functional myocardial imaging tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—resting and stress single-photon emission computed tomography/positron emission tomography—cardiac magnetic resonance imaging, if available and supported by local expertise—Section 3		
In individuals with suspected CCS and moderate or high (>15–85%) pretest likelihood of obstructive CAD, SPECT or, preferably, PET myocardial perfusion imaging is recommended to: • Diagnose and quantify myocardial ischemia and/or scar • Estimate the risk of MACE • Quantify myocardial blood flow (PET)	I	B
In patients selected for PET or SPECT myocardial perfusion imaging, it is recommended to measure CACS from unenhanced chest CT imaging (used for attenuation correction) to improve detection of both nonobstructive and obstructive CAD	I	B
In individuals with suspected CCS and moderate or high (>15–85%) pretest likelihood of obstructive CAD, CMR perfusion imaging is recommended to diagnose and quantify myocardial ischemia and/or scar and estimate the risk of MACE	I	B
Definition of high risk of adverse events		
An initial stratification of risk of adverse events is recommended based on basic clinical assessment (e.g., age, ECG, anginal threshold, diabetes, CKD, and LVEF)	I	B
The use of one or more of the following test results is recommended to identify individuals at high risk of adverse events: • *Exercise ECG:* Duke Treadmill Score < −10 • *Stress SPECT or PET perfusion imaging:* Area of ischemia ≥10% of the LV myocardium • *Stress echocardiography:* ≥3 of 16 segments with stress-induced hypokinesia or akinesia • *Stress CMR:* – ≥2 of 16 segments with stress perfusion defects, or – ≥3 dobutamine-induced dysfunctional segments • *CCTA:* – Left main disease with ≥50% stenosis – Three-vessel disease with ≥70 stenosis, or – Two-vessel disease with 70% stenosis, including the proximal LAD, or – One-vessel disease of the proximal LAD with ≥70% stenosis and FFR-CT ≤0.8	I	B
Cardiovascular risk, lifestyle changes, and exercise interventions in patients with established chronic coronary syndrome—Section 4		
An informed discussion on CVD risk and treatment benefits tailored to individual patient needs is recommended	I	C
Multidisciplinary behavioral approaches to help patients to achieve healthy lifestyles, in addition to appropriate pharmacological management, are recommended	I	A
Aerobic physical activity of at least 150–300 mins/week of moderate intensity or 75–150 mins/week of vigorous intensity and reduction in sedentary time are recommended	I	B
Home-based cardiac rehabilitation and mobile health interventions should be considered to increase patients' long-term adherence to healthy behaviors, and to reduce hospitalizations or cardiac events	IIa	B
Antianginal drugs in patients with chronic coronary syndrome—Section 4		
It is recommended to tailor the selection of antianginal drugs to the patient's characteristics, comorbidities, concomitant medications, treatment tolerability, and underlying pathophysiology of angina, also considering local drug availability and cost	I	C
Ivabradine should be considered as add-on antianginal therapy in patients with left ventricular systolic dysfunction (LVEF <40%) and inadequate control of symptoms, or as part of initial treatment in properly selected patients	IIa	B
Ivabradine is not recommended as add-on therapy in patients with CCS, LVEF > 40%, and no clinical heart failure	III	B
Combination of ivabradine with non-DHP-CCB or other strong *CYP3A4* inhibitors is not recommended	III	B

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Recommendations	Class[a]	Level[b]
Antithrombotic therapy in patients with chronic coronary syndrome—Section 4		
Long-term antithrombotic therapy in patients with chronic coronary syndrome and no clear indication for oral anticoagulation		
In CCS patients with a prior MI or PCI, clopidogrel 75 mg daily is recommended as a safe and effective alternative to aspirin monotherapy	I	A
After CABG, aspirin 75–100 mg daily is recommended lifelong	I	A
In CCS patients *without* prior MI or revascularization but with evidence of significant obstructive CAD, aspirin 75–100 mg daily is recommended lifelong	I	B
Lipid-lowering drugs in patients with chronic coronary syndrome—Section 4		
Lipid-lowering treatment with an LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction in LDL-C vs. baseline is recommended	I	A
For patients who are statin intolerant and do not achieve their goal on ezetimibe, combination with bempedoic acid is recommended	I	B
For patients who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with bempedoic acid should be considered	IIa	C
Sodium-glucose cotransporter-2 inhibitors and/or glucagon-like peptide-1 receptor agonists in patients with chronic coronary syndrome—Section 4		
SGLT-2 inhibitors with proven CV benefit are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication	I	A
The GLP-1 receptor agonist semaglutide should be considered in CCS patients without diabetes, but with overweight or obesity (BMI >27 kg/m^2), to reduce CV mortality, MI, or stroke	IIa	B
Anti-inflammatory drugs in patients with chronic coronary syndrome—Section 4		
In CCS patients with atherosclerotic CAD, low-dose colchicine (0.5 mg daily) should be considered to reduce myocardial infarction, stroke, and need for revascularization	IIa	A
Revascularization in patients with chronic coronary syndrome—Section 4		
Informed and shared decisions		
For complex clinical cases, to define the optimal treatment strategy, in particular when CABG and PCI hold the same level of recommendation, a Heart Team discussion is recommended, including representatives from interventional cardiology, cardiac surgery, noninterventional cardiology, and other specialties if indicated, aimed at selecting the most appropriate treatment to improve patient's outcomes and quality of life	I	C
It is recommended that the decision for revascularization and its modality be patient-centered, considering when possible patient's preferences, health literacy, cultural circumstances, and social support	I	C
Revascularization to improve outcomes		
In CCS patients with LVEF ≤35%, it is recommended to choose between revascularization or medical therapy alone, after careful evaluation, preferably by the Heart Team, of coronary anatomy, correlation between coronary artery disease and LV dysfunction, comorbidities, life expectancy, individual risk-to-benefit ratio, and patient perspectives	I	C
Assessment of procedural risks and postprocedural outcomes		
Intracoronary imaging guidance by IVUS or OCT is recommended for performing PCI on anatomically complex lesions, in particular left main stem, true bifurcations and long lesions	I	A
Intracoronary pressure measurement (FFR or iFR) or computation (QFR):		
• Is recommended to guide lesion selection for intervention in patients with multivessel disease	I	A

