Coronary artery disease: stable angina

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Abstract

A global public health issue, coronary artery disease (CAD) is recognized as the leading cause of morbidity and mortality worldwide. Stable angina, a symptom of CAD, is defined as chest pain typically triggered by exertion or emotional distress and relieved by rest. Effective history-taking, assessing the nature and frequency of symptoms, a good physical examination and identifying key risk factors is vital in the initial care of patients with stable angina, allowing clinicians to opt for the most suitable test to investigate further. Over the last three decades, research has explored the most effective treatment modalities for the management of stable angina, in the form of percutaneous coronary intervention, coronary artery bypass graft surgery and medical therapy. Furthermore, understanding the definition of stable angina, its pathophysiology and patient symptomatology is key to developing trials to address some of the remaining unanswered questions. This chapter outlines some of the most important randomized controlled trials that have played a key role in developing our understanding of the complex aetiology of symptom management, most effective treatments and long-term outcomes of patients with stable angina.

Keywords Coronary artery disease; evidence-based medicine; pathophysiology; percutaneous coronary intervention; randomized controlled trials; research; stable angina

Key points

- Understanding the definition of stable angina and its varying presentation in the clinical setting is vital to reach a diagnosis quickly
- A thorough history and physical examination are key to selecting the most appropriate investigation in the management of stable angina
- Anatomical and functional imaging are complementary modalities when investigating coronary artery disease
- Randomized controlled trials have played an important role in guiding management decisions in terms of both optimal medical therapy and revascularization
- Patient education remains essential to optimize long-term outcomes

Definition and pathogenesis

Angina is defined as chest pain resulting from a reduced oxygen supply during periods of increased myocardial oxygen demand, triggered by physical exertion or psychological disturbance.

Atherosclerotic plaque formation involves a series of complex pathophysiological processes including lipoprotein deposition, immunological pathways and inflammatory responses. A reduction in coronary blood flow caused by atherosclerosis or perfusion abnormalities in the microcirculation results in myocardial ischaemia. In the absence of epicardial coronary artery disease (CAD), patients can present with angina/ischaemia with non-obstructive coronary arteries.[1]

How common is cardiovascular disease?

In the UK, >7.6 million people are living with cardiovascular disease – approximately 4 million male and 3.6 million female patients. Approximately 26% of deaths in the UK are caused by cardiovascular disease, with around 49,000 deaths each year occurring at <75 years of age. CAD is one of the leading causes of death in the UK. Early diagnosis and treatment initiation is vital to reduce the incidence of events and improve patient outcomes.[2]

Diagnosis: the importance of history taking and physical examination

The history is key. Typically, in 'stable angina', individuals complain of central chest pain or 'tightness' radiating to the left arm with heaviness occurring on exertion, such as climbing stairs or performing strenuous activities, and relieved by rest or the use of glyceryl trinitrate sublingual spray. Symptoms such as a dull ache or breathlessness have been described as 'angina-equivalent' or 'atypical'. Patients can also complain of pain triggered by cold weather or eating a heavy meal.

In contrast to stable CAD, patients presenting with an acute coronary syndrome typically complain of a crushing chest pain occurring acutely at rest for a prolonged period with no relief at rest or with the use of glyceryl trinitrate spray. The treatment and outcomes of patients with stable angina and those presenting as an acute coronary syndrome are different, so differentiation between the two is vital, ensuring that acute events requiring immediate attention are not missed.

A variety of tools are used to help diagnose angina. Classification models can be divided into physician assessment of anginal pain and patient-reported symptoms. The Canadian

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Cardiovascular Society (CCS) model to assess pain severity is a physician's estimate of angina in which a 4-point grading system is used to evaluate a patient's degree of limiting angina.

In contrast, patient-reported symptoms can be assessed through a number of questionnaires including the Seattle Angina Questionnaire (SAQ), EuroQol 5-dimensions 5-level (EQ-5D-5L), Rose angina questionnaire, McGill pain questionnaire, and Medical Research Council (MRC) dyspnoea scale looking at shortness of breath (Table 1 and Figure 1). These resources allow clinicians to work together with their patients to identify both the nature of their symptoms and their severity.

