FUTURE CARDIOLOGY
2025, VOL. 21, NO. 5, 291–303
https://doi.org/10.1080/14796678.2025.2479970

Taylor & Francis
Taylor & Francis Group

PERSPECTIVE

OPEN ACCESS Check for updates

Diagnosing and treating stable angina: a contemporary approach for practicing physicians

Athanasios J. Manolis[a], Peter Collins[b] and José López-Sendón [c]

[a]Metropolitan Hospital, Piraeus, Greece; [b]National Heart & Lung Institute, Imperial College London and Royal Brompton Hospital, London, UK; [c]Cardiology Department, IdiPaz Research Institute, Hospital Universitario La Paz, Universidad Autonoma de Madrid, Madrid, Spain

ABSTRACT

Longer life expectancy and advancements in coronary artery disease management have improved life expectancy and survival, increasing the prevalence of chronic coronary syndromes (CCS). Angina is a common symptom in patients with CCS but remains underdiagnosed and undertreated. Contemporary guidelines provide detailed information on diagnosing and treating angina based on evidence and expert consensus; however, their extensive nature may hinder uptake by non-specialists. This review presents a practical approach to diagnosing stable angina, followed by the three pillars of CCS management: 1) healthy lifestyle including appropriate exercise, diet, and avoiding toxic habits; 2) optimal medical therapy, including treatment recommended to prevent cardiovascular events and drugs for the control of myocardial ischemia and angina tailored to the patient's comorbidities; and 3) myocardial revascularization when indicated. This approach may be useful for practicing physicians but is not intended to substitute more detailed and authoritative documents. Checklists are proposed to help focus patient–physician interactions and make follow-up visits more efficient. This approach seeks to increase the proportion of correct angina diagnoses and patients receiving evidence-based treatments, emphasizing the importance of patient education, managing residual angina, and reducing cardiovascular risk. We include reference to the recently published 2024 ESC guidelines on chronic coronary syndromes.

PLAIN LANGUAGE SUMMARY

Advances in the diagnosis and treatment of coronary heart diseases have greatly increased survival after a heart attack and increased life expectancy. As a result, an increasing number of people are living with chronic heart diseases that impair blood flow to the heart muscle, causing chest pain (angina). This can limit one's quality of life and capacity to perform daily functions without pain. There are several underlying causes of angina, and it also occurs in people who have not had a heart attack. Management should address three important areas: (i) Lifestyle changes should include regular exercise, a heart-healthy diet, and avoidance of smoking, while keeping blood pressure, serum cholesterol levels, and other so-called risk factors under control to prevent future cardiovascular events. (ii) Anti-angina medications (antianginal drugs) should be personalized based on the underlying cause of a patient's angina, their cardiovascular characteristics, the presence of other medical conditions and the medications that they are currently taking. The physician may need to adjust this tailored treatment to achieve optimal results for the individual patient. (iii) If this optimal medical therapy does not provide sustained relief, the physician may refer the patient to a cardiology center for further testing and to evaluate whether a revascularization procedure would be appropriate. Administering the optimal antianginal treatment for each patient, and careful adherence to lifestyle recommendations provide the best chance for restoring quality of life, reducing medical visits and improving long-term outcomes.

ARTICLE HISTORY
Received 11 November 2024
Accepted 12 March 2025

KEYWORDS
Chronic coronary syndromes; stable angina; diagnosis; antiischemic drugs; coronary revascularization

1. Introduction

The longer life expectancy in the general population and the improved survival of patients with myocardial ischemic syndromes has increased the number of patients living with chronic stable angina; a growing major medical problem [1–3]. Although angina is common among patients with non-acute myocardial ischemic syndromes [4], it is often underdiagnosed and undertreated [5,6]. Contemporary guidelines for the diagnosis and treatment of non-acute myocardial ischemic syndromes (variously referred to as chronic coronary syndromes [CCS] [7], chronic coronary artery disease [CAD] [8,9], or stable ischemic heart disease [10]), provide detailed information for the diagnosis and treatment of angina based on evidence and expert consensus [7–9]. Arguably, their length and granularity may limit their use by non-specialists. This document aims to provide practical guidance for the diagnosis and treatment of stable angina that may be useful for the practicing physician; it is not intended to substitute more detailed and authoritative documents.

CONTACT José López-Sendón jlopezsendon@gmail.com IdiPaz Research Institute, C. de Pedro Rico, 6, Madrid 28029, Spain
This article has been corrected with minor changes. These changes do not impact the academic content of the article.

Supplemental data for this article can be accessed online at https://doi.org/10.1080/14796678.2025.2479970

Article highlights

- Angina is a common symptom of chronic coronary syndromes and is increasing in prevalence, but often underdiagnosed and undertreated, leading to reduced quality of life.
- Major types include *Stable Angina*, characterized by transient symptoms under predictable conditions, and *Unstable Angina* that is persistent/progressive, and often unpredictable; these are further classified into epicardial, microvascular, or vasospastic based on the underlying pathophysiology.
- The *diagnostic algorithm* and assessment criteria provide a practical approach to diagnosing a patient presenting with chest pain.
- Management should include *lifestyle* advice that covers exercise, diet, and control of toxic habits.
- The *optimal medical therapy* for each patient should be identified using the algorithm to select treatment according to angina type, hemodynamic profile, comorbidities and concurrent medications.
- *Revascularization* is indicated for angina with significant anatomical or functional coronary stenosis, very high cardiovascular risk and/or debilitating angina despite optimal medical treatment.
- At *follow-up*, patient education must emphasize the importance of prevention, the need for adherence to therapy and treatment to targets.
- Following this approach will increase the proportion of patients receiving correct diagnoses and evidence-based treatment.

2. Definition of angina

Angina is defined as chest pain or discomfort *secondary to myocardial ischemia*. It has been described as pressure, tightness or heaviness that may be retrosternal or occur in the upper back, neck, jaw, or arms, and may radiate to arms, shoulders, neck, jaw [7,8]. It is typically brought on with exertion, particularly walking up an incline or stairs, and is relieved within a few minutes with rest or sublingual nitrates. Emotional stress can also be a trigger. Symptoms alone may not be sufficient for the diagnosis as they should be correlated to myocardial ischemia, and an ischemia test, preferably complemented with imaging, should be considered. Coronary angiography alone provides anatomical information but the presence of epicardial coronary stenosis does not imply myocardial ischemia or permit a clear diagnosis of angina; myocardial ischemia must be documented, except in patients with CCS who have a history of similar episodes. Dyspnea on exertion is often considered an angina equivalent. Symptoms are transient and generally resolve in minutes when the provoking stimulus is removed. Pain associated with chest trauma, body position, movement or breathing is less likely to be anginal.

2.1. Angina types

Typical angina refers to symptoms that fit well with the above description. The term *atypical* to describe variations or ambiguous symptoms is discouraged, however, as it may confound the importance of the diagnosis. Therefore, current guidelines recommend that atypical suggestive symptoms should be considered angina until further investigation excludes myocardial ischemia or chest pain not related to myocardial ischemia [7,8]. Angina severity has been classified by the Canadian Cardiovascular Society into 4 groups based on the types of activities that trigger angina [11]:

(I) Angina only with strenuous exertion or physical activity above normal, daily physical activities.
(II) Angina with moderate exertion, occurring during ordinary daily activities.
(III) Angina occurring during normal walking, short distances or climbing one flight of stairs.
(IV) Angina triggered by minimal activities such as dressing or washing up.

2.1.1. Stable and unstable angina [7–9]

- *Stable angina* is characterized by transient symptoms that occur under predictable conditions, with constant frequency over the course of weeks or months and are relieved in minutes with rest or sublingual nitrates.
- *Unstable angina* is prolonged (i.e., not relieved in a few minutes with rest or sublingual nitrates), or progressive (occurring with increasing frequency, duration, or intensity, or with new cardiac symptoms such as dizziness, syncope, or dyspnea, or occurring at rest or lower exercise activity). This is especially important in patients without a previous diagnosis of CCS, and in new onset angina (first episodes) or after a prolonged asymptomatic period in patients that already have a diagnosis of CCS. Angina onset within the first month after an episode of acute myocardial infarction and chest pain with ST segment elevation should always be considered unstable. Only patients with unstable angina require urgent treatment with hospital admission.

2.2. Angina according to underlying pathophysiology

Angina results from an imbalance between oxygen and nutrient supply to, and demand by the myocardium, but other conditions may also play a role (Figure 1) [12]. Myocardial ischemia may result from (combinations of) obstructive epicardial coronary lesions, endothelial dysfunction, microvascular dysfunction, metabolic abnormalities, inflammation, thrombi, and/or vasospasms or may be secondary to conditions that increase the metabolic demands of the myocardium, e.g.: hypertension, or aortic stenosis. Two distinctive phenotypes of angina have been clearly identified, based on the presence or absence of *significant epicardial coronary stenosis* [13–15].