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Recommendations	Class[a]	Level[b]
• Should be considered at the end of the procedure to identify patients at high risk of persistent angina and subsequent clinical events • May be considered at the end of the procedure to identify lesions potentially amenable to treatment with additional PCI	IIa IIb	B B
Choice of revascularization modality		
It is recommended that physicians select the most appropriate revascularization modality based on patient's profile, coronary anatomy, procedural factors, LVEF, patient's preferences and outcome expectations	I	C
Mode of revascularization in patients with chronic coronary syndrome *Left main disease*		
In CCS patients at low surgical risk with significant left main coronary stenosis, CABG: • Is recommended over medical therapy alone to improve survival • Is recommended as the overall preferred revascularization mode over PCI, given the lower risk of spontaneous myocardial infarction and repeat revascularization	 I I	 A A
In CCS patients with significant left main coronary stenosis of low complexity (SYNTAX score ≤22), in whom PCI can provide equivalent completeness of revascularization to that of CABG, PCI is recommended as an alternative to CABG, given its lower invasiveness and noninferior survival	I	A
Management of chronic coronary syndrome patients with chronic heart failure—Section 5		
In HF patients with LVEF ≤35% in whom obstructive CAD is suspected, ICA is recommended with a view toward improving prognosis by CABG, taking into account the risk-to-benefit ratio of the procedures	I	B
In HF patients with LVEF >35% and suspected CCS with low or moderate (>5–50%) pretest likelihood of obstructive CAD, CCTA, or functional imaging is recommended	I	C
In patients with HFpEF with angina or equivalent symptoms and normal or nonobstructive epicardial coronary arteries. PET or CMR perfusion or invasive functional coronary testing should be considered to detect or rule out coronary microvascular dysfunction	IIa	B
In selected patients with HFrEF undergoing high-risk PCI for complex CAD, the use of a microaxial flow pump may be considered in experienced centers	IIb	C
It is recommended that CCS patients with heart failure be enrolled in a multidisciplinary heart failure management program to reduce the risk of heart failure hospitalization and to improve survival	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I or ARB in CCS patients with HFrEF to reduce the risk of heart failure hospitalization and death	I	B
Diagnosis and management of patients with angina/ischemia with nonobstructive coronary arteries—Section 5 *Management of ANOCA/INOCA*		
In symptomatic patients with ANOCA/INOCA, medical therapy based on coronary functional test results should be considered to improve symptoms and quality of life	IIa	A
For the management of endothelial dysfunction. ACE-I should be considered for symptom control	IIa	B
For the management of microvascular angina associated with reduced coronary/myocardial blood flow reserve, β-blockers should be considered for symptom control	IIa	B
For the treatment of isolated vasospastic angina: • Calcium-channel blockers are recommended to control symptoms and to prevent ischemia and potentially fatal complications • Nitrates should be considered to prevent recurrent episodes	 I IIa	 A B
In patients with evidence of overlapping endotypes, combination therapy with nitrates, calcium-channel blockers, and other vasodilators may be considered	IIb	B

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Recommendations	*Class*[a]	*Level*[b]
Older, female, high-bleeding risk, comorbid, and socially/geographically diverse patients—Section 5		
Similar guideline-directed cardiovascular preventive therapy is recommended in women and men	I	C
Bleeding risk assessment is recommended using the PRECISE-DAPT score, the qualitative ARC-HBR tool or other, validated methods	I	B
Attention to interaction between antiretroviral treatment and statins is recommended in patients with HIV	I	B

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

DIAGNOSTIC MANAGEMENT OF PATIENTS WITH ANGINA AND SUSPECTED CORONARY ARTERY DISEASE

A Detailed History Including Signs and Symptoms

A detailed history is required including various symptoms and risk factors such as family history of CVD, dyslipidemia, diabetes, hypertension, smoking, and other lifestyle factors. The characteristics of chest pain may be divided into four categories: Location, character, duration, its relationship to exertion, and other exacerbating or relieving factors. Exacerbations of symptoms after a heavy meal or after waking up in the morning are classic features of angina **(Table 2)**. Angina may paradoxically be reduced with further exercise (walk-through angina) or on second exertion (warm-up angina). Sublingual nitrates rapidly relieve angina.

Classification of Different Angina Symptoms (Table 2)

The Canadian Cardiovascular Society classification is still used as a grading system for angina to quantify the threshold at which symptoms occur in relation to physical activities.[3]

TABLE 2: Classification of different angina symptoms.

Type of chest pain	*Characteristics*
Typical angina	*Meets the following three characteristics:* 1. Constricting discomfort in the front of the chest or in the neck, jaw, shoulder, or arm 2. Precipitated by physical exertion 3. Relieved by rest or nitrates within 5 minutes
Atypical angina	Meets two of these characteristics
Nonanginal chest pain	Meets only one or none of these characteristics

Physical examination of a patient with suspected CAD is important to assess the presence of anemia, hypertension, valvular heart disease, hypertrophic cardiomyopathy, or arrhythmias. Microvascular disease should also be evaluated.

Various Comorbidities

It is necessary to assess the patient's general health, comorbidities, and quality of life. Noninvasive functional imaging for ischemia is an option to verify the diagnosis. If the pain is clearly nonanginal, other diagnostic test should be indicated to diagnose gastrointestinal,

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TABLE 3: Testing for suspected patients with coronary artery disease (CAD).

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

[a]Class of recommendation.
[b]Level of evidence.
(ACS: acute coronary syndrome; CCS: chronic coronary syndrome; ECG, electrocardiogram)
Source: © ESC 2024

TABLE 4: Recommendations for basic biochemistry in the initial diagnostic management of individuals with suspected chronic coronary syndrome.

Recommendations	*Class*[a]	*Level*[b]
The following blood tests are recommended in all individuals to refine risk stratification, diagnose comorbidities, and guide treatment:		
• Lipid profile including LDL-C	I	A
• Full blood count (including hemoglobin)	I	B
• Creatinine with estimation of renal function	I	B
• Glycemic status with HbA1c and/or fasting plasma glucose	I	B
In patients with suspected CCS, it is recommended to assess thyroid function at least once	I	B
Additionally, hs-CRP and/or fibrinogen plasma levels should be considered	IIa	B

[a]Class of recommendation.
[b]Level of evidence.
(CCS: chronic coronary syndrome; hs-CRP: high-sensitivity C-reactive protein; ECG: electrocardiogram; HbA1c: glycated hemoglobin; LDL-C: low-density lipoprotein cholesterol)
Source: ESC 2024.

pulmonary, or musculoskeletal causes of chest pain. Risk charts such as SCORE (Systematic Coronary Risk Evaluation) can be used as a guideline for risk factor modification.[4]

Testing for Suspected Patients with Coronary Artery Disease (Table 3)

Basic testing in patients with suspected CAD **(Tables 3 to 8)** includes standard laboratory biochemical testing **(Table 4)**, a resting ECG, possible ambulatory ECG monitoring **(Table 5)**, resting echocardiography, and chest X-ray.

Table 4 *shows recommendations for basic biochemistry in the initial diagnostic management of individuals with suspected chronic coronary syndrome.*

Table 5 shows ambulatory ECG for diagnosing patients with suspected CAD.

Table 6 shows recommendations for exercise ECG in the initial diagnostic management of individuals with suspected CAD.

Table 7 shows recommendations for resting transthoracic ultrasound and cardiac magnetic resonance imaging in the initial diagnostic management of individuals with suspected chronic coronary syndrome.

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TABLE 5: Ambulatory ECG for diagnosing patients with suspected coronary artery disease (CAD).

Recommendations	*Class*[a]	*Level*[b]
Ambulatory ECG monitoring is recommended in subjects with chest pain and suspected arrhythmias	I	C
Ambulatory ECG monitoring should be considered in subjects with suspected vasospastic angina	IIa	B

[a]Class of recommendation.
[b]Level of evidence.
(ECG: electrocardiogram)
Source: ESC 2024.

TABLE 6: Recommendations for exercise ECG in the initial diagnostic management of individuals with suspected coronary artery disease (CAD).

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

[a]Class of recommendation.
[b]Level of evidence.
[c]When this information will have an impact on diagnostic strategy or management.
(BP: blood pressure; CCTA: coronary computed tomography angiography; ECG: electrocardiogram)
Source: ESC 2024.

