Ischaemic heart disease: stable angina

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Abstract

Stable angina is a clinical syndrome reflecting inadequate myocardial perfusion. This is typically, but not always, caused by atherosclerotic coronary artery disease. A detailed history is important to establish the diagnosis, presence of risk factors and unstable symptoms. A range of tests is available to investigate patients with stable angina. Anatomical tests, including CT coronary angiography and invasive coronary angiography, aim to assess the presence and extent of atheroma or structural coronary abnormalities. CT coronary angiography/coronary angiography with fractional flow reserve assessment, aims to detect the presence and extent of coronary flow insufficiency. Stress echocardiography, stress cardiac MRI and nuclear perfusion scans aim to assess territorial myocardial ischaemia and viability. Appropriate drug therapy can potentially improve symptoms and prognosis. Risk stratification requires the integration of age, risk factors, anatomical distribution and characteristics of coronary disease and ventricular function. Revascularization should be considered to improve symptoms when angina has a significant impact on the person's quality of life despite optimal medical therapy, or to improve prognosis in certain settings. The choice of revascularization method (percutaneous coronary intervention or coronary artery bypass graft) is influenced by the extent and complexity of disease, presence of co-morbidities, bleeding risk and patient preference.

Keywords Coronary artery disease; fractional flow reserve; ischaemia; medical therapy; revascularization; stable angina

Key points

- A detailed history is paramount to establish the likelihood of coronary artery disease (CAD) and whether symptoms are compatible with angina. Patients with unstable symptoms should be identified at the outset and managed accordingly
- Anatomical tests (CT coronary angiogram, invasive coronary angiogram) and physiological tests for ischaemia/viability (stress echocardiography, stress MRI, nuclear stress tests, fractional flow reserve) are complementary
- Optimal medical therapy, ideally with aspirin, statin, β-blockers and angiotensin-converting enzyme inhibition, should be considered in all cases, with additional anti-anginal drugs as required for symptom control
- The location of CAD on CT or angiography (if performed) should be assessed alongside the presence of symptoms on optimal medical therapy to determine whether revascularization is appropriate
- The choice of revascularization method where appropriate (percutaneous coronary intervention, coronary artery bypass grafting) is determined by the extent and complexity of disease, presence of diabetes, co-morbidities that increase surgical risk, ability to take dual antiplatelet therapy and patient preference

Introduction

Angina is a clinical syndrome that is:

- characterized by discomfort (pain, tightness, heaviness, pressure) in the front of the chest or the neck, shoulders, jaw, or arms
- precipitated by physical exertion
- relieved by rest or glyceryl trinitrate (GTN) within about 5 minutes.

The presence of all three characteristics defines typical angina. If only two features are present, it is defined as atypical angina. If one or none of the above features are elicited in the history, it is probably non-anginal chest pain.[1] Chronic stable angina implies that symptoms have been unchanged in frequency and severity for at least 2 months.

Pathophysiology

Angina reflects transient myocardial ischaemia caused by inadequate coronary perfusion to meet the metabolic demands of the myocardium. The most common cause is atherosclerotic coronary artery disease (CAD) (Figure 1). Other causes include aortic stenosis, coronary spasm and hypertrophic cardiomyopathy. Conditions such as poorly controlled hypertension, anaemia, tachyarrhythmia or thyrotoxicosis can also cause or worsen angina.

Epidemiology

Prevalence increases with age for men (from 0.05% at <45 years to 17% at >75 years) and women (0.02% <45 years to 11.15% >75 years). Interestingly, angina is more prevalent in middle-aged women than men, probably reflecting microvascular CAD.[1] Estimates suggest that >2.3 million people in the UK are living with CAD.