Stable angina is a common symptom in patients with obstructive CAD, when atherosclerotic narrowing of one or more coronary artery reduces perfusion of cardiac muscle [8,16]; however, angina may occur without obstructive epicardial coronary stenosis, which is known as Ischemia and Non-Obstructive Coronary Arteries (INOCA) [13]. Patients with INOCA are at increased risk of major adverse cardiovascular events [17]. Up to half of patients undergoing invasive testing for angina with signs of ischemia do not have significant obstructive CAD [15], and up to 20% of patients with moderate to severe myocardial ischemia do not present significant epicardial coronary stenosis [18]. In patients with INOCA, ischemia results from endothelial or microvascular dysfunction, increased vascular tone/vasospasm, myocardial bridging, or may be secondary to other causes [8,16,19–21]. Accordingly, different INOCA subtypes should be considered:

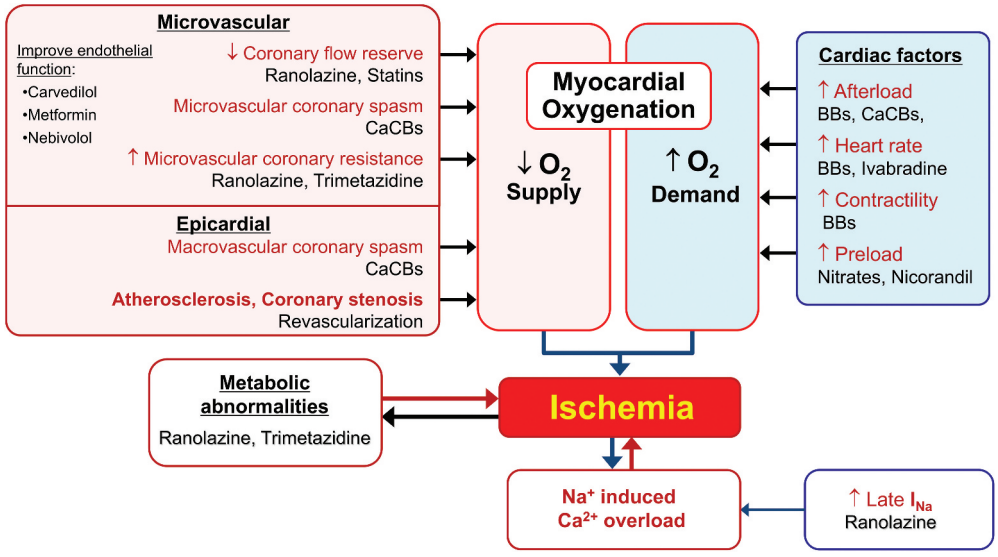

Figure 1. Pathophysiological mechanisms of myocardial ischemia and corresponding therapeutic options. Patients with significant epicardial coronary artery stenosis frequently have vascular and/or microvascular dysfunction. Conversely, patients without significant epicardial coronary artery stenosis frequently present non obstructive coronary epicardial coronary stenosis.

- *Microvascular angina* refers to ischemia due to an increase in microvascular resistance and/or inappropriate vasodilatory capacity. Diagnosis of microvascular disfunction is based on evidence of impaired coronary flow reserve, abnormal coronary microvascular resistance, abnormal micro-vasoconstriction, or slow coronary flow.
- *Vasospastic angina* occurs when *transient* total or subtotal epicardial coronary artery occlusion causes an episode of severely decreased myocardial perfusion. It may occur in subjects with normal appearing coronary arteries or in the presence of epicardial coronary stenosis. The vasoconstriction can be spontaneous or induced by provocation tests.
- *Angina secondary* to other cardiovascular conditions, e.g., hypertension, arrhythmias, aortic stenosis, spontaneous coronary artery dissection.
- *Other forms of angina* represent clinical settings with special difficulties for treatment, including angina after revascularization, angina with non-revascularizable epicardial coronary stenosis and angina refractory to standard appropriate treatment.

It is important to note that most patients with INOCA present some degree of epicardial coronary atherosclerosis. Conversely, 40–75% of patients with obstructive epicardial coronary stenosis present evidence of microvascular dysfunction [22,23].

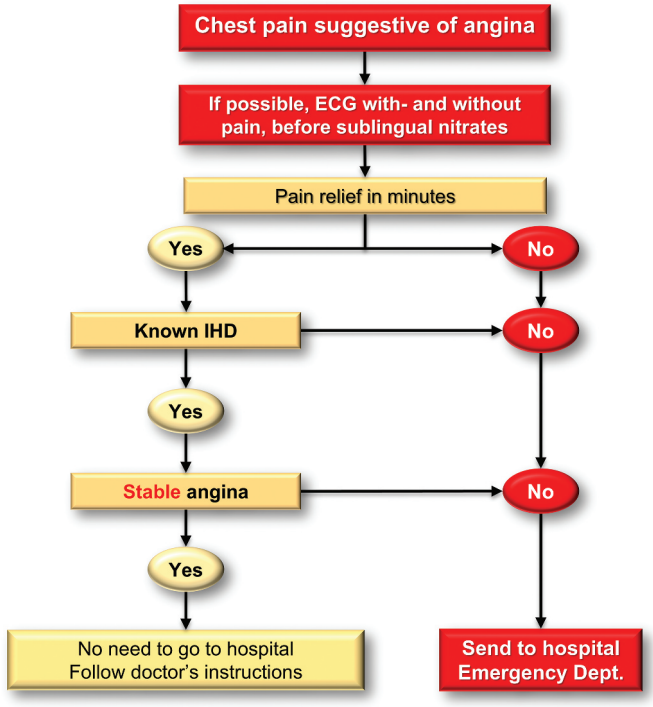

Figure 2. Strategy to avoid false negative diagnosis of potential acute coronary syndromes in presence of chest pain. ECG, electrocardiogram; IHD, ischemic heart disease.

3. Assessment and diagnosis

The first concern is to determine if the chest pain suspected to be ischemic results from an acute coronary syndrome or other serious condition (Figure 2). Once acute coronary syndromes and other potential life-threatening conditions are excluded, numerous algorithms have been proposed for diagnosis, and these should be adapted to the individual patient and the available resources at each institution. Detailed algorithms are useful during the progressive evaluation of the patient [19,20,24]; however, for practical purposes, we believe that the initial algorithm should be as simple as possible, to avoid delays that may result from ordering complementary testing and invasive procedures. Diagnostic criteria for the different forms of angina have been detailed in the previous section and are summarized in Table 1 [25,26]. The 2024 ESC Guidelines for the management of CCSs recommend noninvasive anatomic or functional imaging as first-line diagnostic

Table 1. Common diagnostic criteria in different forms of angina [25,26].

Form of angina	Diagnostic criteria
Angina with obstructive epicardial coronary lesions	• Angina • Documented ischemia (ECG changes during pain, stress test; preferably wall motion abnormalities during an imaging stress test) and • Epicardial coronary stenosis > 70%; >50% in left main stem in coronary angiogram or CCTA angiogram or • Borderline lesions with Fractional Flow Reserve ≤ 80

Ischemia and Non-Obstructive Coronary Arteries (INOCA)
Microvascular angina
	• Angina
	• Documented ischemia (ECG changes during pain, stress test; preferably wall motion abnormalities during an imaging stress test)
	• No significant epicardial coronary stenosis as defined above
	• Any of the following:
	  • Slow coronary flow (TIMI flow count > 25)
	  • Coronary micro-vasoconstriction during acetylcholine testing
	  • Abnormal microvascular resistance index (IMR > 25)

Vasospastic angina	• Angina, usually in the early morning • Epicardial coronary arteries may be normal or present significant stenosis • Responds to nitrates or calcium channel blockers • Coronary artery spasm in angiogram, spontaneous or in response to provocation (e.g., acetylcholine, ergonovine) or • ECG changes (ST elevation/depression) during spontaneous chest pain or in response to provocation (e.g., acetylcholine, ergonovine)

CCTA, coronary computed tomography angiography; ECG, electrocardiogram; IMR, index of microcirculatory resistance; TIMI, thrombolysis in myocardial infarction.

testing of suspected CCS in most patients, with invasive coronary angiography reserved for those with a very high likelihood of obstructive CAD, severe angina refractory to guideline-directed medical therapy, symptoms on low level exertion, and/or a very high risk of cardiovascular events [7]. The diagnostic yield of coronary angiography or CT is low. In a study including almost 400,000 patients referred for invasive coronary angiography, between 30% and 40% of asymptomatic patients had obstructive coronary disease, whereas 45% to 55% of symptomatic patients had non-obstructive coronary disease [27]. The real value of these exams is in their ability to identify patients with coronary artery lesions that should be considered for revascularization, mainly left main stem or triple vessel disease.