TABLE 7: Recommendations for resting transthoracic ultrasound and cardiac magnetic resonance imaging in the initial diagnostic management of individuals with suspected chronic coronary syndrome.

Recommendations	*Class*[a]	*Level*[b]
A resting transthoracic echocardiogram is recommended to measure LVEF, volumes, and diastolic function: • Identify regional wall motion abnormalities • Identify noncoronary cardiac disease (e.g., hypertrophy, cardiomyopathy, valve disease, and pericardial effusion) • Assess right ventricular function and estimate systolic pulmonary artery pressure; to refine risk stratification and guide treatment	I	B
CMR, if available, may be considered as an alternative imaging test in individuals with inconclusive echocardiographic evaluation	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
(CMR: cardiac magnetic resonance; LVEF: left ventricular ejection fraction)
Source: ESC 2024.

Assessment of Pretest Probability and Clinical Likelihood of Coronary Artery Disease (Table 8)

If the likelihood of CAD is intermediate diagnostic testing is most useful. If the likelihood is high, a large number of patients need to be studied to identify the few patients that do not have disease, and a negative test result can seldom rule out the presence of obstructive CAD. A simple predictive model can be used to estimate the pretest probability (PTP) of obstructive CAD based on age, sex, and the nature of symptoms.[5]

Table 8 shows determinants of clinical likelihood of CAD.

Lifestyle Modification in Patients with Chronic Coronary Syndrome (Table 9)

Management of CCS aims to reduce symptoms and improve prognosis of patients through appropriate medications and interventions, and to control risk factors through lifestyle behaviors. Optimal medical therapy in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial included the promotion of medication adherence, behavioral counseling, and support for the managing

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TABLE 8: Determinants of clinical likelihood of coronary artery disease (CAD).

Decreases likelihood	*Increases likelihood*
• Normal exercise ECG[a] • No coronary calcium by CT (Agatston score = 0)[a]	• Risk factors for CVD (dyslipidemia, diabetes, hypertension, smoking, and family history of CVD) • Resting ECG changes (Q-wave or ST-segment/T-wave changes) • LV dysfunction suggestive of CAD • Abnormal exercise ECG[a] • Coronary calcium by CT[a]

[a]When available.
(CVD: cardiovascular disease; LV: left ventricular)

lifestyle risk factors delivered by nurse case managers.[6] Smoking cessation improves the prognosis in patients by 36% risk reduction in mortality for those who quit.[7]

Box 1 shows recommended diet.

Lifestyle factors and implementation of healthy behaviors (including smoking cessation, physical activity, a healthy diet **(Box 1)**, and maintaining a healthy weight, significantly decreases the risk of future cardiovascular events and death. Clinical trials have shown that psychological (e.g., counseling and/or cognitive behavioral therapy) and pharmacological interventions have a beneficial effect on depression, anxiety, and stress, with some evidence of a reduction in cardiovascular mortality.

TABLE 9: Lifestyle interventions in patients with chronic coronary syndrome (CCS).

Topic	*Recommendation and treatment goals in patients with established CCS*
Lifestyle counseling	
Immunization	Vaccination against influenza, pneumococcal disease, and other widespread infections, e.g., COVID-19
Sleep quality	Treat sleep-related breathing disorders
Sexual activity	• *Males and females:* Low risk for stable patients who are not symptomatic at low-to-moderate activity levels • *Males:* PDE-5 inhibitors are generally safe, not to be taken in combination with nitrate medications because of risk of severe hypotension
Psychosocial aspects	• Avoid psychosocial stress • Treat depression and anxiety by psychological or pharmacological interventions
Environment/pollution	• Avoid passive smoking • Reduce environmental noise • Avoid exposure to air pollution
Lifestyle interventions for risk-factor control	
Smoking and substance abuse	• Use pharmacological and behavioral strategies to assist in smoking cessation • Avoid e-cigarettes • Abstain from substance abuse
Obesity and being overweight	• Obtain and maintain a healthy weight (BMI = 18.5–25 kg/m^2) • Reduce weight through recommended energy intake and increased physical activity and through pharmacological/surgical interventions in selected patients
Hyperlipidemia	• Ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction in LDL-C vs. baseline is recommended
Diabetes	• HbA1c < 70% (53 mmol/mol)
Arterial hypertension	• SBP 120–129 mm Hg, provided the antihypertensive treatment is well tolerated
Diet and alcohol consumption	• Limit alcohol consumption to <100 g/week • Diet high in vegetables, fruit, and wholegrains (Mediterranean diet) • Limit saturated fat to <10% of total calorie intake
Physical activity and exercise	• 30–60 minutes moderate activity, >5 days/week • Reduce sedentary time and engage in at least light activity throughout the day

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

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Pharmacological Management (Table 10)

Short-acting Nitrates

Nitroglycerin spray acts more rapidly than sublingual nitroglycerine. At the onset of angina, the patient should be in a sitting position because standing promotes syncope, and lying down enhances venous return and preload and take nitroglycerin (0.3–0.6 mg tablet sublingually, or 0.4 mg spray to the tongue) every 5 minutes until the pain disappears, or a maximum of 1.2 mg has been taken within 15 minutes. Isosorbide dinitrate (5 mg sublingually) has a slightly slower onset of action than nitroglycerin due to hepatic conversion to mononitrate.

BOX 1: Recommended diet.

Characteristics:

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

Long-acting Nitrates

Long-acting nitrate formulations (e.g., nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate) should be considered as second-line therapy for angina relief when initial therapy with a β-blocker or nondihydropyridine (non-DHP) is contraindicated. Nitroglycerin can be administered orally or transdermally through slow-release patch systems. It should be gradually tapered to avoid a rebound increase in angina. The most common side effects are hypotension, headache, and flushing. Contraindications include hypertrophic obstructive cardiomyopathy, severe aortic valvular stenosis, and co-administration of phosphodiesterase inhibitors such as sildenafil, tadalafil, or vardenafil or riociguat.

TABLE 10: Pharmacological management of chronic coronary syndrome (CCS).

	Standard therapy	*High heart rate (e.g., >80 bpm)*	*Low heart rate (e.g., <50 bpm)*	*LV dysfunction of heart failure*	*Low blood pressure*
1st step	BB or CCB[a]	BB or non-DHP-CCB	DHP-CCB	BB	Low-dose BB or low-dose non-DHP-CCB[c]
	↓	↓	↓	↓	↓
2nd step	BB + DHP-CCB	BB + CCB[b]	Switch to LAN	BB + LAN or BB + ivabradine	Switch to ivabradine,[d] ranolazine or trimetazidine[e]
	↓	↓	↓	↓	↓
3rd step	Add 2nd line drug	BB + ivabradine[d]	DHP-CCB + LAN	Add another 2nd line drug	Combine two 2nd line drugs
			↓		
4th step			Add nicorandil, ranolazine or trimetazidine		

[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.
[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: nondihydropyridine calcium-channel blocker]

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Beta-blockers

Beta-blockers can be combined with DHP CCBs to reduce DHP-induced tachycardia. A combination of β-blocker is with verapamil or diltiazem should be cautiously used due to the potential for developing worsening of HF, excessive bradycardia, and/or atrioventricular block. Combination of a β-blocker with a nitrate attenuates the reflex tachycardia. The principal side effects of β-blockers are fatigue, depression, bradycardia, heart block, bronchospasm, peripheral vasoconstriction, postural hypotension, impotence, and masking of hypoglycemia symptoms. In patients with recent MI and those with chronic HF with reduced ejection fraction, β-blockers have been associated with a significant reduction in mortality and/or cardiovascular events.