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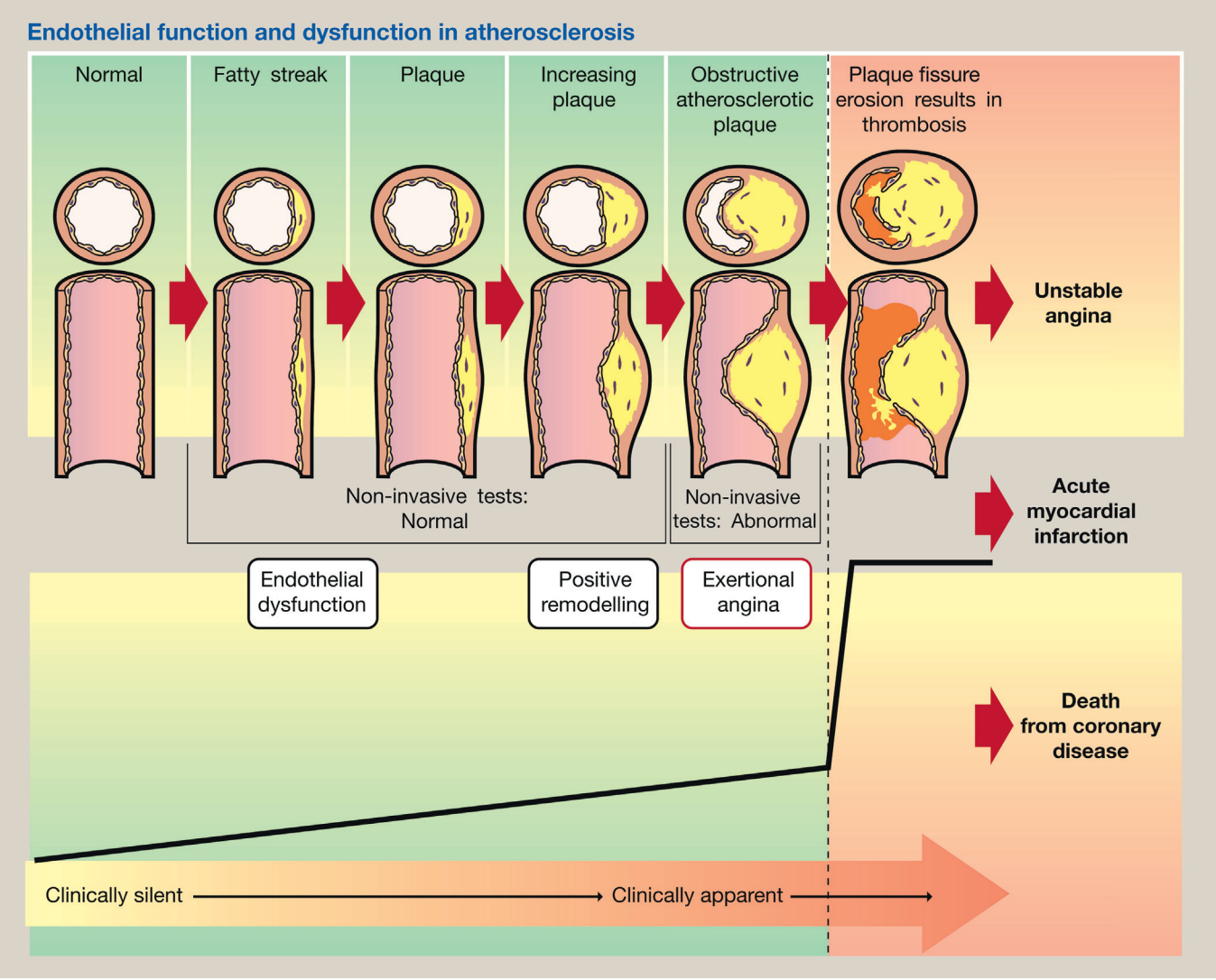

Figure 1 Typical progression of coronary atherosclerosis. Increasing plaque burden initially occurs external to the lumen, preserving luminal diameter; this is known as positive remodelling, or the Glagov effect. Eventually, however, plaque encroaches into the lumen, resulting in haemodynamic obstruction and angina. Disordered endothelial vasomotor function is also common and results in diminished vasodilatation, or even vasoconstriction, in response to stimuli such as exercise. In acute coronary syndromes, vulnerable plaque is a more important factor than the degree of stenosis; acute coronary syndromes result from ulceration or erosion of the fibrous cap, with subsequent intraluminal thrombosis. Source: adapted from Greenland P, Gidding SS, Tracy RP. Commentary: lifelong prevention of atherosclerosis: the critical importance of major risk factor exposures. Int J Epidemiol 2002; 31: 1129–34 and Abrams J. Clinical practice. Chronic stable angina. N Engl J Med 2005; 352: 2524–33.

Incidence: the annual incidence of angina pectoris in Western populations is approximately 1% in 45–65-year-old men and slightly higher in women in this age group. It rises steeply with age, reaching almost 4% in both sexes at age 75–84 years.[1]

Natural history and prognosis: in 2019 CAD was the leading cause of death worldwide. In Western populations advances in pharmacology and revascularization, as well as public health prevention strategies including smoking reduction, have led to a progressive decline in death and non-fatal myocardial infarction (MI) in individuals with stable angina.

Contemporary data in patients given appropriate treatment for stable angina suggest the annual mortality and rate of non-fatal MI are 0.6–1.4% and 0.6–2.7%, respectively. However, in those with a history of MI and significant co-morbidities such as diabetes mellitus and peripheral vascular disease, the annual incidence of death reaches 3.8%.[1] In the UK in 2015, >69,000 deaths were attributed to CAD: >11% of the total annual mortality. In 2020 this number fell to >64,000.