Figure 3 shows a general strategy for the initial management of patients with suspected angina. Table 2 describes common techniques useful for diagnosis that may vary according to local availability and expertise [8,9,16,28]. Once initial episodes of chest pain have been diagnosed as angina, subsequent episodes usually require a simpler workup; the patient already has a diagnosis of CCS, has been instructed on what to do during an episode of chest pain and when to go to the hospital, and should be receiving appropriate treatment for secondary prevention.

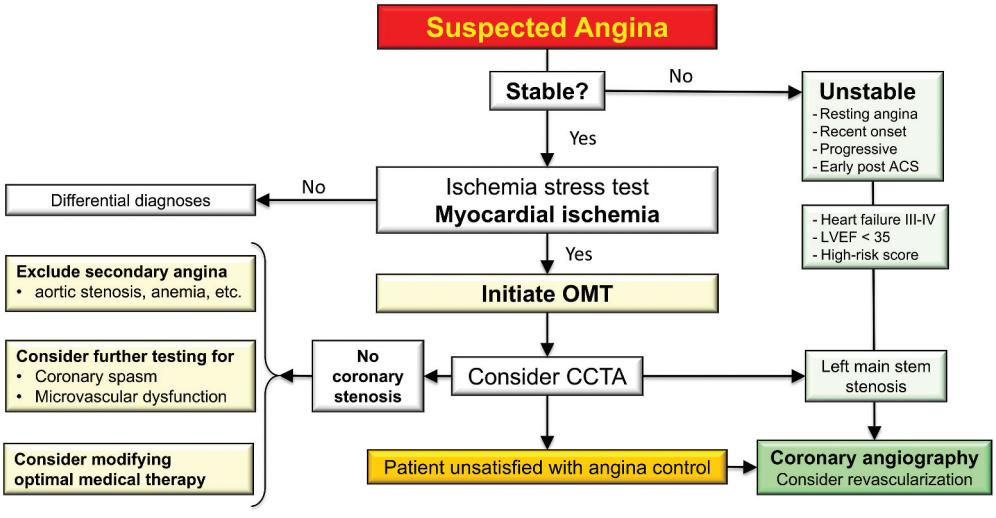

Figure 3. General strategy for diagnosis and treatment of stable angina. ACS, acute coronary syndrome; CCTA, coronary computed tomography angiography; LVEF, left ventricular ejection fraction; OMT, optimal medical therapy. CCTA may quickly rule out significant epicardial coronary stenosis, identify lesions usually considered for surgery (such as main left stem stenosis) but may not be available in all cases. In addition to coronary anatomy, myocardial ischemia should also be confirmed or ruled out, as a significant number of patients present angina without epicardial coronary stenosis.

Table 2. Useful techniques for the initial diagnosis of angina.

Technique	Value	Disadvantages
Symptoms and signs	• Suspicion of myocardial ischemia	• Unstable characteristics should be considered a potential acute cardiac syndrome • Age and cardiovascular risk factors increase the probability of significant epicardial coronary stenosis
Identify Comorbidities	• Hypertension/hypotension, tachycardia/bradycardia, renal dysfunction, diabetes, heart failure, bronchial disease, etc. • Very important to exclude secondary or contributing causes of ischemia • May contraindicate or suggest specific treatments	
Resting ECG	• ECG changes during suspected angina are highly suggestive of ischemic origin. If possible, ECG with and without pain, preferably before sublingual nitrates, should be obtained in patients without previous diagnosis of ischemic heart disease • ST segment elevation is an urgent condition that requires immediate hospital evaluation	• ECG may be normal and without changes during episodes of angina
Holter ECG	• ST segment changes or arrhythmias during episodes of suspected angina	• Usually diagnosis delays; normal ECG does not exclude angina
Biomarkers	• Troponins	• Troponins are biomarkers of myocardial damage, (i.e., not specific for ischemia). • Reliable ischemia-specific biomarkers are not available.
Stress testing	• Identification of myocardial ischemia • Best if imaging techniques are used	• Stress test with imaging not always available May be normal, especially in INOCA
Exercise stress test	• Physiological method	• Not all patients can exercise • Some false negatives and positives
Pharmacological stress test	• Useful if patient cannot exercise	• May not be available in all institutions
Cardiac CT	• Very specific for normal coronary arteries • May identify/exclude coronary lesions that currently are considered a clear indication for revascularization: in particular, significant Main stem/equivalent stenosis, seen in up to 10% of patients with moderate-severe ischemia	• Not available in all sites • Potential delays in diagnosis • Significant coronary stenosis does not necessarily imply myocardial ischemia • Normal epicardial coronary arteries do not exclude angina (INOCA)
Coronary angiography	• Gold standard to identify and quantify (anatomically and functionally) significant coronary stenosis	• Invasive. Potential complications (bleeding, renal dysfunction, stroke, others) • May be normal in presence of myocardial ischemia (e.g., INOCA) • Does not identify myocardial ischemia • May lead to unnecessary revascularization
Resting echocardiogram	• Ventricular function should always be evaluated during the initial diagnostic workup • Identifies other conditions related with ischemia: e.g., aortic stenosis, myocardial hypertrophy.	• Waiting lists should not be allowed to delay diagnosis and treatment
Other Techniques Ergonovine, adenosine, acetylcholine tests, CMR-MPI, PET-MPI, SPECT-MPI	• Quantification of coronary reactivity • Quantification of myocardial perfusion • Quantification of coronary flow reserve • More sensitive for identifying myocardial ischemia, especially in INOCA	• Coronary flow reserve strongly recommended in presence of borderline coronary stenosis • Other techniques: • Not available in most clinical practices • No clear consensus for indications • Reserve for selected patients and research

CMR, cardiovascular magnetic resonance; CT, computed tomography; ECG, electrocardiogram; INOCA, ischemia and no obstructive coronary arteries; MPI, myocardial perfusion imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography; ST, stress test.

For angina secondary to microvascular dysfunction in INOCA, the best diagnostic pathway in clinical practice is still a matter of controversy, pending new research on appropriate pathways and diagnostic tests that can be recommended for a significant proportion of patients. Again, it should be emphasized that microvascular dysfunction is very common in the presence of significant coronary artery stenosis.

3.1. Risk stratification

Risk scores for prediction of epicardial coronary stenosis and prognosis of patients with chronic stable angina may help when planning strategies for diagnosis and treatment. Prediction models for significant obstructive CAD consider patient age, sex, type of angina, diabetes, dyslipidemia, and family history of CAD. They provide guidance for selecting further testing [29]. Prognostic scores in patients with CCS and stable angina consider multiple factors, including age, current smoking status, current angina, diabetes, previous myocardial infarction or stroke [30], as well as major comorbidities that may themselves impose a poor prognosis or limit therapeutic options. Although identifying the key risk factors is important to informing clinical decisions, complex risk scores are not often used in clinical practice. The patient-reported Seattle Angina Questionnaire is a validated metric for assessing

angina symptoms that is recommended to support patient-centered care and evaluate the impact of angina on quality of life and to monitor the effects of treatment [7,31].

4. Treatment

The three pillars of the correct management of CCS are healthy lifestyle, optimal medical treatment, and revascularization (Figure 4). All three are equally important and must be considered in every patient [7]. Key factors for diagnosis and treatment strategies include a) stable versus unstable symptoms, b) presence versus absence of epicardial coronary stenosis; c) the underlying pathophysiology; d) the hemodynamic profile; e) comorbidities; f) cardiovascular risk scores (e.g., SCORE2 [32], or SCORE2-OP [33], as appropriate); and g) control of angina symptoms and their impact on quality of life.

4.1. Lifestyle and patient education

A healthy lifestyle includes appropriate exercise (tailored to patient age and functional capacity) [34], a healthy diet, and control of toxic habitsin particular, cigarette smoking and drug abuse. Annual influenza vaccination prevents acute episodes and is recommended in all patients with CCS [35], as well as in healthy persons aged 65 years and older [36]. Education is crucial and rehabilitation programs play an important role. Patients with CCS must also be instructed on what to do during an angina episode, including the correct use of sublingual nitrates, when to consult their physician, when to go to the hospital and whether to go directly or to summon emergency transportation (Figure 2). In addition, control of common risk factors (smoking and other toxic habits, blood pressure, diabetes, dyslipidemia) are far from ideal and require better education of patients as well as physicians.