Nondihydropyridine Agents

Verapamil: It has a large range of approved indications, including all varieties of angina (effort, vasospastic, and unstable), supraventricular tachycardias, and hypertension. Risks of heart block, bradycardia, and HF. Compared with metoprolol, the antianginal activity was similar. Compared with atenonol in hypertension with CAD, verapamil is associated with fewer cases of diabetes, fewer anginal attacks, and less psychological depression. Beta-blockade combined with verapamil is not advised due to the risk of heart block.

Diltiazem: Like verapamil, it acts by peripheral vasodilation, relief of exercise-induced coronary constriction, a modest negative inotropic effect, and sinus node inhibition. Use of non-DHP CCBs in patients with LV dysfunction is not advised.

Dihydropyridine Agents

Nifedipine: ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system) trial, addition of long-acting nifedipine (60 mg o.d.) to conventional treatment of angina had no effect on major cardiovascular event-free survival.[8] Long-acting nifedipine proved to be safe, and reduced the need for coronary angiography and cardiovascular interventions. Relative contraindications to nifedipine are severe aortic stenosis, hypertrophic obstructive cardiomyopathy, or HF, and careful combination with β-blockade is usually feasible and desirable. Vasodilatory side effects include headache and ankle edema.

Amlodipine: Side effects are mainly ankle edema. In patients with CCS and normal BP, amlodipine 10 mg/day reduces coronary revascularizations and hospitalizations for angina. Exercise-induced ischemia is also reduced.

Ivabradine

Adding ivabradine 7.5 mg bd twice a day to atenolol therapy gives better control of heart rate and anginal symptoms.

Nicorandil

Nicorandil is a nitrate derivative of nicotinamide, with antianginal effects similar to those of nitrates or β-blockers. Side effects include nausea, vomiting, and severe oral, intestinal, and mucosal ulcerations. In IONA (Impact Of Nicorandil in Angina) trial, nicorandil significantly reduced the composite of coronary heart disease (CHD) death, nonfatal MI, or unplanned hospital admission for suspected anginal symptoms in patients with CCS, but there was no effect on death from ischemic heart disease or nonfatal MI.[9]

Ranolazine

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

Trimetazidine

Trimetazidine (35 mg b.i.d.) added to β-blockade (atenolol) improves effort-induced myocardial ischemia. It is contraindicated in Parkinson's disease, motion disorders, such as tremor, muscle rigidity, walking disorders, and restless leg syndrome.

Allopurinol

The role of allopurinol in reducing clinical events in CVD remains unclear. An observational study of 29, 298 episodes of incident allopurinol use found an association of allopurinol use with a reduction in the risk of incident MI in the elderly, particularly when used for >2 years.

Recommendation for Prevention of Event

See **Table 11**.

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TABLE 11: Recommendations for antianginal drugs in patients with chronic coronary syndrome.

Recommendations	*Class*[a]	*Level*[b]
General strategy		
It is recommended to tailor the selection of antianginal drugs to the patient's characteristics, comorbidities, concomitant medications, treatment tolerability, and underlying pathophysiology of angina, also considering local drug availability and cost	I	C
Selection of antianginal medication		
Short-acting nitrates are recommended for immediate relief of angina	I	B
Initial treatment with β-blockers and/or CCBs to control heart rate and symptoms is recommended for most patients with CCS[c]	I	B
If anginal symptoms are not successfully controlled by initial treatment with a beta-blocker or a CCB alone, the combination of a β-blocker and a DHP-CCB should be considered, unless contraindicated	IIa	B
Long-acting nitrates or ranolazine should be considered as add-on therapy in patients with inadequate control of symptoms while on treatment with β-blockers and/or CCBs, or as part of initial treatment in properly selected patients[d]	IIa	B
When long-acting nitrates are prescribed, a nitrate-free or low-nitrate interval should be considered to reduce tolerance	IIa	B
Ivabradine should be considered as add-on antianginal therapy in patients with left ventricular systolic dysfunction (LVEF <40%) and inadequate control of symptoms, or as part of initial treatment in properly selected patients	IIa	B
Nicorandil or trimetazidine may be considered as add-on therapy in patients with inadequate control of symptoms while on treatment with β-blockers and/or CCBs, or as part of initial treatment in property selected patients	IIb	B
Ivabradine is not recommended as add-on therapy in patients with CCS, LVEF >40%, and no clinical heart failure	III	B
Combination of ivabradine with non-DHP-CCB or other strong *CYP3A4* inhibitors is not recommended	III	B
Nitrates are not recommended in patients with hypertrophic cardiomyopathy or in coadministration with phosphodiesterase inhibitors	III	B

[a]Class of recommendation.
[b]Level of evidence.
[c]These drugs may require caution or may be contraindicated in certain patients with low BP (β-blockers and DHP-CCB), DM (β-blockers), atrioventricular conduction disorders (β-blockers and non-DHP-CCB), chronic obstructive pulmonary disease (noncardioselective β-blockers).
[d]Consideration for initial therapy: Ivabradine, nicorandil, long-acting nitrates, ranolazine, or trimetazidine for patients with intolerance or contraindications to β-blockers and/or CCBs; ranolazine and trimetazidine for patients with microvascular angina; nicorandil or nitrates for patients with coronary artery spasm. The drugs are listed in alphabetical order.
(CCB: calcium-channel blocker; CCS: chronic coronary syndrome; *CYP3A4:* cytochrome P450 3A4; DHP: dihydropyridine; DM: diabetes mellitus; LVEF: left ventricular ejection fraction)
Source: © ESC 2024
Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024;45(36):3415-537.

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Recommendations for Antithrombotic Therapy in Patients with Chronic Coronary Syndrome

See **Table 12.**

Treatment for Dual Antithrombotic Therapy with Aspirin in High or Moderate Risk Patients Who do not have High Bleeding Risk

See **Table 13.**

Recommendations for Lipid-lowering Drugs in Patients with Chronic Coronary Syndrome

See **Table 14.**

Dyslipidemia

The goal of treatment is to lower LDL-C by at least 50% from baseline and to <1.4 mmol/L (<55 mg/dL) although a lower target LDL-C of <1.0 mmol/L (<40 mg/dL) may be considered in patients who have experience a second vascular event within 2 years. When this level cannot be achieved, the addition of ezetimibe has been demonstrated to decrease cholesterol and cardiovascular events in post-ACS patients, and in those with diabetes. Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors (evolocumab and alirocumab) are very effective at reducing cholesterol, lowering LDL-C in a stable fashion to <1.3 mmol/L (50 mg/dL).

TABLE 12: Recommendations for antithrombotic therapy in patients with chronic coronary syndrome.