Diagnosis and assessment

The diagnostic management of patients with suspected angina involves clinical assessment, laboratory tests and cardiac investigations (Figure 2).

Clinical assessment

Careful history-taking is essential for diagnosis. Anginal pain is usually described as pressure, tightness, heaviness or burning across the chest that can radiate to the jaw, arms or back. It is

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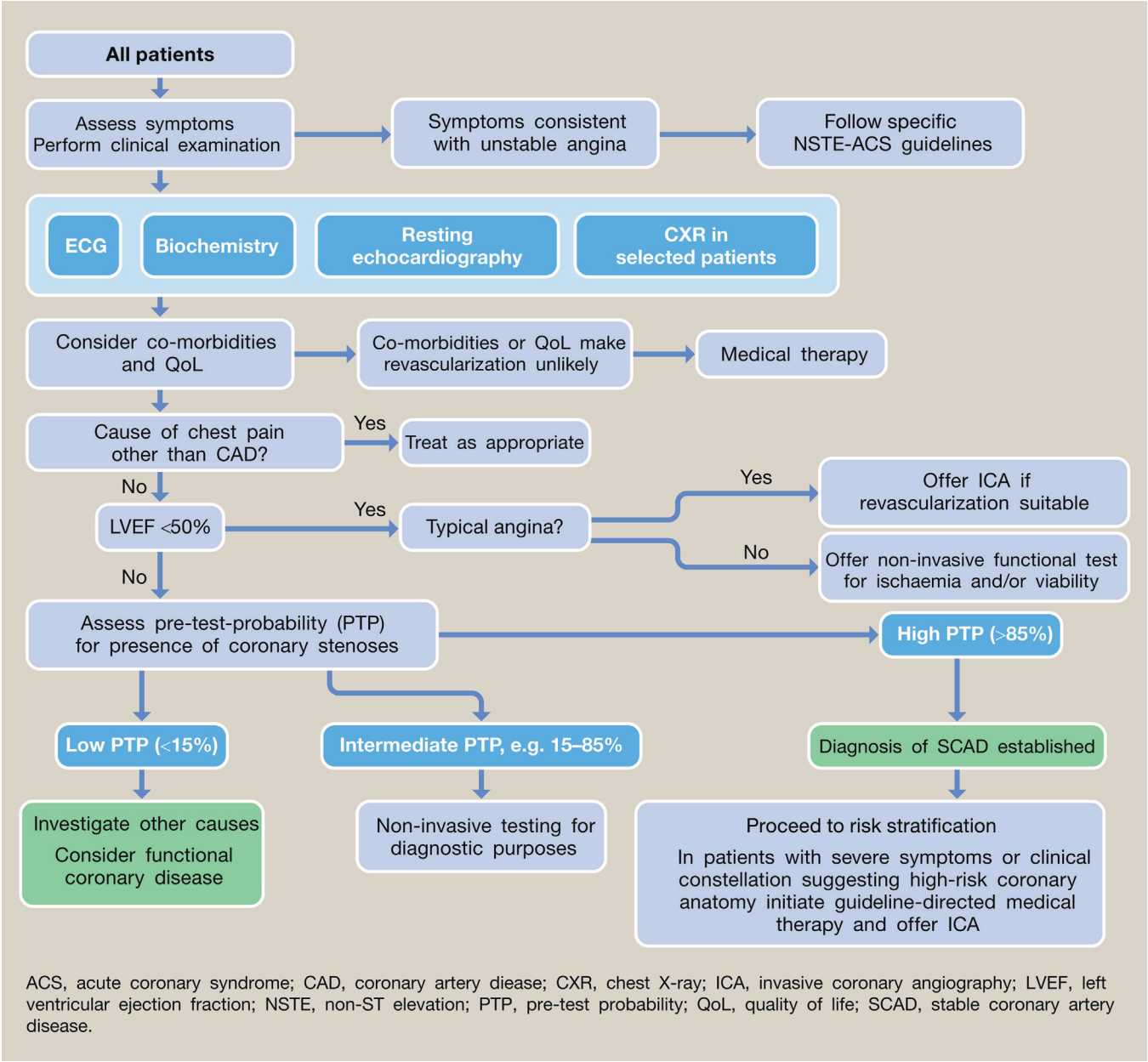

ACS, acute coronary syndrome; CAD, coronary artery diease; CXR, chest X-ray; ICA, invasive coronary angiography; LVEF, left ventricular ejection fraction; NSTE, non-ST elevation; PTP, pre-test probability; QoL, quality of life; SCAD, stable coronary artery disease.

Figure 2 European Society of Cardiology algorithm for the diagnosis of angina. Source: adapted from Montalescot G, Sechtem U, Achenbach S, et al., 2013.[1]

typically brought on by exertion, cold weather or emotional stress, but can also occur after a heavy meal or first thing in the morning. It is brief and generally resolves with rest or sublingual nitrates.