Risk factors are important: a background of hypertension, hypercholesterolaemia, diabetes mellitus, smoking history and a known family history of CAD, suggests a higher risk of CAD and metabolic syndrome. The past medical history, coupled with a detailed history of the nature of chest pain, plays an important role in guiding decision making when selecting the most appropriate investigation for the patient being treated.

Furthermore, a physical examination highlights any additional medical issues that could be contributing to symptoms presented. A full cardiovascular and respiratory examination should be performed.[1]

Investigations

Selecting the most appropriate investigation in individuals presenting with angina is key to their immediate and long-term management. Table 2 illustrates some key baseline tests used to assess patients with stable angina, including both anatomical and functional imaging, which are used to diagnose the degree of CAD and ischaemia, respectively.

Non-invasive anatomical imaging in the form of computed tomography coronary angiography (CTCA) in patients with chronic coronary syndromes is recommended in patients with a low or moderate likelihood of obstructive CAD (Figure 2). However, CTCA is typically not recommended in individuals with a history of chronic kidney disease (CKD) and an estimated glomerular filtration rate (eGFR) <30 ml/minute/1.73 m^2, decompensated heart failure, extensive calcification of the coronary arteries or inability to perform breath-holding exercise to ensure optimal image quality.

Patient reported symptom questionnaires

Patient reported symptom tools
Seattle angina questionnaire (SAQ)
Measures health status through assessing how angina affects 5 key areas: Physical limitation, angina stability, angina frequency, treatment satisfaction and quality of life
ROSE angina questionnaire
Developed as a tool for research purposes in CAD. Angina defined as stopping completely or needing to slow down, with symptoms of chest pain resolving within 10 min and pain localized either to the sternum or involving both left chest/left arm
EuroQol 5-dimension 5-level (EQ-5D-5L)
Categorized according to mobility, self-care, usual activities, pain/discomfort and anxiety/depression, concluding with a patient reported health scale scoring from 0 to 100, 100 indicating the best health experienced
McGill pain questionnaire
Used to access nature of pain and classify this on a scale of mild, moderate and severe
MRC dyspnoea scale
Used to access degree of shortness of breath using 5 -point scale