4.2. Optimal medical therapy

Optimal medical therapy in CCSs can be classified in two categories: drugs recommended to prevent cardiovascular events (secondary prevention), and drugs for the control of angina

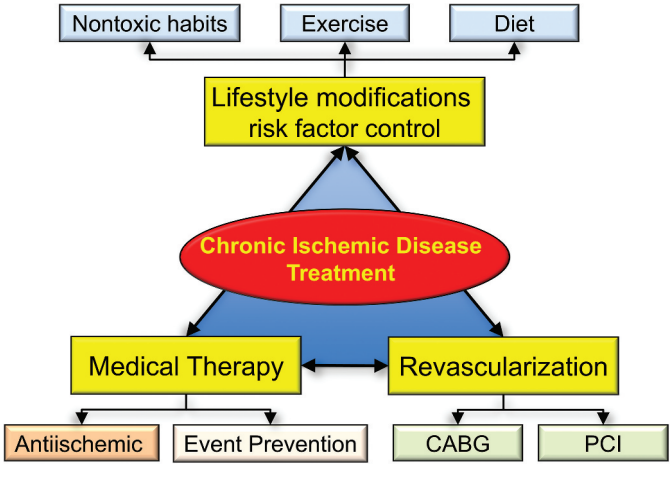

Figure 4. Pillars of therapy in chronic coronary disease. CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention.

[8,16]. The first includes the best possible control of risk factors and the use of medications with proven benefit for long term outcomes, including antiplatelet agents and statins [8,16].

4.2.1. Antianginal therapy

There is a lack of evidence to support the superior efficacy of any antiischemic drug (beta-blockers, calcium channel blockers, ivabradine, nicorandil, nitrates, ranolazine, trimetazidine), or to justify categorizing them into treatment lines [37]. None of the antiischemic drugs has demonstrated consistent improvement in cardiovascular outcomes in patients with CCSs; therefore, it would be reasonable to base treatment decisions on a) the type of angina, b) the hemodynamic profile, c) comorbidities, d) drug contraindications and potential drug–drug interactions, rather than on groups of drugs in predefined treatment lines [38–40]. The 2024 ESC CCS guidelines reinforce this concept [7], no longer considering a first line with priority going to beta-blockers and calcium channel blockers, thereby marking a change from the previous guideline [16]. Figure 1 depicts treatment preferences according to the pathophysiological mechanisms involved in myocardial ischemia. Table 3 details the mechanisms of action, adverse events, and contraindications of the various antiischemic drugs.

The so-called “diamond approach” presented by Ferrari et al. [39] is an algorithm for selecting antiischemic drugs based on angina type, hemodynamics, comorbidities, drug mechanism of action, contraindications, and potential drug–drug interactions (Supplemental Figure S1); an updated version is presented in the 2024 ESC Guidelines [7]. A simplified algorithm for selecting antiischemic drugs according to the patient’s hemodynamic profile and common comorbidities is presented in Figure 5 [38].

Patients with blood pressure < 120 mm Hg, should start with ranolazine or trimetazidine [16]. Meanwhile, bradycardic patients should receive agents that do not influence heart rate; if this is unavoidable, they may receive beta-blockers or heart rate lowering CCBs, but these must be initiated at very low doses with careful monitoring.

In patients with heart failure, beta-blockers are the first choice for treatment, whereas in patients with vasospastic angina, calcium channel blockers should be used first, and beta-blockers are contraindicated. In diabetic patients, beta blockers (except vasodilating beta-blockers) should be avoided [38]. The largest clinical trial specifically in patients with type 2 diabetes mellitus (T2DM) and CAD is the TERESA study, which showed a significant benefit of ranolazine on exercise parameters, angina frequency and nitroglycerin use [41]. Ranolazine improves glycemic control, reducing fasting blood glucose and providing a moderate, dose-dependent reduction in hemoglobin A1c levels in diabetic patients with CAD [42,43]. A scientific statement from the American Heart Association on the clinical management of patients with stable CAD and T2DM specifies that, in the absence of competing considerations, “T2DM friendly” medications should be selected when angina treatment is indicated [44]. A recent meta-analysis shows that ranolazine is associated with a lower incidence of atrial fibrillation, in addition to its antiischemic effects [45]. Several studies also support the benefit

Table 3. Anti-ischemic drugs: mechanisms of action adverse events and contraindications.

Proposed mechanism of action	Common adverse effects	Contraindications	Comments
Beta-blockers Competitive antagonists of β-adrenergic receptors Reduce myocardial oxygen consumption (reduce heart rate, blood pressure, contractility) Additional vasodilation: carvedilol, nebivolol	• Bradycardia, atrioventricular block, bronchospasm, peripheral vasoconstriction, impotence, insomnia	• Asthma • Bradycardia, sinus node disease, second- or third-degree atrioventricular block (unless a functioning pacemaker is present) • Hypotension • Vasospastic angina • Unstable heart failure	• Preferred choice for exertional angina, heart failure, hypertension • May increase coronary spams due to a predominance of α-mediated coronary vasoconstriction. • Proven prognostic benefit in patients with previous heart failure • Cardioselective β-blockers preferred
Calcium channel blockers Block Ca+ entry in cardiac and smooth muscle cells Peripheral and coronary vasodilators	• Abdominal pain, nausea, dyspepsia, constipation • Hypotension • Somnolence, dizziness • Dihydropyridines increase heart rate. Palpitations. ankle edema • Non-dihydropyridines reduce heart rate and contractility. May induce sinus bradycardia, atrioventricular block, and decompensate heart failure.	• Hypotension • Dihydropyridines: tachycardia • Non dihydropyridine: bradycardia sick sinus syndrome, second or third-degree atrioventricular block, and sick sinus syndrome (unless a functioning pacemaker is present) • Atrial fibrillation/flutter in Wolff-Parkinson-White syndrome • Heart failure, left ventricular dysfunction	• Preferred choice for vasospastic angina (dihydropyridines) • Avoid combination of diltiazem or verapamil with β-blockers or ivabradine
Nitrates Nitric oxide-mediated vasodilation	• Headache, dizziness, flushing • Tachycardia • Hypotension	• Hypotension • Hypertrophic obstructive cardiomyopathy, constrictive pericarditis, severe mitral/aortic stenosis, cardiac tamponade • Coadministration of phosphodiesterase inhibitors (e.g., sildenafil)	• Sublingual nitrates are first choice for angina relief • Preference choice: patients with vasospastic angina, along with calcium channel blockers • Tachyphylaxis and tolerance frequent with long-term use • Long-term use may worsen outcomes
Ranolazine Blocks late inward Na^+ current, preventing ischemia induced Ca^{2+} overload Improves microvascular dysfunction, increasing coronary blood flow reserve and decreasing coronary vascular resistance	• Dizziness, headache, constipation, nausea, vomiting, asthenia	• Concomitant use of potent CYP3A4 inhibitors* • Coadministration with class I or class III antiarrhythmics other than amiodarone. • Severe renal impairment (crCL <30 mL/min) • Hepatic impairment, cirrhosis	• Preferred choice for diabetes, INOCA • No hemodynamic side effects • Improves Hemoglobin A1c. • Safe in patients with acute coronary syndromes, heart failure and arrhythmias
Trimetazidine Inhibits mitochondrial 3ketoacylCoA thiolase. Shifts cardiac metabolism from fatty acid βoxidation to glucose oxidation during ischemia	• Abdominal pain, nausea and vomiting, diarrhea, headache • Parkinsonism, gait disorders	• Parkinson disease, parkinsonism, and other related movement disorders • Tremors and movement disorders	• No hemodynamic side effects • Improves Hemoglobin A1c. • Safe in patients with, heart failure • Not available in all countries
Nicorandil Nitric oxide donor: vasodilation K_{ATP} channel opener: systemic and coronary vasodilation	• Headache, dizziness, weakness, hypotension, abdominal pain, nausea, vomiting • Ulcerations of skin, mucosa (anal, colonic, rectal, vulvovaginal, and penile), and eyes. • Hyperkaliemia	• Hypotension • Tachycardia • Coadministration of phosphodiesterase inhibitors (e.g., sildenafil), metformin or dapoxetine, medicines that increase potassium levels (especially in patients with renal dysfunction)	• Acceptable substitute for long-acting nitrates • Does not produce tolerance with chronic use • Not available in all countries
Ivabradine Blocks hyperpolarization-activated pacemaker current (I[f]) in sinus node cells causing pure reduction of sinus heart rate	• Bradycardia • Phosphenes dizziness	• Resting heart rate <70 bpm • Bradycardia, sinus node disease, second or third-degree atrioventricular block (unless functioning pacemaker present) • Atrial fibrillation (no effect) • Severe hepatic impairment • Combination with verapamil or diltiazem	• Preferred choice for patients with HF • Concomitant use with calcium verapamil or diltiazem may be harmful • Not approved for this indication in some countries