Atypical presentations are more common in women (localized or inframammary pain). Individuals who are elderly or have diabetes mellitus can present with dyspnoea on exertion; when it is proved to be caused by myocardial ischaemia, rather than one of the many other causes of exertional breathlessness, it is referred to as 'angina equivalent' or 'silent ischaemia'.

The severity of symptoms can be formally graded (Table 1). It is important to distinguish individuals with 'unstable' angina or other acute coronary syndromes who may present with recent-onset, severe, limiting angina, rapidly worsening symptoms after previously being stable or rest pain.

Certain factors should be taken into consideration as they increase the likelihood that a presenting symptom is angina. Age, gender and many clinical features including a history of smoking, diabetes mellitus, hypertension, dyslipidaemia, family history of premature CAD and past history of ischaemic heart disease (previous acute coronary syndrome, previous revascularization) increase the pre-test likelihood of significant ischaemic heart disease (Table 2).[1]

Physical examination can be normal or reveal the presence of obesity, hypertension, valvular heart disease, cardiomyopathy, heart failure or peripheral vascular disease.

Investigations

The role of investigations is to confirm the clinical diagnosis and assess risk by determining the presence and extent of:

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Classification of angina severity according to the Canadian Cardiovascular Society

Class	Level of symptoms
Class I	'Ordinary activity does not cause angina'. Angina with strenuous, rapid or prolonged exertion only
Class II	'Slight limitation of ordinary activity'. Angina on walking or climbing stairs rapidly, walking uphill or exertion after meals, or only during the first few hours after waking
Class III	'Marked limitation of ordinary physical activity'. Angina on walking one or two blocks on the level or one flight of stairs at a normal pace under normal conditions
Class IV	'Inability to carry out any physical activity without discomfort' or 'angina at rest'

Table 1

- alternative or associated conditions such as cardiomyopathy or valvular disease (chest X-ray, echocardiography)
- CAD (coronary computed tomography (CT), invasive coronary angiography)
- myocardial ischaemia (functional or stress tests)
- risk of subsequent cardiac events.

Investigations to consider in all patients

Laboratory tests: full blood count including haemoglobin, white blood cell and platelet counts, serum creatinine, blood glucose and lipid profile should be routinely measured, and abnormalities addressed. If clinical signs indicate possible dysfunction, thyroid function tests should be performed. Liver function tests should be performed in patients starting statins. The routine testing of brain natriuretic protein/N terminal (BNP/NT)-pro-BNP or C-reactive protein is not supported by the UK National Institute for Health and Care Excellence (NICE) for individuals presenting with stable angina.

Troponin assay should be reserved for patients who demonstrate features of unstable CAD and should therefore be managed according to appropriate unstable angina/acute coronary syndromes guidelines.

Electrocardiogram (ECG): an ECG should be performed in every individual presenting with typical or atypical angina and also in those with non-cardiac chest pain but additional risk factors. A normal resting ECG is not uncommon and does not exclude ischaemia. However, resting ECG abnormalities such as ST depression, Q waves or left bundle branch block are associated with an adverse prognosis.

Resting transthoracic echocardiogram (TTE): a TTE is recommended for all patients with a first presentation with stable angina. The main purposes are to:

- identify other causes of ischaemia (e.g. hypertrophic cardiomyopathy, aortic stenosis)
- asses for regional wall motion abnormalities suggestive of previous infarction or ischaemia in a specific coronary artery territory
- evaluate systolic function and left ventricular ejection fraction for prognostic purposes and to guide management. There is no benefit in regularly repeating TTE, but a repeat scan should be considered if the clinical situation changes.

Confirming the diagnosis of stable angina

A range of both invasive and non-invasive tests can help to establish the diagnosis. These fundamentally ask one of two sets of questions:

1. Is there coronary atheroma? If so, what is the locality and how extensive is it?
2. Is the coronary atheroma functionally or physiologically significant?

These tests of anatomy and physiology are complementary and essential for guiding management. It is increasingly clear that there is a discrepancy between angiographic appearances and whether a coronary lesion is causing reversible myocardial ischaemia. Thus, particularly in elderly populations, finding coronary artery stenosis does not automatically explain a person's symptoms, nor does it, in itself, provide a mandate for revascularization. In the absence of significant left main stem disease revascularization is supported by demonstrating functional significance of the stenosis in patients with continuing symptoms despite optimal medical therapy (OMT).