Table 1

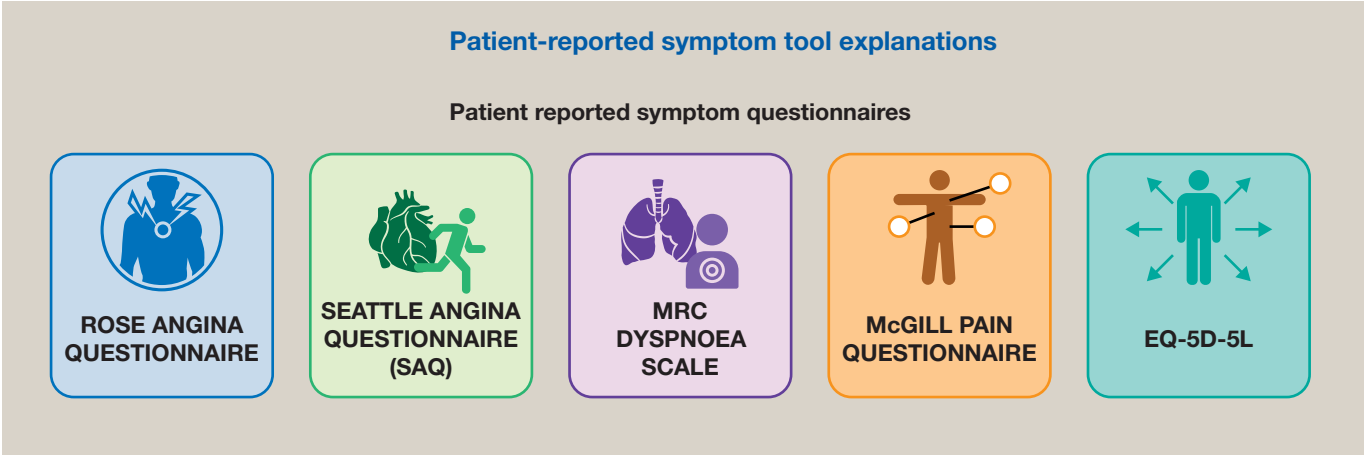


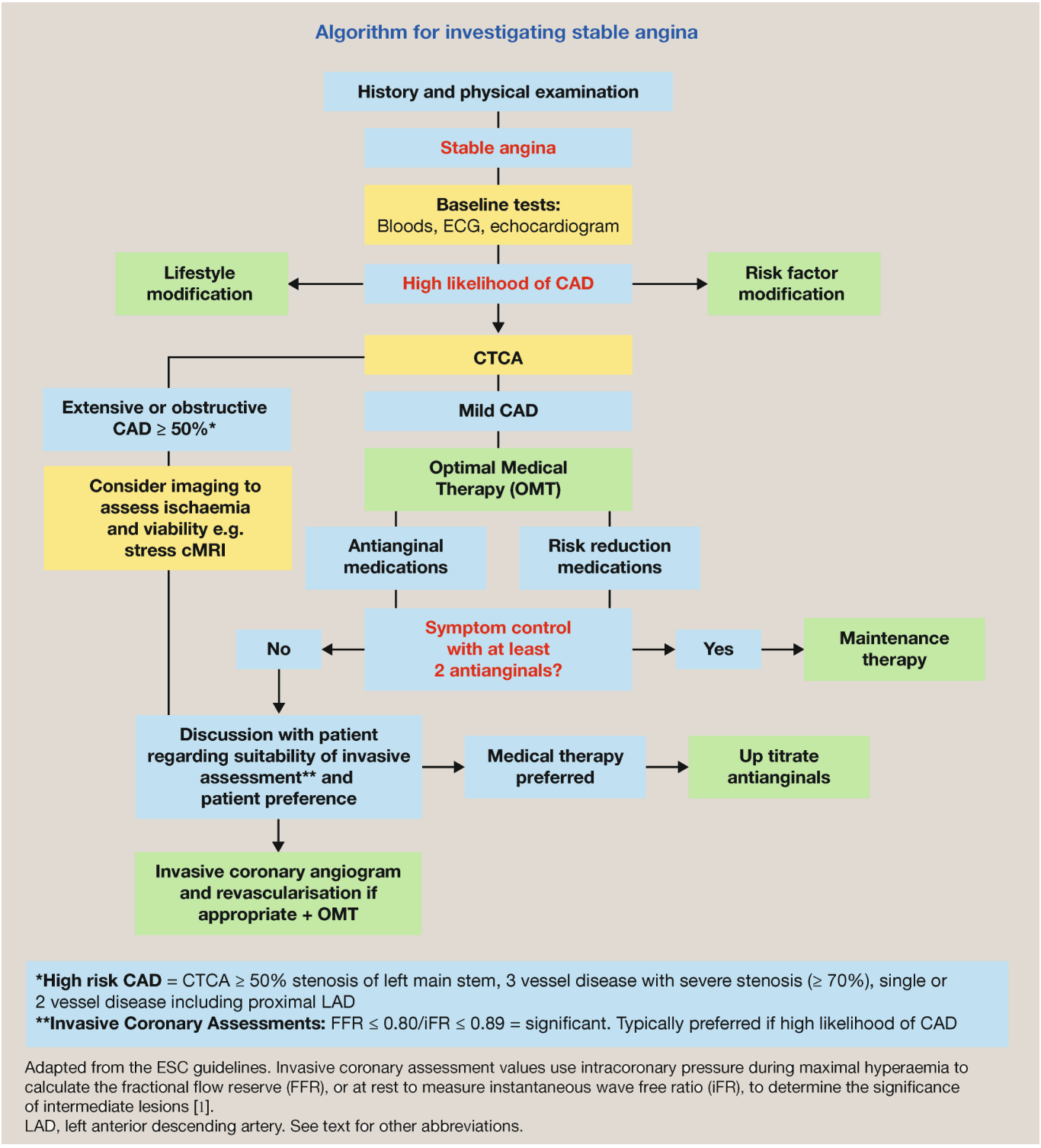
Figure 1

Baseline investigations

Investigation	Description	Indications	Examples of key findings
Blood tests	Full blood count (FBC) Urea and electrolytes (U&Es) C-reactive protein (CRP) HbA_{1c} Full lipid profile Thyroid function tests (TFTs)	To identify any underlying conditions requiring urgent attention particularly if opting for invasive intervention and as part of risk factor modification	Low Hb suggestive of iron deficiency anaemia (IDA), low eGFR influencing decisions regarding invasive intervention, evidence of hyperlipidaemia, raised HbA_{1c} and undiagnosed diabetes mellitus
Electrocardiogram (ECG)	Assess the heart's electrical activity, revealing underlying rhythm and rate	To rule out an acute ST evaluation myocardial event requiring urgent attention	Rhythm abnormalities, ST segment changes, right or left bundle branch blocks, presence of Q waves
Chest X-ray (CXR)	Assess the heart, lungs, blood vessels and bones using a small dose of radiation	To identify underlying pulmonary conditions and to rule our non-cardiac causes of chest pain	Cardiomegaly, pulmonary oedema, calcification, presence of medical devices
Transthoracic echocardiogram (TTE)	Assess cardiac structure, valves and blood flow using ultrasound	To identify the underlying cause of a patient's presentation and determine acute and chronic management	Regional wall motion abnormalities (RWMA), reduced left ventricular systolic function (LVSF), cardiomyopathy, pericardial effusion, valvular abnormalities
Anatomical imaging: CT coronary angiogram (CTCA)	Assess coronary anatomy and evidence of atherosclerosis. Computed tomography angiography derived fractional flow reserve (FFR CT) can be used in conjunction to assess ischaemia: FFR CT>0.8 = normal, $0.76-0.8$ = borderline, ≤ 0.75 = abnormal	To investigate if any evidence of obstructive CAD and use FFR CT to assess lesion specific ischaemia to aid decisions regarding revascularization	Obstructive CAD, ischaemia, anatomical abnormalities
Functional imaging: stress echocardiogram, CMRI, SPECT, PET	Assess myocardial perfusion and coronary flow reserve using exercise, dobutamine and vasodilators	To provide information on left ventricular ejection fraction (LVEF) ischaemia and viability to determine suitability for revascularization	Ischaemia in the coronary territories, microvascular ischaemia, nonviable myocardium, anatomical abnormalities

Adapted from the 2024 ESC guidelines for the management of chronic coronary syndromes.[1]
CMRI, cardiovascular magnetic resonance imaging; Hb, haemoglobin; HBA_{1c}, haemoglobin A1c; SPECT, single-photon emission computed tomography. See text for other undefined abbreviations.

Table 2