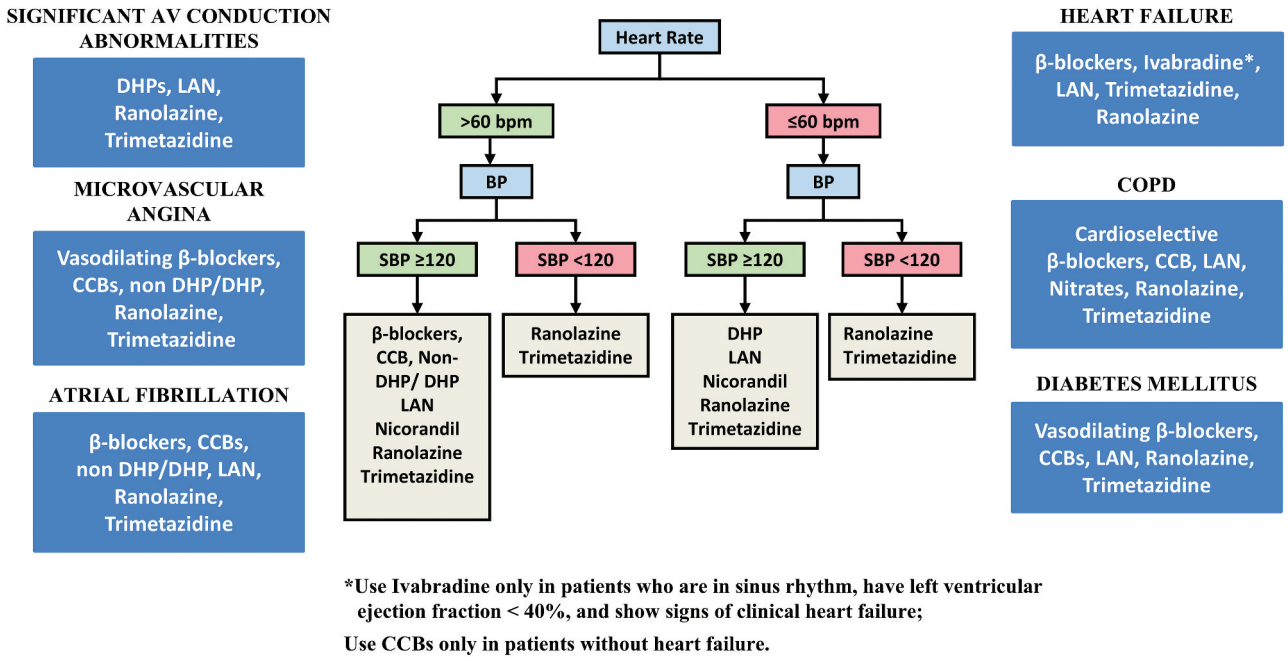

Figure 5. Optimal medical therapy considering the hemodynamic profile and common comorbidities. BP, blood pressure; bpm, beats per minute; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; DHP, dihydropyridine; LAN, long-acting nitrates; SBP, systolic BP. (Modified from Manolis et al. Eur J Intern Med 2021;92:40–7 [33]).

of trimetazidine in diabetic patients with CCS. In a meta-analysis of 8 carefully selected controlled clinical trials with a total of 946 diabetic patients, trimetazidine was associated with an improvement in serum glucose metabolism, lipid profile, ventricular function parameters, and a reduction in myocardial ischemia episodes without a significant improvement in exercise tolerance [46].

4.2.1.1. Patients with angina and no evidence of significant epicardial coronary stenosis. Heterogeneity in the underlying pathophysiological mechanism complicates treatment of angina in patients with INOCA, and management should follow a multidisciplinary, patient-oriented approach [7,47]. Patients with demonstrated impairment of coronary flow reserve appear to respond better to antiischemic therapy [48]. Ranolazine improves microvascular dysfunction, increasing coronary blood flow reserve and decreasing coronary vascular resistance [49], and was shown to improve some quality of life domains, including angina stability, physical functioning, and quality of life in randomized placebo controlled trials in patients with INOCA [50].

Statins, carvedilol, nebivolol and metformin may improve endothelial dysfunction, while calcium channel blockers are effective for controlling macro and micro coronary vasoconstriction. In most patients, optimal medical therapy will require a combination of two or more drugs for effective control of angina [51]. If the response is not sufficient after an adequate trial duration, an increase in dosage or switch to another combination should be considered. Possible combinations of classes of antiischemic drugs according to patient characteristics are presented in Supplemental Figure S1 [39]. Women with stable angina have been underrepresented in clinical trials of antianginal therapies; therefore, there is less evidence to support treatment recommendations for women [52].

Sublingual nitrates are the first choice during episodes of angina and are still recommended in guidelines for the general control of angina. However, continuous long-term use has been associated with endothelial dysfunction [53], and may increase the risk of cardiac death [54]; therefore, they should be used as a second-line option in cases of persisting angina. It should be noted that, for various reasons, some drugs have not been approved for the treatment of angina by the US Food and Drug Administration (i.e., ivabradine, nicorandil and trimetazidine).

4.3. Myocardial revascularization

Revascularization remains controversial in stable patients with CCS. Guidelines recommend the use of noninvasive (i.e., coronary computed tomography angiography) or invasive coronary angiography in moderate- to high-risk patients [7]. Revascularization is recommended in many patients who have angina and significant anatomical or functional coronary stenosis [55]. Nevertheless, optimal medical therapy must always be implemented and there is no clear evidence to support revascularization in many stable patients, especially when ischemic symptoms are controlled with medical therapy. In a recent meta-analysis of randomized trials performed during the last 50 years, revascularization plus medical therapy was associated with a lower risk of cardiac death, but no differences were found in all cause death, myocardial infarction or stroke [56]. Similar results were found in another recent meta-analysis where relief from angina was more frequent after revascularization [57]. In addition, both medical therapy

and revascularization procedures have improved significantly over time and information from older trials may not be reliable in contemporary medicine.

The recent ISCHEMIA trial in stable patients with moderate-to-severe ischemia compared optimal medical therapy plus initial coronary angiography and complete revascularization, if feasible, to patients receiving optimal medical therapy alone, with revascularization possible during follow-up for persisting symptoms or acute coronary syndromes. After a median follow-up of 3.2 years [58–60], and an extended median follow-up of 5.7 [61], there was no difference in the primary endpoint clinical outcomes between the two groups. In the initially invasive group, the number of days out of hospital was lower during the initial follow-up [62], but results were better on angina function and quality of life questionnaires [63], highlighting the growing relevance of patient opinion and questionnaires to better understanding the impact of angina on quality of life [64]. Of note, potential candidates had undergone coronary computed tomography angiography to rule out patients without significant coronary artery stenosis or left main stem stenosis or equivalent lesions. The study also excluded patients with very high-risk disease (e.g., left main disease or left ventricular ejection fraction < 30). According to these results, myocardial revascularization in patients with CCSs should be reserved for very high-risk patients and patients with angina that limits their quality of life despite optimal medical treatment (Figure 3). Revascularization remains controversial in patients with ischemic heart failure/dysfunction [65,66], as well as those with occluded coronary arteries [67,68], and individual decisions should follow a multidisciplinary heart team approach [7].

4.3.1. Surgical versus percutaneous revascularization

In general, coronary artery bypass grafting (CABG) is considered a better mode of revascularization, with more favorable long-term results, but percutaneous coronary intervention (PCI) provides a more convenient approach. The choice of revascularization technique is based on patient characteristics [55]. PCI is generally favored in frail patients, those with comorbidities that raise the risks associated with surgery (Euroscore [69]), those with low complexity coronary anatomy (SYNTAX [70] score 0–22), chest deformities, or porcelain aorta. CAGB is favored in patients with reduced left ventricular function, moderate to high complexity coronary anatomy (SYNTAX score > 22), contraindications to double antiplatelet therapy, and those with recurrent restenosis [55]. CABG is superior to PCI in patients with diabetes and advanced CAD, where it is associated with significantly reduced rates of death and myocardial infarction [71–73].