Anatomical/structural assessment

Invasive coronary angiography has been the gold-standard test for the anatomical assessment of coronary stenosis. However,

Clinical pre-test probabilities in patients with stable chest pain syndromes

	Typical angina		Atypical angina		Non-anginal chest pain	
Age	Men	Women	Men	Women	Men	Women
30–39	59	28	29	10	18	5
40–49	69	37	38	14	25	8
50–59	77	47	49	20	34	12
60–69	84	58	59	28	44	17
70–79	89	68	69	37	54	24
>80	93	76	78	47	65	32

Source: adapted from Montalescot G, Sechtem U, Achenbach S, et al, 2013.[1]

Table 2

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non-invasive assessment with CT coronary angiography (CTCA) has been well validated in multiple studies.[2]

The rapidly developing modality of CTCA allows the detection of coronary stenosis (>70% major epicardial coronary artery segment stenosis or >50% left main coronary artery stenosis being considered significant) after injection of intravenous contrast and ECG gating. By referencing the gold-standard invasive coronary angiographic estimation of coronary stenosis, CTCA assessment reached a sensitivity of 85–95% in prospective observational studies. Inter-vessel variation in the sensitivity has also been described, with greater sensitivity for left main stem compared with left circumflex stenosis (95% and 85%, respectively). Heterogeneity in the reported negative predictive value (NPP) also exists, ranging from 83% to 100%. A trade-off between sensitivity and NPP is apparent after stratifying by calcium score and pre-test probability, with a higher NPP at the cost of lower sensitivity in patients with low coronary calcification and low (<30%) pre-test probability. The SCOT-HEART trial showed that the use of CTCA in stable chest pain patients resulted in a lower non-fatal MI and death from CAD rate at 5 years relative to standard care without resulting in significantly higher rates of invasive angiography and revascularization.

Assessing coronary calcification with CT coronary calcium scoring is a quicker and more basic investigation, requiring less radiation and no intravenous contrast. It is used to detect the amount of calcium in the walls of the coronary arterial circulation, a surrogate for the extent of atheroma build-up. Coronary calcium score increases is predictive of ischaemia with an increased frequency of ischaemia with higher calcium scores. An absence of coronary calcification does not completely exclude ischaemia, but calcium scores in symptomatic patients are associated with a very low annual event rate (0.2%–0.3%).

Functional assessment

A range of non-invasive and invasive tests of ischaemia and functional significance of coronary disease are clinically available.

Non-invasive functional tests include ECG exercise stress test, myocardial perfusion scintigraphy with single-photon emission CT (SPECT), stress echocardiography, cardiac stress perfusion magnetic resonance imaging MR, and CT fractional flow reserve (FFR_{CT}).

Most of these tests use exercise or pharmacological agents (adenosine, dipyridamole, dobutamine) to induce stress and then detect regional wall motion abnormalities or perfusion deficits. Between them, these 'stress tests' are useful tools to investigate individuals with suspected angina for the presence and extent of reversible myocardial ischaemia. Hybrid techniques such as SPECT/CT, positron emission tomography (PET)/CT and PET/cardiac magnetic resonance imaging, now available in a few research centres, hold great potential. The performance of a given test in stratifying patients into low or high post-test probability for functionally important CAD is dependent on its optimal range of pre-test probabilities.

An ECG exercise stress test is the simplest and cheapest test to perform but appears to have a very limited diagnostic power, with no pre-test probability range within which the test can reliably rule-out or rule-in significant CAD. This test is therefore no longer recommended by NICE as a frontline investigation for chest pain, except in a minority of cases.

Imaging based ischaemia/function tests have been well validated for the prediction of CAD and future events. However, the performance of a given test in different publications varies for many reasons such as population selection and referral bias. Similarly, robust studies with head-to-head comparisons of the diagnostic performance between the different modalities are limited and should be interpreted with caution; additionally, accessibility, expertise, and costs are important determinants for choosing a given test.

Lesion-specific functional information about coronary physiology can now be accurately and reliably assessed via non-invasive coronary CT. FFR_{CT} uses computer modelling of fluid dynamics and provides a non-invasive method of estimating FFR using standard raw data from CTCA. FFR_{CT} is well validated for the estimation of lesion-specific functional significance against FFR via invasive coronary angiography as a reference. Compared with contemporary standard clinical care pathways, a FFR_{CT}-based evaluation strategy in patients with stable angina reduces the use of invasive coronary angiography and does not appear to significantly improve clinical outcomes or reduce costs.[3] In patients with chest pain despite OMT it can be used to identify targets for further invasive investigation and where appropriate revascularization.