Adapted from the ESC guidelines. Invasive coronary assessment values use intracoronary pressure during maximal hyperaemia to calculate the fractional flow reserve (FFR), or at rest to measure instantaneous wave free ratio (iFR), to determine the significance of intermediate lesions [1].
LAD, left anterior descending artery. See text for other abbreviations.

Figure 2

An invasive angiogram may be better if there is a high likelihood of coronary disease, but this comes with its own risks and potential complications. If there are queries regarding the person's suitability for revascularization (e.g. to determine viability or assess the degree of ischaemia), functional imaging in the form of a stress cardiovascular magnetic resonance imaging (cMRI) or positron emission tomography (PET) can provide further information to guide management.[1]

Management and prognosis

Early identification and treatment of patients with CAD and known risk factors, improve long-term outcomes. The primary

goal of treating stable angina is a reduction in symptoms, improved quality of life and a decrease in the incidence of cardiovascular events and death.

Opting for the most suitable management option involves a review of both the history and examination, together with choice of investigation. Understanding the coronary anatomy and evidence of ischaemia guides decision-making when assessing the suitability of invasive procedures.

Treatment options include pharmacological therapy, percutaneous coronary intervention (PCI) and surgical intervention with coronary artery bypass grafting (CABG) for individuals with multivessel disease.

Patient education

When managing stable angina, an informed patient working closely with their physician to select the most appropriate treatment modality can contribute to more successful outcomes. However, in clinical practice challenges can arise related to language barriers, mental health concerns such as depression and anxiety, and impaired cognitive function; therefore, prioritizing communication for shared decision making is essential (Figure 3).

Furthermore, lifestyle modification such as increasing physical activity, weight loss and smoking cessation programmes, monitoring blood pressure and glycaemic control in the community are important interventions that help patients to become autonomous in their healthcare.

Medical therapy

Optimization of medical therapy is a key factor in managing stable CAD; the two predominant goals of treatment in such patients are to reduce cardiovascular events and improve anginal symptoms.

Preventive therapy in the form of lipid-lowering medications reduce the risk of cardiovascular events, in combination with antiplatelet agents such as aspirin and clopidogrel. In individuals with a known background of hypertension, left ventricular ejection fraction (LVEF) ≤40%, CKD or diabetes mellitus, an angiotensin-converting enzyme inhibitor (ACEi), or angiotensin receptor blocker (ARB) if an ACEi is not tolerated, is also recommended.