Revascularization decisions must consider numerous factors to determine the most convenient and effective type of revascularization for each patient. Guidelines highlight the value and need for multidisciplinary "*Heart Teams*" that base these decisions on evidence, patient profiles, coronary anatomy, team experience (and results) as well the patient preference [8,16,55]. The team should include clinicians, interventional cardiologists, cardiac surgeons, and other specialists as the complexity of the case may demand (anesthesiologist, etc.). Simple, routine cases repeated very frequently may need only discussion by the responsible physician and an interventional cardiologist, but this should be the exception. A common complaint is the extra time required for heart team sessions, but they provide consensus decisions, ensure a uniform standard of care, and represent an opportunity for teaching and continuing medical education.

5. Follow-up

5.1. Physician/Patient relationship

As in any chronic disease, angina patients must be educated and play a major role in their care, in the context of recommendations and periodic supervision by the physician. Effective, two-way communication between physicians and patients is essential for exchanging information and establishing a relationship [74]. Rehabilitation programs should include a strong focus on patient education in addition to physical exercise during the relatively short rehabilitation period. During medical visits, the use of a simple checklist (Box 1) or a more complete instrument like the STable Angina Record (STAR) [75] for both patients and physicians (Supplemental Checklist) can help focus patient–physician interactions and make visits more efficient.

Telemedicine and similar technologies may allow more frequent patient contact, but in-person visits may be a better option for some patients and circumstances [76,77]. Remote visits cannot substitute for regular personal visits to the outpatient clinic in case of new complaints or problems that may require physical examination, accurate blood pressure measurement, electrocardiogram, or laboratory testing. Further research is needed to determine the value and best circumstances for telemonitoring.

Furthermore, a multidisciplinary health team-based approach that promotes an individualized treatment plan based on shared decision-making is of paramount importance for coordinating care in patients with CCS [9,78,79]. It should include educational resources and programs to empower and motivate patients in self-management to improve outcomes and quality of life.

5.1.1. Specific recommendation for the patient

- Lifestyle recommendations: exercise, diet, abstain from toxic habits.

Box 1. Questions to ask at each visit.
1. How do you feel today, or since the last visit? (better/the same/worse)
2. Did you need to limit your physical activity? (yes [which?]/no).
3. What physical activity do you normally do? (None, Sports, walking, cycling)
4. Are you following your dietary recommendations? (yes/no)
5. Have you experienced any episodes of chest pain? (yes/no)
6. Did you need to visit an emergency department or be admitted to hospital?
7. Have you had trouble breathing? (yes/no)
8. Have you experienced dizziness, or fainted? (yes/no)
9. Have you felt chest palpitations? (yes/no)
10. Have you taken your medications according to recommendations? (Yes/no; what have you missed, why?)
11. Do you know your blood pressure and heart rate? How do you know?
12. Have you had blood testing? Results? Approximate date?

- Always consult the physician before discontinuing medications.
- When and how to use sublingual nitroglycerin.
- When to consult the physician or arrange an unscheduled visit.
- When to go rapidly to the hospital.
- When to call an emergency number, which number, and what to tell the operator.

5.2. Adherence issues

Only a fraction of patients meets all risk factor reduction goals: clinicians need to emphasize the importance of prevention with their patients and educate them on the need for adherence to therapy. More than 1 in 4 patients in the ISCHEMIA study reported nonadherence to therapy, and this was associated with poorer health [80]. Physicians should establish whether adherence is a problem and, if so, try to identify possible causes. This is particularly important for patients who are starting or changing therapy. Strategies for improving adherence can include engendering better or more frequent physician–patient interactions (e.g., via telemedicine). Mobile health interventions can be effective for improving adherence to healthy lifestyle and medical therapy, and are recommended (1-A) in the ESC 2024 CCS guidelines [7].

6. Conclusions

Angina is common but often underdiagnosed and undertreated. This proposed approach should increase the proportion of patients receiving correct angina diagnoses and evidence-based, guideline-recommended treatment. More attention is needed to educating patients, addressing residual angina burden, and reducing cardiovascular risk by treating patients to target with cardioprotective medications.

7. Future perspective

Future management of chronic stable angina will benefit from wider use of noninvasive imaging, which will become more relevant in the initial diagnosis of suspected angina, replacing invasive coronarography as an initial approach in a significant number of cases. Microvascular dysfunction will be considered an important pathophysiological component of myocardial ischemia both in patients with and without epicardial coronary stenosis, and functional testing in patients with myocardial ischemia and normal epicardial coronary arteries will be better defined for use in everyday clinical practice. Management will be tailored to each individual patient based on the pathophysiological mechanism(s) underlying their myocardial ischemia, their hemodynamic status such as heart rate and systolic blood pressure, and their comorbidities, such as hypertension, diabetes, pulmonary disease, heart failure or atrial fibrillation. Future management will also acknowledge that most patients require a combination of anti-ischemic drugs to adequately control symptoms, and that optimized medical therapy and lifestyle recommendations must be administered in the context of a comprehensive approach that includes better patient education and motivation to promote adherence and persistence. Revascularization will remain an important treatment in CCSs, but potential candidates will be better selected, and more attention will be paid to secondary prevention to reduce residual angina burden as well as cardiovascular risk by control the "usual suspect" risk factors that drive many myocardial ischemic syndromes – microvascular and epicardial, structural and functional – including dyslipidemia, hypertension, sedentary lifestyle, and diabetes. Patients will benefit from an increased role for family and social relations.

Author contributions

Athanasios Manolis – conceptualization, critical reviewing and revision, approval of the version submitted; Peter Collins – conceptualization, critical reviewing and revision, approval of the version submitted; José López-Sendón – conceptualization, writing original draft, reviewing and revision, approval of the version submitted.

Disclosure statement

AM has received honoraria from Menarini, Servier, Berlin Chemie, Ferrer, and Pfizer; PC has received honoraria from Menarini, Pfizer and Berlin Chemie; JLS has received research grants from: Amgen, Bayer, Merk, Pfizer, and honoraria from Menarini. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Medical writing assistance was provided by Richard Vernell with Elma Academy Srl. funded through the unrestricted grant from Menarini Group.

Funding

This work was supported by an unrestricted educational grant from Menarini Group. Menarini Group had no role in the planning or writing of the publication. The terms of the financial support from Menarini Group included freedom for the authors to reach their own conclusions and freedom to publish the results of this work, irrespective of the conclusions reached.

ORCID

José López-Sendón http://orcid.org/0000-0002-0871-9197

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019. J Am Coll Cardiol. 2020;76(25):2982–3021. doi: 10.1016/j.jacc.2020.11.010
2. Manolis AJ, Ambrosio G, Collins P, et al. Impact of stable angina on health status and quality of life perception of currently treated patients. The BRIDGE 2 survey. Eur J Intern Med. 2019;70:60–67. doi: 10.1016/j.ejim.2019.09.013
3. Schopfer DW, Beatty AL, Meyer CS, et al. Longitudinal association between angina pectoris and quality of life. Am J Cardiol. 2022;164:1–6. doi: 10.1016/j.amjcard.2021.10.037
4. Mesnier J, Ducrocq G, Danchin N, et al. International observational analysis of evolution and outcomes of chronic stable angina: the multinational CLARIFY study. Circulation. 2021;144(7):512–523. doi: 10.1161/CIRCULATIONAHA.121.054567
5. Borrás X, Garcia-Moll X, Gómez-Doblas JJ, et al. Estudio de la angina estable en España y su impacto en la calidad de vida del paciente.