The gold-standard tests for assessing the functional or haemodynamic significance of coronary stenosis are FFR and instantaneous wave – free ratio (iFR) during invasive coronary angiography, both performed with high fidelity pressure wires that are passed distal to the coronary stenosis. During invasive coronary angiography, lesion specific functional information in the form of FFR or iFR can be obtained using coronary pressure wires. Pressure wires use a specialized coronary guidewire housing a sensor that measures the intracoronary pressure and can determine whether a coronary stenosis can induce myocardial ischaemia. FFR derived from the pressure wire is very well validated against non-invasive tests for the detection of ischaemia and can reliably be used to predict prognosis at lesion and patient levels. The risk of major cardiovascular events increases steeply when the FFR drops to <0.80. FFR requires hyperaemia (maximum blood flow) which is achieved using adenosine. iFR is increasingly widely used, is a resting measure and has been validated against FFR. An iFR measurement <0.89 translates into haemodynamically significant CAD with a risk of adverse clinical outcome.

A series of high-quality randomized trials using FFR/iFR versus angiography as the main method of guiding therapy in patients committed to percutaneous coronary intervention (PCI) has demonstrated the following key findings:

- Stenting a coronary lesion that is not ischaemic according to FFR, regardless of angiographic severity, is associated with no clinical outcome advantage over OMT alone.
- Routine measurement of FFR in patients with multi-vessel CAD significantly reduces the rate of the composite end point of death, non-fatal MI, and repeat revascularization for up to 2 years, with a lower number stents and vessels

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stented, compared with patients treated with angiographic guidance alone.
- FFR-guided PCI plus best available medical therapy, compared with best available medical therapy alone, decreased the need for urgent revascularization.
- Using FFR measurement during diagnostic angiography (i.e. before the patient is committed to medical therapy alone, PCI or coronary artery bypass grafting (CABG)) changes the management of 22–42% of patients.

Coronary angiography defines therapeutic options and is considered in patients:
- at high risk of cardiac events based on risk factors, non-invasive testing demonstrating reversible myocardial ischaemia and anatomically important lesions on imaging.
- with symptoms despite OMT
- with a reduced left ventricular ejection fraction without explanation
- who have ventricular arrhythmias or have had a cardiac arrest with no obvious non-cardiac cause
- with recurrence of symptoms after revascularization.

Risk stratification

Individuals presenting with stable angina should be risk-stratified by:
- clinical evaluation – frequency of angina, presence of risk factors (e.g. age, diabetes mellitus, smoking, previous MI), resting ECG abnormalities and signs of heart failure or peripheral vascular disease
- extent of ischaemia – regional wall motion abnormalities in >10% of the myocardium or >3 segments (the left ventricle conventionally being divided into 17 segments) defining high risk
- quantification of left ventricular function – the strongest predictor of long-term survival
- extent and location of CAD at angiography – high-risk subsets include left main stem disease and multivessel disease, especially when the proximal left anterior descending coronary artery is included.

Data suggest that the most important determinant of risk in patients with significant coronary disease is the presence and extent of myocardial ischaemia and atheroma burden.

Management

The aims of management are to minimize or abolish symptoms and to improve prognosis by preventing MI and death. These aims, which are not mutually exclusive, can be achieved by a combination of patient education and general measures, pharmacological therapy and revascularization.

Education and general measures

Patients should be informed of the nature of their condition, risk factors, symptoms, treatments, and prognosis. Advice should be given about smoking cessation, weight reduction, exercise and adoption of a healthy 'Mediterranean-style' diet. Associated conditions such as diabetes mellitus and hypertension should be treated appropriately, and anaemia or hyperthyroidism corrected if present.

Pharmacological treatment

Drugs that improve prognosis: antiplatelet therapy reduces the risk of coronary thrombosis in stable CAD. Low-dose aspirin is the mainstay of treatment (75–150 mg/day being optimal dosage as higher doses carry a greater risk of bleeding). Clopidogrel has similar antithrombotic effects. It is indicated in patients who are intolerant of aspirin, and is used in combination with aspirin after coronary stenting.

Statins inhibit cholesterol synthesis through inhibition of the enzyme HMG-CoA reductase. In clinical trials, the main benefits in reducing cardiovascular events paralleled the reduction in cholesterol. For example, coronary mortality was decreased by one-fifth for every 1 mmol/litre reduction in low-density lipoprotein-cholesterol. The Joint British Societies' guidelines recommend a 'lower is better' approach to achieve values of at least <2.5 mmol/litre for non-high-density lipoprotein-cholesterol (equivalent to <1.8 mmol/litre for low-density lipoprotein-cholesterol). Statins exert other so-called 'pleiotropic effects' such as increasing nitric oxide, stabilizing atherosclerotic plaques, reducing the production of proinflammatory cytokines and reactive oxygen species, inhibiting platelet reactivity and preventing the development of cardiac hypertrophy and fibrosis. They are thus genuinely disease-modifying drugs. For these reasons, statin therapy is indicated in all patients with CAD, including elderly individuals and patients with 'normal' serum cholesterol as it reduces cardiovascular events by approximately 23%.