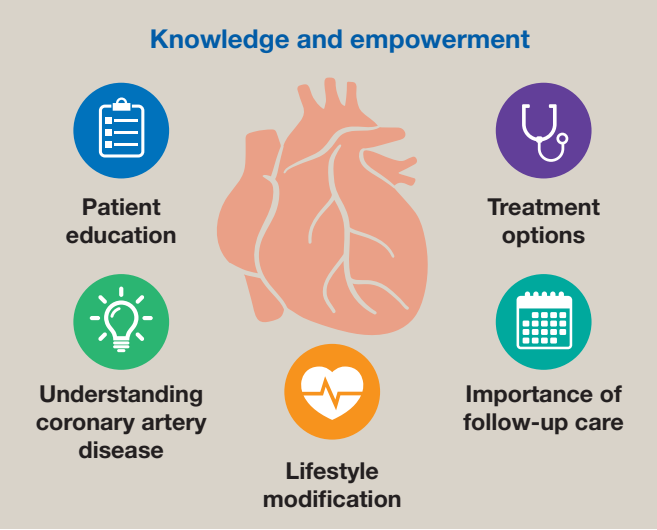


Figure 3

Anti-anginal medications are prescribed to reduce symptoms. β-adrenoceptor blockers such as bisoprolol, either alone or in combination with a calcium channel blocker, are typically recommended as initial therapy, while short-acting nitrates are recommended for immediate relief.

The European Society of Cardiology (ESC) guidelines recommend a stepwise approach when selecting anti-anginal agents, taking account of the person's baseline profile including blood pressure and heart rate, tolerability of treatment, medical co-morbidities and drug interactions if uptitration is indicated (Figure 4).

In clinical practice, particularly with an ageing population where frailty and co-morbidities can be important considerations, an awareness of the issues of polypharmacy is essential. Invasive procedures in combination with medical therapy carry their own risks in an ageing population, where bleeding, kidney injury and neurological sequelae can be seen. For example, in elderly individuals, a shorter duration of dual antiplatelet therapy with drug-eluting stents could improve safety in the medium and long term.

Revascularization

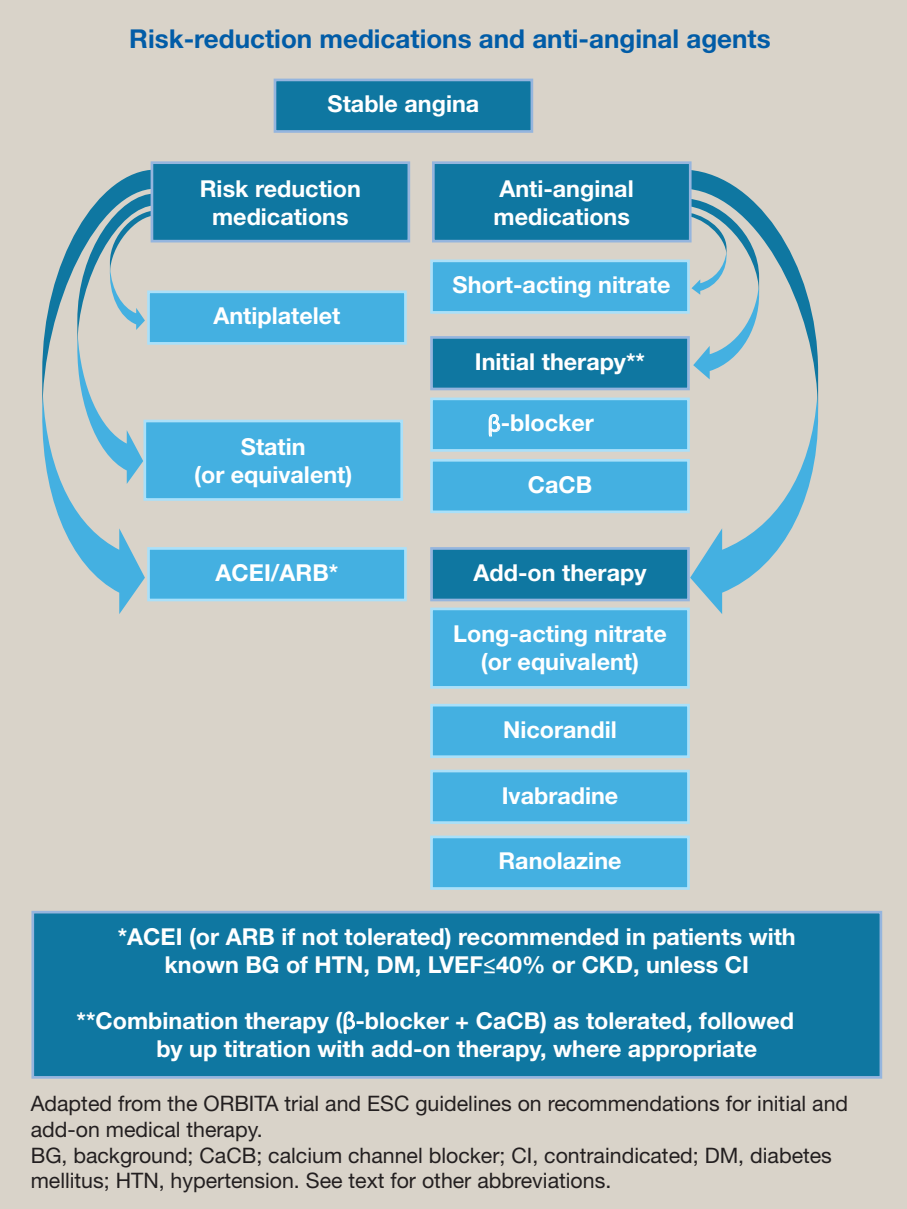
Guidelines recommend revascularization if patients experience continuing anginal symptoms despite achieving optimal medical therapy, which is typically tailored to a combination of patient expectations, degree of CAD and prognosis. Multiple randomized controlled trials have compared outcomes with CABG surgery and PCI, particularly in the context of multivessel and left main stem disease.