Recommendations	*Class*[a]	*Level*[b]
Long-term antithrombotic therapy in patients with chronic coronary syndrome and no clear indication for oral anticoagulation		
In CCS patients with a prior MI or remote PCL aspirin 75–100 mg daily recommended lifelong after an initial period of DAPT	I	A
In CCS patients with a prior MI or remote PCL, clopidogrel 75 mg daily is recommended as a safe and effective alternative to aspirin monotherapy	I	A
Alter CABG, approximate 75–100 mg daily a recommended lifelong	I	A
In patients without prior MI or revascularization but with evidence of significant obstructive CAD, aspirin 75–100 ng daily is recommended lifelong	I	B
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients at enhanced ischemic risk[c] without high bleeding risk[d]	IIa	A
In CCS or stabilized post-ACS patients who underwent PC and were initially treated with ticagrelor-based DAPT, who remain at high ischemic risk and are not at high bleeding risk, ticagrelor monotherapy 90 mg BID may be considered as an alternative to dual or other single antiplatelet therapy	IIb	C
Antithrombotic therapy postpercutaneous coronary intervention in patients with chronic coronary syndrome and no indication for oral anticoagulation		
In CCS patients with no indication for oral anticoagulation DAPT consisting of aspirin 75–100 mg and clopidogrel 75 mg daily for up to 6 months is recommended as the default antithrombotic strategy after PCI-stenting	I	A
In patients at high bleeding risk[d] but not at high ischemic risk,c it is recommended to discontinue DAPT 1–3 months after PCI and to continue with single antiplatelet therapy	I	A
Stopping DAPT alter 1–3 months from PCI stenting may be considered in patients who are not at high bleeding risk nor at high risk of ischemic events[c,d]	IIb	B
In CCS patients undergoing high-thrombotic risk stenting (e.g., complex left main stent, two-stent bifurcation, suboptimal stenting result, prior stent thrombosis, previously known CYP2C19*/*23 polymorphism), prasugrel or ticagrelor (in addition to aspirin) may be considered instead of clopidogrel, for the first month, and up to 3–6 months	IIb	C
Long-term antithrombotic therapy in patients with chronic coronary syndrome and an indication for oral anticoagulation		
In CCS patients with a long-term indicator for OAC, an AF therapeutic dose of VKA alone or, preferably of DOAC alone (unless contraindicated) is recommended lifelong	I	B
Antithrombotic therapy postpercutaneous coronary intervention in chronic coronary syndrome patients with an indication for oral anticoagulation		
In patients with an indication for OAC who undergo PCI, initial low-dose aspirin once daily recommended (loading dose when not on maintenance dose) in addition to OAC and clopidogrel	I	C
In patients who are eligible for OAC DOACs contradicted, recommended in preference to VIKA	I	A
Alter uncomplicated PCI in CCS patients with concomitant indication for OAC: • Early cessation of aspirin (≤1 week) • *Followed by the continuation of OAC and clopidogrel:* – Up to 6 months in patients not at high ischemic risk,[c] or – Up to 12 months in patients at high ischemic risk[c] – Followed by OAC alone is recommended	I	A
Continuation of aspirin up to 1 month after PCI. In addition to OAC and clopidogrel, it should be considered in patients at high ischemic risk[c] or with anatomical characteristics judged to outweigh the blending risk[e]	IIa	B
When concerns about high bleeding risk prevail over concerns about stent thrombosis or ischemic stroke: • Rivaroxaban 15 mg daily should be considered in preference to rivaroxaban 20 mg daily for the duration of concomitant antiplatelet therapy • Dabigatran 110 mg twice daily should be considered in preference to dabigatran 150 mg daily for the duration of concomitant antiplatelet therapy	IIa IIa	B B

Contd…

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Contd…

Recommendations	Class[a]	Level[b]
In patients with an indication for VKA in combination with single or dual antiplatelet therapy targeting VKA to an INR in the lower part of the recommended range and to a time in therapeutic range >70% should be considered	IIa	B
The use of prasugrel and ticagrelor is generally not recommended as part of antithrombotic therapy with aspirin and an OAC	III	C
Antithrombotic therapy postcoronary artery bypass grafting		
It is recommended to initiate aspirin postoperatively as soon as there is no concern over bleeding	I	B
DAFT may be considered after CABG in selected patients at greater risk of graft occlusion[f] and at low risk of bleeding	IIb	B
Use of proton-pump inhibitors		
A proton-pump inhibitor is recommended in patients at increased risk of gastrointestinal bleeding for the duration of combined antithrombotic therapy (antiplatelet therapy and for OAC)	I	A
A proton-pump inhibitor should be considered when a single antithrombotic (antiplatelet or anticoagulant drug) is used, considering the gastrointestinal bleeding risk of the individual patient	IIa	A

[a]Class of recommendation.
[b]Level of evidence.
[c]Enhanced thrombotic/ischemic risk criteria for extended treatment with a second antithrombotic agent.
[d]Bleeding-risk criteria according to PRECISE-DAPT or ARC-HBR.
[e]Anatomical/procedural thrombotic risk characteristics: stenting of left main, proximal LAD, or last remaining patent artery; suboptimal stent deployment; stent length of >60 mm; bifurcation with two stents implanted; treatment of chronic total occlusions.
[f]For example, stentectomy, endarterectomy, poor venous graft quality.
(ACS: acute coronary syndrome; AF; atrial fibrillation; ARC-HBR: Academic Research Consortium for High Bleeding Risk; b.i.d., bis in die (twice daily); CABG: coronary artery bypass grafting; CAD: coronary artery disease; CCS: chronic coronary syndrome; CKD: chronic kidney disease; CYP2C19: cytochrome P450 2C19; DAPT: dual antiplatelet therapy; DOAC: direct oral anticoagulant; INR: international normalized ratio; LAD: left anterior descending; MI: myocardial infarction; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; PRECISE-DAPT: PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy; VKA: vitamin K antagonist)
Source: © ESC 2024
Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024;45(36):3415-537.

TABLE 13: Treatment for dual antithrombotic therapy with aspirin in high- or moderate-risk patients who do not have high bleeding risk.

Drug option	Dose	Indication	Additional cautions
Clopidogrel	75 mg OD	Post-MI in patients who have tolerated DAPT for 1 year	
Prasugrel	*10 mg OD or 5 mg OD*: 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 BID	Post-MI >1 year or multivessel CAD	Creatinine clearance 15–29 mL/min
Ticagrelor	60 mg BID	Post-MI in patients who have tolerated DAPT for 1 year	

(CAD: chronic artery disease; DAPT: dual antiplatelet therapy; MI: myocardial infarction; PCI: percutaneous coronary intervention)

Renin Angiotensin System Blockers

ACE inhibitors can reduce mortality, MI, stroke, and HF among patients with LV dysfunction, previous vascular disease, and high-risk diabetes. It is recommended that ACE inhibitors or ARBs in cases of intolerance can be considered for the treatment of patients with CCS with coexisting hypertension, LVEF <40%, diabetes, or CKD, unless contraindicated (e.g., severe renal impairment, hyperkalemia, etc.). The first in class is *LCZ696* can be used in patients with HF (LVEF <35%) who remain symptomatic despite optimal treatment with an ACE inhibitor, a β-blocker, and a mineralocorticoid receptor antagonist (MRA), sacubitril/valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients.