Angiotensin-converting enzyme inhibitors are widely used to treat hypertension and heart failure. They also have a role in secondary prevention in patients with stable CAD without heart failure. Ramipril and perindopril reduce cardiovascular morbidity and mortality in moderate-to high-risk patients and should therefore be considered in all patients with stable angina after MI, or with coexisting hypertension, diabetes, heart failure or left ventricular dysfunction. For example, in the HOPE trial, ramipril 10 mg, compared with placebo, reduced the occurrence of heart attack, stroke and cardiac arrest in a population with established CAD or multiple risk factors for it, with preserved left ventricular function.

β-Adrenoceptor blockers reduce myocardial ischaemia and are effective in improving symptoms. Their prognostic value has been demonstrated only in patients with heart failure or previous MI. They are more efficient than nitrates in improving exercise tolerance and are therefore indicated as first-line anti-anginal drugs. Contraindications include bradycardia, hypotension and severe asthma. All individuals with suspected angina should be prescribed β-blockers.

Drugs that relieve angina: short-acting nitrates have a direct relaxant effect on vascular smooth muscle, producing coronary artery dilatation leading to improved myocardial oxygen supply. They also induce vasodilatation, with a subsequent reduction in cardiac preload and improved subendocardial perfusion. Short-acting nitrate preparations, such as sublingual GTN, provide rapid symptom relief during attacks, and can increase effort tolerance if used prophylactically.

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Calcium channel antagonists cause coronary and systemic vasodilatation by inhibiting cellular calcium influx. Non-dihydropyridine calcium channel antagonists (diltiazem, verapamil) lower heart rate, thereby reducing myocardial oxygen consumption; however, they also reduce cardiac contractility and should be avoided in heart failure and in patients taking β-blockers. Dihydropyridine calcium channel antagonists can cause reflex sympathetic activation and resulting tachycardia, but this is minimized by the use of long-acting preparations (e.g. amlodipine) and concurrent β-adrenoceptor blockers.

NICE recommends using β-blockers and calcium channel antagonists as first-line anti-anginal medication. If patients are intolerant of these and/or symptoms are not well controlled, a third-line agent from the following can be added:

- Longer-acting nitrates, such as isosorbide mononitrate or GTN patches, reduce the frequency and severity of anginal attacks but require a 'nitrate-free' interval each day to preserve their therapeutic effect.
- Nicorandil, a potassium channel activator with nitrate-like effects, is an effective anti-anginal agent and reduces hospital readmissions for cardiac chest pain, but has no significant effects on death and non-fatal MI.
- Ivabradine is a sinus node inhibitor that acts solely by lowering heart rate, thereby reducing ischaemia. It can be appropriate in patients who are intolerant of β-blockers or have suboptimal heart rate control despite β-blockers. There is clear evidence of the benefits of ivabradine in patients with heart failure and pulse rate >70 beats per minute. However, in those with stable CAD but without heart failure, the addition of ivabradine to standard care did not improve the prognosis and was associated with significantly more bradycardia.
- Ranolazine inhibits the late inward sodium current, thus preventing cellular calcium overload. It can be used as adjunctive therapy in patients with inadequate symptom control who are already taking or are intolerant of first-line anti-anginal agents. Recent meta-analyses show an improvement in angina frequency but no effect on major cardiovascular events or revascularization, with the cost of increased non-severe adverse effects (dizziness, nausea, constipation). There is also a risk of QT_c prolongation on ECG.

In a substudy of the larger COMPASS trial, the addition of low-dose rivaroxaban in combination with single or dual antiplatelet agents after acute coronary syndromes has been shown to reduce overall mortality in patients with stable CAD. However, more data will be required before this is adopted in mainstream clinical practice, given that the combination of rivaroxaban and aspirin was associated with significantly more bleeding.

Revascularization

For appropriately risk-stratified patients felt to be suitable for medical management, the European Society of Cardiology guidelines recommend the use of two anti-anginal agents at optimal dosage before considering revascularization or the addition of a third agent. However, if the person has continuing symptoms despite OMT clinically significant left CAD, low ejection fraction or class III or IV heart failure, an invasive strategy may be appropriate.

CABG provides excellent relief from anginal symptoms and compared with medical therapy, has prognostic benefit in patients with high-risk anatomy such as left main or multivessel disease with impaired left ventricular function. Typical operative mortality varies from 1% to 4%; other procedural morbidity risks include stroke. Consideration of individual risk is an important part of assessing the patient's suitability for CABG.