The international SYNTAX trial recruited 1800 patients with left main and multivessel disease, suitable for both CABG and paclitaxel-eluting stents, and randomly assigned these patients to CABG or PCI. The primary endpoint was the composite rate of major adverse cardiac or cerebrovascular events (MACCE) at 1 year, defined as all-cause mortality, myocardial infarction (MI), stroke and repeat revascularization. At 1 year, higher rates of repeat revascularization and stroke were seen in the PCI and CABG groups, respectively, while mortality and MI rates were similar between the groups.

As part of the SYNTAX trial, the SYNTAX score was developed to provide clinicians with a quantitative anatomical assessment of coronary disease, with higher scores indicating more extensive and complex disease. The SYNTAX trial showed that, in individuals with a low SYNTAX score (0–22), there were no significant difference between the groups at 5 years. In patients with intermediate SYNTAX scores (23–32), the rates of MI and repeat revascularization at 5 years were higher in the PCI group. Finally, in the highest SYNTAX score patients (≥33), all clinical endpoints, except stroke, were more common in the PCI group than the CABG group.

These results indicated that while CABG may be superior to PCI in severe and complex multivessel disease, PCI may be a sensible alternative in less severe disease. At 10-year follow-up in the SYNTAXES analysis, all-cause death remained similar between PCI and CABG.

One of the highest risk subsets of CAD is left main stem stenosis; therefore, multiple trials have assessed the best specific



Adapted from the ORBITA trial and ESC guidelines on recommendations for initial and add-on medical therapy.
BG, background; CaCB; calcium channel blocker; CI, contraindicated; DM, diabetes mellitus; HTN, hypertension. See text for other abbreviations.

Figure 4

treatment for these patients, with contrasting results. The EXCEL trial investigated PCI versus CABG in 1905 patients with predominant left main stem disease and low/intermediate SYNTAX scores (≤32). The primary endpoint was a composite of death from any cause, stroke or MI, with repeat revascularization as a major secondary endpoint. For the primary composite endpoint, PCI was non-inferior to CABG at 3 years.

The NOBLE trial also compared patients with left main stem disease randomized to PCI or CABG, but the results differed from those of EXCEL. The primary endpoint was MACCE, encompassing all-cause mortality, non-procedural MI, repeat revascularization or stroke. At 5 years, the trial showed the superiority of CABG, with MACCE rates of 29% for PCI and 19% for CABG.