Registro AVANCE. Revista Española de Cardiología. 2012;65 (8):734–741. doi: 10.1016/j.recesp.2012.03.011
6. Kureshi F, Shafiq A, Arnold SV, et al. The prevalence and management of angina among patients with chronic coronary artery disease across US outpatient cardiology practices: insights from the Angina Prevalence And Provider Evaluation Of Angina Relief (APPEAR) study. Clin Cardiol. 2017;40(1):6–10. doi: 10.1002/clc.22628
7. Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024;45 (36):3415–3537. doi: 10.1093/eurheartj/ehae177
- **For readers seeking more detailed information/guidance on management of chronic patients with coronary syndromes.**
8. Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. Circulation. 2021;144(22):e368–e454.
- **For readers seeking more detailed guidance on evaluating and diagnosing patients presenting with chest pain.**
9. Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on clinical practice guidelines. Circulation. 2023;148(9):e9–e119. doi: 10.1161/CIR.0000000000001168
- **For readers seeking more detailed information/guidance on management of chronic patients with coronary syndromes.**
10. Boden WE, De Caterina R, Kaski JC, et al. Myocardial ischaemic syndromes: a new nomenclature to harmonize evolving international clinical practice guidelines. Eur Heart J. 2024;45 (36):3701–3706. doi: 10.1093/eurheartj/ehae278
11. Campeau L. Letter: grading of angina pectoris. Circulation. 1976;54 (3):522–523. doi: 10.1161/circ.54.3.947585
12. Tamargo J, Lopez-Sendon J. Ranolazine: a better understanding of its pathophysiology and patient profile to guide treatment of chronic stable angina. Future Cardiol. 2022;18(3):235–251. doi: 10.2217/fca-2021-0058
13. Berry C. Stable coronary syndromes: the case for consolidating the nomenclature of stable ischemic heart disease. Circulation. 2017;136(5):437–439. doi: 10.1161/CIRCULATIONAHA.117.028991
14. Kunadian V, Chieffo A, Camici PG, et al. An EAPCI expert consensus document on ischaemia with non-obstructive coronary arteries in collaboration with european society of cardiology working group on coronary pathophysiology & microcirculation endorsed by coronary vasomotor disorders international study group. Eur Heart J. 2020;41(37):3504–3520. doi: 10.1093/eurheartj/ehaa503
15. Reeh J, Therming CB, Heitmann M, et al. Prediction of obstructive coronary artery disease and prognosis in patients with suspected stable angina. Eur Heart J. 2019;40(18):1426–1435. doi: 10.1093/eurheartj/ehy806
16. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407–477. doi: 10.1093/eurheartj/ehz425
17. Jespersen L, Hvelplund A, Abildstrøm SZ, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. Eur Heart J. 2012;33(6):734–744. doi: 10.1093/eurheartj/ehr331
18. Hochman JS, Reynolds HR, Bangalore S, et al. Baseline characteristics and risk profiles of participants in the ISCHEMIA randomized clinical trial. JAMA Cardiol. 2019;4(3):273–286. doi: 10.1001/jamacardio.2019.0014
19. Beltrame JF, Crea F, Kaski JC, et al. International standardization of diagnostic criteria for vasospastic angina. Eur Heart J. 2017;38 (33):2565–2568. doi: 10.1093/eurheartj/ehv351
20. Ong P, Camici PG, Beltrame JF, et al. International standardization of diagnostic criteria for microvascular angina. Int J Cardiol. 2018;250:16–20. doi: 10.1016/j.ijcard.2017.08.068
21. Mileva N, Nagumo S, Mizukami T, et al. Prevalence of coronary microvascular disease and coronary vasospasm in patients with nonobstructive coronary artery disease: systematic review and meta-analysis. J Am Heart Assoc. 2022;11(7):e023207. doi: 10.1161/JAHA.121.023207
22. Lee B-K, Lim H-S, Fearon WF, et al. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. Circulation. 2015;131(12):1054–1060. doi: 10.1161/CIRCULATIONAHA.114.012636
23. Hansen B, Holtzman JN, Juszczynski C, et al. Ischemia with No obstructive arteries (INOCA): a review of the prevalence, diagnosis and management. Curr Probl Cardiol. 2023;48(1):101420. doi: 10.1016/j.cpcardiol.2022.101420
24. Meeder JG, Hartzema-Meijer MJ, Jansen TPJ, et al. Outpatient management of patients with angina with No obstructive coronary arteries: how to come to a proper diagnosis and therapy. Front Cardiovasc Med. 2021;8:716319. doi: 10.3389/fcvm.2021.716319
25. Ford TJ, Berry C. How to diagnose and manage angina without obstructive coronary artery disease: lessons from the british heart foundation CorMicA trial. Interv Cardiol. 2019;14(2):76–82. doi: 10.15420/icr.2019.04.R1
26. Gutiérrez E, Gómez-Lara J, Escaned J, et al. Assessment of the endothelial function and spasm provocation test performed by intracoronary infusion of acetylcholine. Technical report from the ACI-SEC. RECICE; 2021;p. 6489.
27. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med. 2010;362(10):886–895. doi: 10.1056/NEJMoa0907272
28. Palicherla A, Ismayl M, Thandra A, et al. Evaluation of stable angina by coronary computed tomographic angiography versus standard of care: a systematic review and meta-analysis. Cardiovasc Revasc Med. 2024;59:67–75. doi: 10.1016/j.carrev.2023.07.019
29. Bjerking LH, Winther S, Hansen KW, et al. Prediction models as gatekeepers for diagnostic testing in angina patients with suspected chronic coronary syndrome. Eur Heart J Qual Care Clin Outcomes. 2022;8(6):630–639. doi: 10.1093/ehjqcco/qcac025
30. Sorbets E, Fox KM, Elbez Y, et al. Long-term outcomes of chronic coronary syndrome worldwide: insights from the international CLARIFY registry. Eur Heart J. 2020;41(3):347–356. doi: 10.1093/eurheartj/ehz660
31. Thomas M, Jones PG, Arnold SV, et al. Interpretation of the seattle angina questionnaire as an outcome measure in clinical trials and clinical care: a review. JAMA Cardiol. 2021;6(5):593–599. doi: 10.1001/jamacardio.2020.7478
32. Hageman S, Pennells L, Ojeda F, et al. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in europe. Eur Heart J. 2021;42(25):2439–2454. doi: 10.1093/eurheartj/ehab309
33. de Vries TI, Cooney MT, Selmer RM, et al. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. Eur Heart J. 2021;42 (25):2455–2467. doi: 10.1093/eurheartj/ehab312
34. Valenzuela PL, Ruilope LM, Santos-Lozano A, et al. Exercise benefits in cardiovascular diseases: from mechanisms to clinical implementation. Eur Heart J. 2023;44(21):1874–1889. doi: 10.1093/eurheartj/ehad170
35. Yedlapati SH, Khan SU, Talluri S, et al. Effects of influenza vaccine on mortality and cardiovascular outcomes in patients with cardiovascular disease: a systematic review and meta-analysis. J Am Heart Assoc. 2021;10(6):e019636. doi: 10.1161/JAHA.120.019636
36. Davidson JA, Banerjee A, Douglas I, et al. Primary prevention of acute cardiovascular events by influenza vaccination: an observational study. Eur Heart J. 2023;44(7):610–620. doi: 10.1093/eurheartj/ehac737
37. Ferrari R, Pavasini R, Camici PG, et al. Anti-anginal drugs–beliefs and evidence: systematic review covering 50 years of medical treatment. Eur Heart J. 2019;40(2):190–194. doi: 10.1093/eurheartj/ehy504
38. Manolis AJ, Boden WE, Collins P, et al. State of the art approach to managing angina and ischemia: tailoring treatment to the evidence. Eur J Intern Med. 2021;92:40–47. doi: 10.1016/j.ejim.2021.08.003
39. Ferrari R, Camici PG, Crea F, et al. Expert consensus document: a "diamond" approach to personalized treatment of angina. Nat Rev Cardiol. 2018;15(2):120–132. doi: 10.1038/nrcardio.2017.131