Revascularization

Revascularization by PCI **(Fig. 1)** or CABG may effectively relieve angina, reduce the use of antianginal drugs, and improve exercise capacity and quality of life compared with a strategy of medical therapy alone. In the 5-year follow-up of the FAME 2 (Fractional Flow Reserve

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TABLE 14: Recommendations for lipid-lowering drugs in patients with chronic coronary syndrome.		
Recommendations	***Class***[a]	***Level***[b]
Lipid-lowering treatment with an LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction in LDL-C vs. baseline is recommended	I	A
A high-intensity statin up to the highest tolerated dose to reach the LDL-C goals is recommended for all patients with CCS	I	A
If a patient's goal is not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended	I	B
For patients who are statin intolerant and do not achieve their goal on ezetimibe, combination with bempedoic acid is recommended	I	B
For patients who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with a PCSK9 inhibitor is recommended	I	A
For patients who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with bempedoic acid should be considered	IIa	C
For patients with a recurrent atherothrombotic event (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered	IIb	B

[a]*Class* of recommendation.
[b]Level of evidence.
(CCS: chronic coronary syndrome; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9)
Source: ESC 2024.

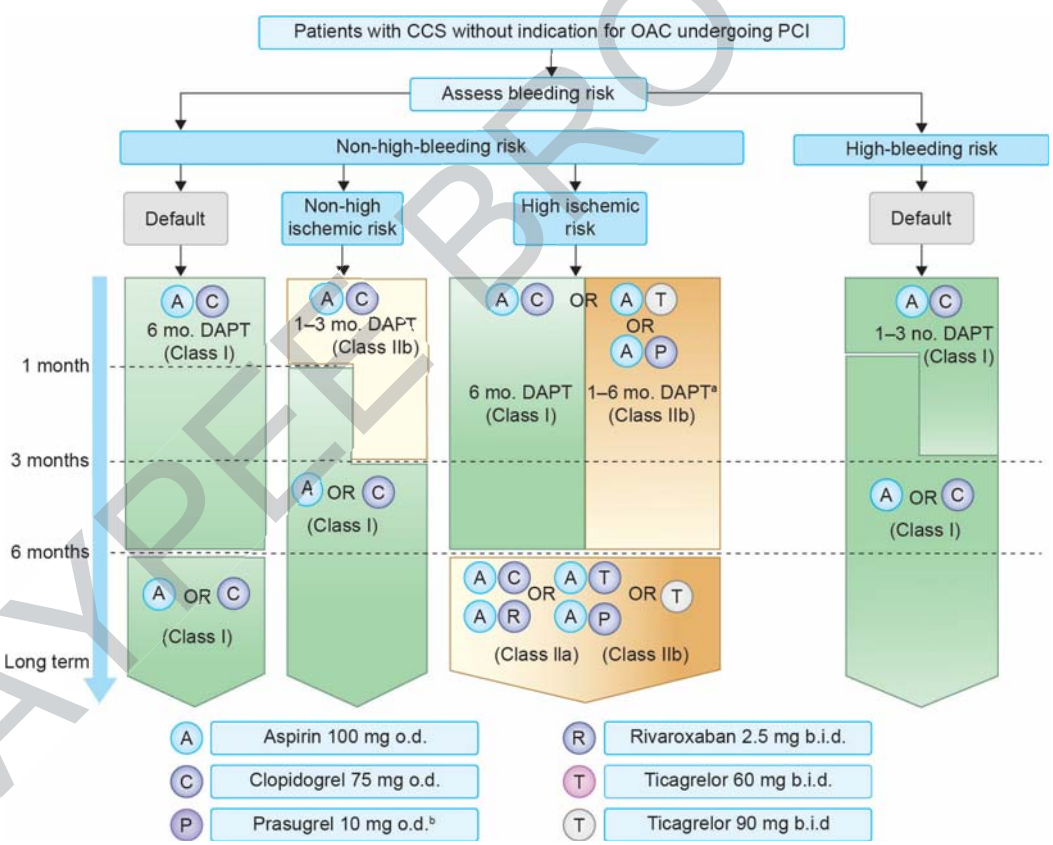


Fig. 1: Recommendation for event prevention.
[a]In CCS patients undergoing high-thrombotic risk stenting (e.g., complex left main stem, two-stent bifurcation, suboptimal stenting result, prior stent thrombosis, previously known CYP2C19*2/*3 polymorphisms), prasugrel or ticagrelor (in addition to aspirin) may be considered instead of clopidogrel for the first month, and up to 3–6 months.
[b]Prasugrel 5 mg o.d. for patients aged ≥75 years or with a body weight <60 kg.
(b.i.d.: bis in die (twice daily); CCS: chronic coronary syndrome; DAPT: dual antiplatelet therapy; mo.: months; OAC: oral anticoagulant; o.d.: once daily; PCI: percutaneous coronary intervention)
Source: European Society of Cardiology (ESC)

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versus Angiography for Multivessel Evaluation 2) trial, revascularization improved quality of life, and reduced the use of antianginal drugs and associated side effects.[10] The ORBITA (Objective Randomized Blinded Investigation with optimal medical Therapy or Angioplasty in stable angina) study, entailing a sham procedure in the control group, found no significant improvement in exercise capacity with PCI[11] **(Flowchart 1)**.

Decision for Revascularization in Patients with Chronic Coronary Syndrome

See **Flowchart 1**.

Management of Patients with Ischemic Cardiomyopathy and Left Ventricular Dysfunction

See **Table 15**.

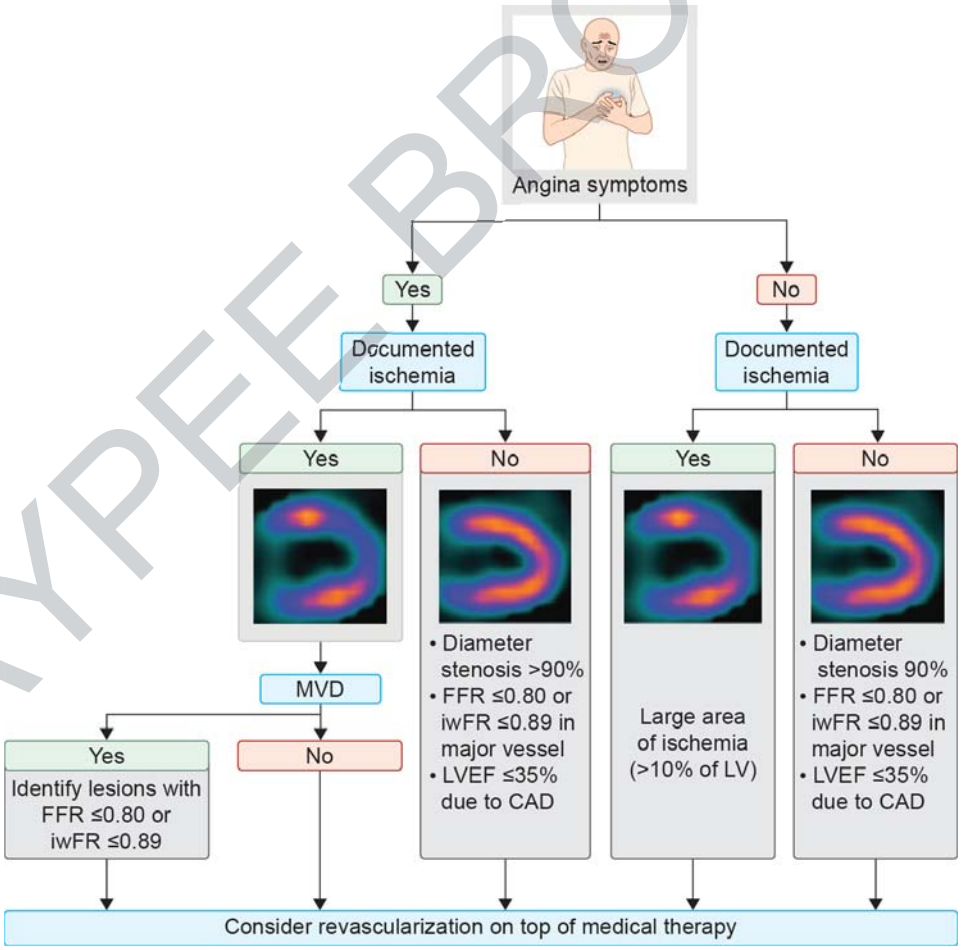
Recommendation for Patients with Longstanding Chronic Coronary Syndrome

See **Table 16**.