Notably, these trials along with other randomized controlled trials, have shaped guidelines on the management of left main stem CAD as well as low-, intermediate- and high-complexity coronary disease. Determining the optimal revascularization strategy involves a combination of risk assessment, patient preference and consideration of outcomes.

Evolving techniques, generalization and variations in the definition of endpoints can impact decision-making. Nevertheless, developments in coronary assessments and imaging such as intravascular ultrasound have led to improved outcomes with PCI in advanced coronary disease. Yet, patient adherence to medical therapy together with revascularization remains vital in treating the progression of CAD.

The COURAGE trial was designed to assess whether PCI in combination with medical therapy would reduce the risk of death and MI in people with stable CAD when compared with medical therapy alone. A total of 1149 patients were randomized to PCI

combined with medical therapy, while 1138 were given medical therapy alone. The results showed that during a follow-up period of 2.5–7 years, there was no reduction in the primary composite endpoint of death and non-fatal MI with PCI when added to optimal medical therapy, compared with medical therapy alone.[3]

The ISCHEMIA trial recruited patients with stable CAD and moderate or severe ischaemia to determine whether an invasive intervention approach, compared with a conservative approach, would lead to better clinical outcomes. A total of 5179 patients were randomly assigned to either an initial invasive treatment arm whereby they underwent angiography and revascularization when appropriate, with medical therapy, or a conservative treatment arm with medical therapy alone, and angiography only if conservative treatment failed.

The primary outcome was a composite of death from cardiovascular causes, MI or hospitalization for heart failure, resuscitated cardiac arrest or unstable angina. Over a median follow-up of 3.2 years, an initial invasive approach did not reduce the rates of the primary composite outcomes compared with an initial conservative approach.[4]

The primary goal of PCI for stable angina is a reduction in symptoms, but placebo-controlled randomized trials to investigate its efficacy have previously been absent. Symptom evaluation and efficacy of PCI is vital in clinical decision-making.

The ORBITA trial was the first placebo-controlled trial to assess the efficacy of PCI for angina relief. After optimizing the background anti-anginal therapy, 200 patients were randomized to be given PCI or a placebo procedure, the primary endpoint being treadmill exercise time. The trial showed that, in patients with severe CAD and maximal anti-anginal therapy, PCI did not increase exercise time more than a placebo procedure. Furthermore, PCI did not improve CCS score and angina and quality of life as assessed by the SAQ and EQ-5D-5L.

Figure 5 illustrates the decision-making process for anti-anginal therapy based on the UK National Institute for Health and Care Excellence and ESC guidelines, which were used in the ORBITA trial.

ORBITA illustrated that an uptitration of anti-anginal agents was well tolerated over the 12-week period of the trial, with participants taking an average of three anti-anginal medications by the time of randomization. In clinical practice, it may not be possible to achieve this intensive anti-anginal therapy. Patient and clinician preference, adverse effects of medication and pill burden, among other factors, may lead to a desire to use lower levels of medical therapy, leading to a choice of upfront PCI.

The most recent ORBITA-2 trial was a double-blind, randomized controlled trial of PCI versus placebo for stable angina in patients off anti-anginal medication. After enrolment, anti-anginal medications were stopped and patients underwent a 2-week symptom assessment phase before entering the trial arms. Patients with stable angina and objective evidence of ischaemia who underwent PCI with few or no anti-anginal agents showed a greater improvement in angina symptom score compared with the placebo group.

Notably, while PCI resulted in angina relief in ORBITA-2, the effect of PCI was not universal, and a significant proportion of individuals remained symptomatic with angina at the end of the trial. The frequency of residual symptoms was also similar in both ORBITA and ORBITA-2, at 61% and 59%, respectively. Therefore, the next important focus of research was to find the