40. Tamargo J, Kjeldsen KP, Delpón E, et al. Facing the challenge of polypharmacy when prescribing for older people with cardiovascular disease. A review by the european society of cardiology working group on cardiovascular pharmacotherapy. Eur Heart J Cardiovasc Pharmacother. 2022;8(4):406–419. doi: 10.1093/ehjcvp/pvac005
41. Kosiborod M, Arnold SV, Spertus JA, et al. Evaluation of ranolazine in patients with type 2 diabetes mellitus and chronic stable angina: results from the TERISA randomized clinical trial (type 2 diabetes evaluation of ranolazine in subjects with chronic stable angina). J Am Coll Cardiol. 2013;61(20):2038–2045. doi: 10.1016/j.jacc.2013.02.011
42. Morrow DA, Scirica BM, Chaitman BR, et al. Evaluation of the glycometabolic effects of ranolazine in patients with and without diabetes mellitus in the MERLIN-TIMI 36 randomized controlled trial. Circulation. 2009;119(15):2032–2039. doi: 10.1161/CIRCULATIONAHA.107.763912
43. Teoh IH, Banerjee M. Effect of ranolazine on glycaemia in adults with and without diabetes: a meta-analysis of randomised controlled trials. Open Heart. 2018;5(2):e000706. doi: 10.1136/openhrt-2017-000706
44. Arnold SV, Bhatt DL, Barsness GW, et al. Clinical management of stable coronary artery disease in patients with type 2 diabetes mellitus: a scientific statement from the American heart association. Circulation. 2020;141(19):e779–e806. doi: 10.1161/CIR.0000000000000766
45. Manolis A, Kallistratos M, Poulimenos L, et al. Effects of ranolazine on various outcomes in patients with stable angina: an updated meta-analysis. Hellenic J Cardiol. 2023;71:26–32. doi: 10.1016/j.hjc.2022.12.002
46. Lin Y, Wang ZL, Yan M, et al. Effect of Trimetazidine on diabetic patients with coronary heart diseases: a meta-analysis of randomized, controlled trials. Chin Med Sci J. 2020;35(3):226–238. doi: 10.24920/003678
47. Beltrame JF, Tavella R, Jones D, et al. Management of ischaemia with non-obstructive coronary arteries (INOCA). BMJ. 2021;375:e060602. doi: 10.1136/bmj-2021-060602
48. Sinha A, Rahman H, Douiri A, et al. ChaMP-cmd: a phenotype-blinded, randomized controlled, cross-over trial. Circulation. 2024;149(1):36–47. doi: 10.1161/CIRCULATIONAHA.123.066680
49. Kofler T, Hess S, Moccetti F, et al. Efficacy of Ranolazine for treatment of coronary microvascular dysfunction—A systematic review and Meta-analysis of randomized trials. CJC Open. 2021;3(1):101–108. doi: 10.1016/j.cjco.2020.09.005
50. Ling H, Fu S, Xu M, et al. Ranolazine for improving coronary microvascular function in patients with nonobstructive coronary artery disease: a systematic review and meta-analysis with a trial sequential analysis of randomized controlled trials. Quant Imaging Med Surg. 2024;14(2):1451–1465. doi: 10.21037/qims-23-1029
51. Steg PG, Greenlaw N, Tendera M, et al. Prevalence of anginal symptoms and myocardial ischemia and their effect on clinical outcomes in outpatients with stable coronary artery disease: data from the International observational CLARIFY registry. JAMA Intern Med. 2014;174(10):1651–1659. doi: 10.1001/jamainternmed.2014.3773
52. Webb CM, Collins P. Medical management of anginal symptoms in women with stable angina pectoris: a systematic review of randomised controlled trials. Int J Cardiol. 2021;341:1–8. doi: 10.1016/j.ijcard.2021.07.018
53. Thomas GR, DiFabio JM, Gori T, et al. Once daily therapy with isosorbide-5-mononitrate causes endothelial dysfunction in humans: evidence of a free-radical-mediated mechanism. J Am Coll Cardiol. 2007;49(12):1289–1295. doi: 10.1016/j.jacc.2006.10.074
54. Nakamura Y, Moss AJ, Brown MW, et al. Long-term nitrate use may be deleterious in ischemic heart disease: a study using the databases from two large-scale postinfarction studies. Multicenter myocardial ischemia research group. Am Heart J. 1999;138(3):577–585. doi: 10.1016/S0002-8703(99)70163-8
55. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. 2019;40(2):87–165. doi: 10.1093/eurheartj/ehy394

- **For readers seeking more detailed information/guidance in the area of myocardial revascularization.**

56. Navarese EP, Lansky AJ, Kereiakes DJ, et al. Cardiac mortality in patients randomised to elective coronary revascularisation plus medical therapy or medical therapy alone: a systematic review and meta-analysis. Eur Heart J. 2021;42(45):4638–4651. doi: 10.1093/eurheartj/ehab246
57. Bangalore S, Maron DJ, Stone GW, et al. Routine revascularization versus initial medical therapy for stable ischemic heart disease: a systematic review and Meta-analysis of randomized trials. Circulation. 2020;142(9):841–857. doi: 10.1161/CIRCULATIONAHA.120.048194
58. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. N Engl J Med. 2020;382(15):1395–1407. doi: 10.1056/NEJMoa1915922
59. Bangalore S, Maron DJ, O'Brien SM, et al. Management of coronary disease in patients with advanced kidney disease. N Engl J Med. 2020;382(17):1608–1618. doi: 10.1056/NEJMoa1915925
60. Lopez-Sendon JL, Cyr DD, Mark DB, et al. Effects of initial invasive vs. initial conservative treatment strategies on recurrent and total cardiovascular events in the ISCHEMIA trial. Eur Heart J. 2022;43(2):148–149. doi: 10.1093/eurheartj/ehab509
61. Hochman JS, Anthopolos R, Reynolds HR, et al. Survival after invasive or conservative management of stable coronary disease. Circulation. 2023;147(1):8–19. doi: 10.1161/CIRCULATIONAHA.122.062714
62. White HD, O'Brien SM, Alexander KP, et al. Comparison of days alive out of hospital with initial invasive vs conservative management: a prespecified analysis of the ISCHEMIA trial. JAMA Cardiol. 2021;6(9):1023–1031. doi: 10.1001/jamacardio.2021.1651
63. Spertus JA, Jones PG, Maron DJ, et al. Health-status outcomes with invasive or conservative care in coronary disease. N Engl J Med. 2020;382(15):1408–1419. doi: 10.1056/NEJMoa1916370
64. Kornowski R. Patient-reported outcome measures in cardiovascular disease. Eur Heart J Qual Care Clin Outcomes. 2023;9(2):119–127. doi: 10.1093/ehjqcco/qcab051
65. Hassanabad AF, MacQueen KT, Ali I. Surgical treatment for ischemic heart failure (STICH) trial: a review of outcomes. J Card Surg. 2019;34(10):1075–1082. doi: 10.1111/jocs.14166
66. Perera D, Clayton T, O'Kane PD, et al. Percutaneous revascularization for ischemic left ventricular dysfunction. N Engl J Med. 2022;387(15):1351–1360. doi: 10.1056/NEJMoa2206606
67. Råmunddal T, Holck EN, Karim S, et al. International randomized trial on the effect of revascularization or optimal medical therapy of chronic total coronary occlusions with myocardial ischemia - ISCHEMIA-CTO trial – rationale and design. Am Heart J. 2023;257:41–50. doi: 10.1016/j.ahj.2022.11.016
68. Lee S-W, Lee PH, Ahn J-M, et al. Randomized trial evaluating percutaneous coronary intervention for the treatment of chronic total occlusion. Circulation. 2019;139(14):1674–1683. doi: 10.1161/CIRCULATIONAHA.118.031313
69. Nashef SAM, Roques F, Sharples LD, et al. EuroSCORE II. Eur J Cardio-Thorac Surg. 2012;41(4):734–745. doi: 10.1093/ejcts/ezs043
70. Sianos G, Morel M-A, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention. 2005;1(2):219–227.
71. BARI Investigators. The final 10-year follow-up results from the BARI randomized trial. J Am Coll Cardiol. 2007;49(15):1600–1606. doi: 10.1016/j.jacc.2006.11.048
72. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med. 2012;367(25):2375–2384. doi: 10.1056/NEJMoa1211585
73. Farkouh ME, Domanski M, Dangas GD, et al. Long-term survival following multivessel revascularization in patients with diabetes: the FREEDOM follow-on study. J Am Coll Cardiol. 2019;73(6):629–638. doi: 10.1016/j.jacc.2018.11.001
74. Street RL, Makoul G, Arora NK, et al. How does communication heal? Pathways linking clinician–patient communication to health outcomes. Patient Educ Couns. 2009;74(3):295–301. doi: 10.1016/j.pec.2008.11.015

75. Camm AJ, Manolis A, Ambrosio G, et al. Unresolved issues in the management of chronic stable angina. Int J Cardiol. 2015;201:200–207. doi: 10.1016/j.ijcard.2015.08.045
76. Yuan N, Pevnick JM, Botting PG, et al. Patient use and clinical practice patterns of remote cardiology clinic visits in the era of COVID-19. JAMA Netw Open. 2021;4(4):e214157. doi: 10.1001/jamanetworkopen.2021.4157
77. Kędzierski K, Radziejewska J, Sławuta A, et al. Telemedicine in cardiology: modern technologies to improve cardiovascular patients' outcomes—A narrative review. Medicina (Kaunas). 2022;58(2):210. doi: 10.3390/medicina58020210
78. Batchelor WB, Anwaruddin S, Wang DD, et al. The multidisciplinary heart team in cardiovascular medicine: current role and future challenges. JACC: Adv. 2023;2(1):100160. doi: 10.1016/j.jacadv.2022.100160
79. Smilowitz NR, Prasad M, Widmer RJ, et al. Comprehensive management of ANOCA, part 2—program development, treatment, and research initiatives. J Am Coll Cardiol. 2023;82(12):1264–1279. doi: 10.1016/j.jacc.2023.06.044
80. Garcia RA, Spertus JA, Benton MC, et al. Association of medication adherence with health outcomes in the ISCHEMIA trial. J Am Coll Cardiol. 2022;80(8):755–765. doi: 10.1016/j.jacc.2022.05.045