Microvascular Angina

Patients with microvascular angina typically have exercise-related angina, evidence of ischemia in noninvasive tests,

Flowchart 1: Decision tree for patients undergoing invasive coronary angiography. Decisions for revascularization by percutaneous coronary intervention or coronary artery bypass grafting are based on clinical presentation (symptoms present or absent), and prior documentation of ischemia (present or absent). In the absence of prior documentation of ischemia, indications for revascularization depend on invasive evaluation of stenosis severity or prognostic indications. Patients with no symptoms and ischemia include candidates for transcatheter aortic valve implantation, valve, and other surgery.



(CAD: coronary artery disease; FFR: fractional flow reserve; iwFR: instantaneous wave-free ratio; LV: left ventricle; LVEF: left ventricular ejection fraction; MVD: multivessel disease)

Source: ESC 2019.

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TABLE 15: Management of patients with ischemic cardiomyopathy and LV dysfunction.

Recommendations	*Class*[a]	*Level*[b]
Managing CCS in heart failure patients		
In HF patients with LVEF < 35% in whom obstructive CAD is suspected, ICA is recommended with a view toward improving prognosis by CABG, taking into account the risk-to-benefit ratio of the procedures	I	B
In HF patients with LVEF > 35% and suspected CCS with low or moderate (>5–50%) pretest likelihood of obstructive CAD, CCTA, or functional imaging is recommended	I	C
In HF patients with LVEF > 35% and suspected CCS with very high (>85%) pretest likelihood of obstructive CAD, ICA (with FFR, iFR, or QFR when needed) is recommended	I	C
In patents with HFpEF with persistent angina or equivalent symptoms and normal or nonobstructive epicardial coronary arteries. PET or CMR perfusion or invasive coronary functional testing should be considered to detect or rule out coronary microvascular dysfunction	IIa	B
In selected patients with HFrEF undergoing high-risk PCI for complex CAD, the use of a microaxial flow pump may be considered in experienced centers	IIb	C
Managing heart failure in CCS patients		
It is recommended that CCS patients with HF be enrolled in a multidisciplinary HF management program to reduce the risk of HF hospitalization and to improve survival	I	A
An ACE-I, an MRA, an SGLT-2 inhibitor (dapagliflozin or empagliflozin) and, in stable conditions, a β-blocker is recommended for CCS patents with HFrEF to reduce the risk of HF hospitalization and death	I	A
An SGLT-2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with heart failure with mildly reduced ejection fraction (HFmrEF) or HFpEF to reduce the risk of HF hospitalization or cardiovascular death	I	A
An ARB is recommended in symptomatic patients with CCS and HFrEF unable to tolerate an ACE-I or ARNI to reduce the risk of HF hospitalization and cardiovascular death	I	B
Sacubitril/valsartan is recommended as a replacement for an ACE-I or ARB in CCS patients with HFrEF to reduce the risk of HF hospitalization and of cardiovascular and all-cause death	I	B
Diuretics are recommended in CCS patients with HF and signs and/or symptoms of congestion to alleviate symptoms, improve exercise capacity, and reduce HF hospitalizations	I	B
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of ischemic etiology (unless they have had an MI in the prior 40 days), and an LVEF <35% despite >3 months of optimized medical treatment, provided they are expected to survive substantially longer than 1 year with good functional status	I	A
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing hemodynamic instability, and who are expected to survive for >1 year with good functional status, in the absence of reversible causes or unless the ventricular arrhythmia has occurred <48 hours after an MI	I	A
CRT is recommended for CCS patients with symptomatic HF, sinus rhythm, LVEF < 35% despite GDMT, and a QRS duration >150 ms with an LBBB QRS morphology to improve symptoms and survival and to reduce morbidity	I	A
CRT rather than right ventricular pacing is recommended for patients with HFrEF regardless of NYHA class or QRS width who have an indication for ventricular pacing for high-degree AV block in order to reduce morbidity. This includes patients with AF	I	A

[a]Class of recommendation.
[b]Level of evidence.
(ACE-I: angiotensin-converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin-receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; AV: atrioventricular; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CCS: chronic coronary syndrome; CCTA: coronary computed tomography angiography; CMR: cardiac magnetic resonance; CRT: cardiac resynchronization therapy; FFR: fractional flow reserve; GDMT: guideline-directed medical therapy; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; ICA: invasive coronary angiography; ICD: implantable cardioverter defibrillator; iFR: instantaneous wave-free ratio; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; MI: myocardial infarction; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; PET: positron emission tomography; SGLT2: sodium–glucose cotransporter 2)
Source: Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024;45(36):3415-537.

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TABLE 16: Recommendation for patients with longstanding chronic coronary syndrome (CCS).

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

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

TABLE 17: Investigations to diagnose 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	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	IIb	B
Transthoracic Doppler of the LAD, CMR, and PET may be considered for noninvasive assessment of CFR	IIb	B

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

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with no stenoses or mild-to-moderate stenoses (40–60%). Secondary microvascular angina, in the absence of epicardial obstruction, may result from cardiac or systemic conditions like hypertrophic cardiomyopathy, aortic stenosis, and hypertensive heart disease or inflammation such as myocarditis or vasculitis. Values of IMR >25 units or CFR <2.0 are indicative of abnormal microcirculatory function. Both CFR and IMR are typically measured while using intravenous vasodilators, such as adenosine or regadenoson. In patients with abnormal CFR <2.0 or IMR >25 units, and a negative acetylcholine provocation test, β-blockers, ACE inhibitors, and statins, along with lifestyle changes and weight loss, are indicated. Patients developing ECG changes and angina in response to acetylcholine testing but without severe epicardial vasoconstriction may be treated like vasospastic angina patients.

Investigations to Diagnose Microvascular Angina

See **Table 17**.

TABLE 18: Recommendations for diagnosis of patients with angina/ischemia with nonobstructive coronary arteries.

Recommendations	*Class*[a]	*Level*[b]
Diagnosis of ANOCA/INOCA endotypes		
In persistently symptomatic patients despite medical treatment with suspected ANOCA/INOCA (i.e., anginal symptoms with normal coronary arteries or nonobstructive lesions at noninvasive imaging, or intermediate stenoses with normal FFR/iFR at coronary arteriography) and poor quality of life, invasive coronary functional testing is recommended to identify potentially treatable endotypes and to improve symptoms and quality of life, considering patient's choices and preferences	I	B
In persistently symptomatic patients with documented or suspected ANOCA/INOCA, transthoracic Doppler of the LAD, stress echocardiography, CMR, and PET may be considered for the noninvasive assessment of coronary/myocardial flow reserve	IIb	B

[a]Class of recommendation.
[b]Level of evidence.
(ANOCA: angina with nonobstructive coronary arteries; CMR: cardiac magnetic resonance; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; INOCA: ischemia with nonobstructive coronary arteries; LAD: left anterior descending; PET: positron emission tomography)
Source: Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024;45(36):3415-537.