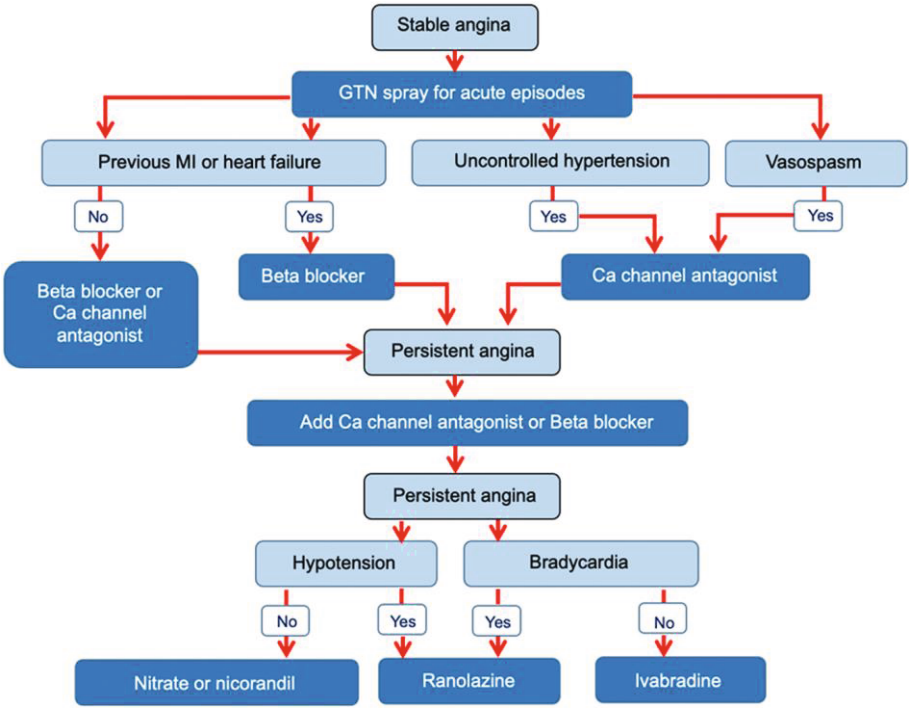


Figure 5 Anti-anginal therapy guidance used in ORBITA. Image reproduced from Foley M, Rajkumar CA, Shun-Shin M, Ganesananthan S, Seligman H, Howard J, et al. Achieving Optimal Medical Therapy: insights from the ORBITA Trial. *J Am Heart Assoc* 2021; **10:** e017381. with permission.

most important predictors of the effect of PCI, to inform patient selection and improve outcomes.

Multiple secondary analyses from ORBITA and ORBITA-2 analysed the predictors of angina relief with PCI. One of the most informative for clinical practice was the symptom-stratified secondary analysis of ORBITA-2. This investigated the relationship between symptoms and disease severity, and the ability of symptoms to predict the placebo-controlled efficacy of PCI.[5]

Assessment of symptoms was based on both their severity and their nature. Severity was assessed using the SAQ and the ORBITA-app, a smartphone application assessing daily angina. The nature of symptoms was assessed using the Rose angina questionnaire, MRC dyspnoea scale and McGill pain questionnaire.

The analysis showed that, although there was a weak association between symptom and disease severity, the nature of symptoms was a powerful predictor of the placebo-controlled efficacy of PCI. The more typical the symptoms were of classical angina, i.e. central chest pain brought on by exertion and relieved by rest, the more likely it was that PCI would result in angina relief compared with placebo.

The results of multiple trials have suggested that in terms of prognostic outcomes such as MI and death, no significant differences are seen between PCI and medical therapy compared with optimal medical therapy alone in patients with stable angina. However, in terms of symptom outcomes, the effect of PCI is greatest in individuals taking few or no anti-anginal medications.

Opting for a conservative approach with optimal medical therapy as an initial treatment strategy may be an option for some patients and can be achieved safely, but some will require revascularization at a later stage for persistent angina or progression of CAD. What happens next may be influenced by the collateral circulation, behavioural and pain threshold adaptation and changes in patient perception over time that influence both the nature and severity of pain.

Hence, there are still many unanswered questions. For example, what are the predictors of PCI efficacy? How do we select patients when opting for revascularization? In individuals with atypical symptoms but evidence of stable CAD, is medical therapy a more sensible initial treatment strategy?

Follow-up

Selecting the optimal treatment tailored to meet the patient's needs involves a multidisciplinary approach where baseline profile, patient preferences and long-term outcomes are considered. Telemedicine and tele-monitoring may be suitable for some patients who are unable to travel but require frequent contact.

Patient education remains at the core of care delivery, with clinic follow-up. Cardiac rehabilitation programmes to aid weight loss and improve cardiovascular risk profile, both at home and in medical settings, remain key to improving health-related quality of life. ◆

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