PCI is effective in reducing anginal symptoms, and improvements in technology have allowed the treatment of increasingly complex disease that was previously the domain of CABG. This has led to a large increase in the number of procedures performed over recent years. Although procedural morbidity and mortality are lower than for CABG, the requirement for repeat revascularization is higher because of re-stenosis. Drug-eluting stents (DESs) have significantly reduced re-stenosis rates (from around 30% for bare metal stents (BMSs) to <5% using new-generation DESs). The ratio of PCI to CABG procedures in the UK has been constantly increasing over the past decade, and is currently 5.9:1. Controversy remains about whether PCI conveys prognostic benefit in individuals with stable angina (see below).

In terms of medical therapy versus revascularization, outside the high-risk population known to benefit prognostically from CABG, most data suggest no evidence of a survival advantage or reduction in MI after revascularization.

In the COURAGE trial, symptomatic patients with evidence of ischaemia on non-invasive testing or coronary stenosis >80%, were randomized to OMT alone or OMT with PCI (with BMS).[4] Angina relief was greater in the PCI group, but the overall incidence of death at up to 15 years' follow-up was similar: 25% in the PCI group, and 24% in the OMT group. Although the study was criticized for various reasons, its conclusion — that PCI offers no survival advantage in most patients with stable angina — is valid. However, the nuclear substudy of COURAGE presented data supporting ischaemia-driven revascularization.

In the BARI 2D trial, in symptomatic patients with evidence of ischaemia on non-invasive testing or coronary stenosis >70%, revascularization with either PCI (BMS or first-generation DES) or CABG did not reduce the primary endpoint of all-cause mortality over a 5-year follow-up.

The FAME II study compared FFR-guided PCI (with second-generation DES) + OMT with OMT alone in patients with stable CAD and an FFR <0.80. The study was stopped early at a median follow-up of only 7 months after an interim analysis revealed that the primary endpoint (a composite of death, MI or urgent revascularization) was substantially reduced in PCI-treated patients, driven solely by a reduction in urgent revascularization. However, there was no difference in mortality at both 2 years and 5 years of follow-up, although a statistically marginal reduction in MI in the PCI-treated patients was observed.

All studies above had limitations, none of them was blinded, patients with only mild amount of ischaemia were included, and an upfront knowledge of anatomy on coronary angiography might have created a selection bias by excluding patients with more severe or extensive CAD.

The ISCHEMIA trial was designed to revisit the 'ischaemia hypothesis' while addressing the limitations of the studies mentioned above.[5] In this study, patients with at least moderate ischemia on non-invasive testing were randomized to an initial invasive strategy with OMT or an initial conservative strategy of

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medical therapy alone and angiography if medical therapy failed or if the patient was suspected of meeting the relevant endpoint. The five-component primary endpoint (composite of cardiovascular death, MI, hospitalization for unstable angina, hospitalization for congestive heart failure and resuscitated cardiac arrest) did not differ between the invasive and conservatively treated patients. Similarly, the occurrence of the secondary composite endpoint of cardiovascular mortality or MI did not differ between the groups. The message carried by the above studies is that OMT in patients with stable CAD is safe, and cardiologists should consider moving towards a paradigm of efficient non-invasive evaluation, OMT and individualized invasive therapy when medical therapy fails or clinical benefit is proven.

With respect to revascularization options in multi-vessel disease, randomized trials have shown a superiority of CABG over PCI in those with higher disease complexity and in patients with diabetes, but the debate continues with evolving PCI technologies and improved prognostication of coronary disease.

FAME III aimed to test whether FFR-guided PCI might make PCI a reasonable alternative (non-inferior) to CABG for patients with three-vessel disease not involving the left main stem. The primary endpoint was the 1-year occurrence of a major adverse cardiac or cerebrovascular event (death from any cause, MI, stroke, repeat revascularization). The trial did not meet the criteria for non-inferiority.

Traditionally, the treatment of left main stem disease with CABG has been regarded as the gold standard. However, owing to recent trial data, advances in stent technology, adjunctive pharmacotherapy and operator experience, left main stem PCI is increasingly regarded as a viable alternative to CABG, with comparable outcomes in select groups. The choice between CABG and PCI can be complex and is best handled by a joint discussion between interventionalists and surgeons (at a multidisciplinary team meeting). Debates often yields to consensus when heart teams work well together. It is often appropriate to offer patients a choice of treatment, having furnished them with the pros and cons of each. The pros of CABG are complete revascularization regardless of diffuse disease or chronic occlusions, and lower repeat revascularization. The pros of PCI are next-day discharge, short recovery time and the avoidance of major surgery. In the real world, many patients are not suitable for both PCI and CABG. For example, individuals with extensive co-morbidities are often deemed unsuitable for surgery. Alternatively, the extent of the stenosis can lead interventionists to feel that revascularization by stenting is technically impossible. ◆

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