TABLE 19: Investigations for suspected vasospastic angina.

Diagnostic tests for vasospastic angina	*Class*	*Level*
In individuals with suspected vasospastic angina, a resting 12-lead ECG recording during angina is recommended	I	C
In patients with suspected vasospastic angina and repetitive episodes of rest angina associated with ST-segment changes that resolve with nitrates and/or calcium antagonists, invasive coronary functional testing is recommended to confirm the diagnosis and to determine the severity of underlying atherosclerotic disease	I	C
In individuals with suspected vasospastic angina and frequent symptoms, ambulatory ST-segment monitoring should be considered to identify ST-segment deviation during angina	IIa	B

Recommendations for Diagnosis of Patients with Angina/Ischemia with Nonobstructive Coronary Arteries

See **Table 18**.

Vasospastic Angina

Vasospastic angina should be suspected in patients with angina symptoms occurring predominantly at rest, with maintained effort tolerance. Attacks follow a circadian pattern with more episodes at night and in the early morning hours. It is suspected in patients with patent coronary stents and persistent angina. The diagnosis is based on detecting transient ischemic ST-segment changes during an angina attack usually at rest. A provocation test for coronary spasm is considered positive when it triggers: (i) anginal symptoms, (ii) ischemic ECG changes, and (iii) severe vasoconstriction of the epicardial vessel. CCBs and long-acting nitrates is the treatment of choice, control of cardiovascular risk factors, and lifestyle changes. Nifedipine has been shown to be effective in reducing coronary spasm associated with stent implantation.

Investigations for Suspected Vasospastic Angina

See **Table 19**.

Recommendation for Screening of Coronary Artery Disease in Asymptomatic Individuals

See **Table 20**.

Management of Diabetes Mellitus

See **Table 21**.

Management of Refractory Angina

See **Table 22**.

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TABLE 20: Recommendation for screening of coronary artery disease (CAD) in asymptomatic individuals.

Recommendations	*Class*[a]	*Level*[b]
Opportunistic screening of healthy individuals for cardiovascular risk factors and to estimate the risk of future cardiovascular events using scoring systems, e.g., SCORE-2 and SCORE-OP, is recommended to detect individuals at high risk and guide treatment decisions	I	C
When coronary artery calcification findings are available from previous chest CT scans, using these findings to enhance risk stratification and guide treatment of modifiable risk factors should be considered	IIa	C
CACS may be considered to improve risk classification around treatment decision thresholds	IIb	C
An ultrasound of the carotid arteries may be considered as an alternative when CACS is unavailable or not feasible to detect atherosclerotic disease and to improve risk classification around treatment decision thresholds	IIb	B

[a]Class of recommendation.
[b]Level of evidence.
(CACS: coronary artery calcium scoring; CT: computed tomography, SCORE2: systematic coronary risk estimation 2; SCORE-OP: systematic coronary risk estimation 2-older persons)
Source: Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024;45(36):3415-537.

TABLE 21: Management of diabetes mellitus.

Recommendations	*Class*[a]	*Level*[b]
CCS patients with type 2 diabetes mellitus (T2DM)		
SGLT-2 inhibitors with proven CV benefit[c] are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication	I	A
GLP-1 receptor agonists with proven CV benefit[d] are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-towering medication	I	A
CCS patients without type 2 diabetes mellitus		
The GLP-1 receptor agonist semaglutide should be considered in overweight (BMI >27 kg/m^2) or obese CCS patients without diabetes to reduce CV mortality, MI, or stroke	IIa	B

[a]Class of recommendation.
[b]Level of evidence.
[c]Canagliflozin, dapagliflozin, empagliflozin, sotagliflozin (listed in alphabetical order).
[d]Dulaglutide, efpeglenatide, liraglutide, and semaglutide (listed in alphabetical order).
(BMI: body mass index; CCS: chronic coronary syndrome; CV: cardiovascular; GLP-1: glucagon-like peptide-1; HbA1c: glycated hemoglobin; MI: myocardial infarction; SGLT2: sodium–glucose co-transporter 2)
Source: Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024;45(36):3415-537.

TABLE 22: Management of refractory angina.

Therapy	*Type of therapy*	*RCT*
External counter pulsation	Enhanced extremal counter pulsation	Must
Extracorporeal shockwave	Low-energy extracorporeal shockwave therapy	Not available
Coronary sinus constriction	Reducer device	COSIRA
Neuromodulation	Spinal cord stimulation	STARTSTIMS
	Transcutaneous electrical neural stimulation	Not available
	Subcutaneous electrical neural stimulation	Not available
	Sympathectomy	Denby et al.

Contd…

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Contd…

Recommendations	*Class*[a]	*Level*[b]
Gene therapy	Adenovirus fibroblast growth factor 5	Not available
Autologous cell therapy	Mononuclear bone marrow-derived hematopoietic progenitor cells	RENEW
In patients with refractory angina leading to poor quality of life and with documented or suspected ANOCA/INOCA invasive coronary functional testing is recommended to define ANOCA/INOCA endotypes and appropriate treatment considering patient choices and preferences	I	B
In patients with debilitating angina and obstructive CAD refractory to optimal medical and revascularization strategies, a reducer device for coronary sinus constriction may be considered to improve symptoms, in experienced centers	IIb	B

[a]Class of recommendation.
[b]Level of evidence.
(ANOCA: angina with nonobstructive coronary arteries; CAD: coronary artery disease; NOCA: ischemia with nonobstructive coronary arteries)
Source: Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024;45(36):3415-537.

CONCLUSION

An initial trial of medical therapy alone is the cornerstone of treatment for CCS. Revascularization is required in patients with persistent symptoms. Ischemia should be established with a noninvasive stress test before angiography. In patients undergoing angiography without a previous noninvasive stress test, FFR may be used to make appropriate decisions regarding revascularization. Revascularization with PCI or CABG is a very effective treatment for CAD.

The method of choice for revascularization depends on the angiographic characteristics of the lesions causing ischemia, LV dysfunction, comorbid conditions, suitability of the patient for surgery. The physician's ultimate decisions regarding patient care must include current evidence-based medicine as well as the patient's preferences and quality-of-life expectations.

In summary, the management of CAD, particularly in patients with CCS and conditions like ANOCA/INOCA, requires a multifaceted approach that encompasses precise diagnostic strategies, guideline-directed medical therapy, and individualized treatment pathways. The emphasis on shared decision-making and patient's education is critical to optimize risk-factor control and long-term outcomes. While advanced imaging techniques and functional testing play pivotal roles in guiding interventions, ongoing research is essential to enhance the understanding of disease endotypes and to develop effective lifestyle modification strategies. Ultimately, a holistic approach that integrates lifestyle changes, evidence-based therapies, and tailored revascularization strategies will be vital in improving patient's outcomes and reducing the burden of cardiovascular disease.

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