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ESC GUIDELINES ADDENDA

2013 ESC guidelines on the management of stable coronary artery disease—addenda

The Task Force on the management of stable coronary artery disease of the European Society of Cardiology

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Web Addenda

The web addenda to the 2013 SCAD Guidelines contains additional material which should be used for further clarifications when reading the main document. The numbering of the chapters in this web document corresponds to the chapter numbering in the main document.

3 Pathophysiology

3.1 Correlation between symptoms and underlying anatomical and functional substrate

The main symptomatic clinical presentations of stable coronary artery disease (SCAD) include: (i) classical chronic stable angina caused by epicardial stenosis; (ii) angina caused by microvascular dysfunction (microvascular angina); (iii) angina caused by vasospasm (vasospastic angina) and (iv) symptomatic ischaemic cardiomyopathy (see below). Dyspnoea, fatigue, palpitations or syncope may occur in addition to, or instead of, angina (angina equivalents). Microvascular angina (see section 6.7.1 of the main text) may be difficult to distinguish from classical angina (see section 6.1 of the main text) as both are mainly exercise-related. Pure vasospastic angina, in contrast to classical and microvascular angina, is characterized by angina at rest with preserved effort tolerance. As symptoms do not reflect the extent of underlying disease, SCAD patients may also be totally asymptomatic despite the presence of ischaemia, or experience both symptomatic and asymptomatic ischaemia, or become symptom-free after a symptomatic phase—either spontaneously, with medical treatment, or after successful revascularization.[1] In this setting, myocardial stress tests help to discriminate between true lack of ischaemia or silent inducible ischaemia.

The relatively stable structural and/or functional alterations of the epicardial vessels and/or coronary microcirculation in SCAD are associated with a fairly steady pattern of symptoms over time. In some patients, however, the threshold for symptoms may vary considerably from day to day—and even during the same day—owing to a variable degree of vasoconstriction at the site of an epicardial narrowing (dynamic stenosis) or of distal coronary vessels or collaterals, or because the determinants of myocardial demand are subject to fluctuations. Factors such as ambient temperature, mental stress and neuro-hormonal influences may play a role.[2] Thus, chest pain may occasionally occur even at rest in stable patients with CAD,[3] irrespective of whether it is of epicardial or microvascular origin. It may be difficult to distinguish such a stable, mixed pattern of effort-induced and functional rest angina from an acute coronary syndrome (ACS) caused by an atherothrombotic complication of coronary artery disease (CAD), although the typical rise and fall of troponins usually identifies the latter mechanism.[4,5]

3.2 Histology of epicardial lesions in stable coronary artery disease vs. acute coronary syndrome

At histology, the epicardial atherosclerotic lesions of SCAD patients, as compared with those of ACS patients, less commonly show an erosion or rupture of the endothelial lining; the lesions are typically fibrotic, poorly cellular, with small necrotic cores, thick fibrous caps and little or no overlying thrombus.[6] In contrast, culprit lesions of ACS patients typically show the rupture or tear of a thin fibrous cap, with exposure towards the lumen of large, soft, prothrombotic, necrotic core material (containing macrophages, cholesterol clefts, debris, monocytic and neutrophilic infiltrates, neovascularization, intraplaque haemorrhage) that can trigger occlusive or sub-occlusive thrombosis.[7]

3.3 Pathogenesis of vasospasm

Severe focal constriction (spasm) of a normal or atherosclerotic epicardial artery determines vasospastic angina.[8] Spasm can also be multifocal or diffuse and, in the latter case, is most pronounced in the distal coronary arteries.[9] It is predominantly caused by vasoconstrictor stimuli acting on hyper-reactive vascular smooth muscle cells, although endothelial dysfunction may also be involved.[10] It is currently unclear whether the more common form of diffuse distal vasospasm has the same or different mechanisms.[10] The causes of smooth muscle cell hyper-reactivity are unknown, but several possible contributing factors have been suggested, including increased cellular rho-kinase activity, abnormalities in Adenosine triphosphate (ATP)-sensitive potassium channels and/or membrane Na + -H+ countertransport.[10] Other contributing factors may be imbalances in the autonomic nervous system, enhanced intracoronary concentrations of vasoconstricting substances, such as endothelin, and hormonal changes such as post-oopherectomy.[10] Whereas a focal and often occlusive spasm is typically associated with ST-segment elevation (variant or Prinzmetal's angina)—which, unlike ST-elevation caused by thrombotic epicardial artery occlusion, is transient and/or quickly relieved by sublingual nitrates,[8]—distal vasoconstriction is rarely occlusive and usually leads to ST-segment depression.[9]

The diffuse distal type of spastic reaction is usually found in patients with a clinical picture of microvascular angina,[9] whereas focal spasm is typically seen in patients presenting with variant angina.[8] Coronary vasospasm, especially the focal occlusive variant, has been found on occasion to cause myocardial infarction (MI).[8]

3.4 Ischaemic cardiomyopathy

The clinical picture of SCAD may be dominated by symptoms and signs of ventricular dysfunction, a condition defined as ischaemic cardiomyopathy. The latter accounts for a large portion of 'dilated cardiomyopathies' in developed countries, as a result of a previous single large infarction (usually >20% of myocardial mass) or of multiple small infarctions. Progressive ventricular dilatation and systolic dysfunction (adverse remodelling) may develop over years. The reasons underlying the development of remodelling in some patients, but not others—despite a similar extent of necrosis—remain debatable. In some patients, dysfunction is the result of myocardial hibernation.[11] Hibernation, in turn, may be the result of multiple episodes of repetitive stunning.[11] Ischaemic cardiomyopathy is discussed in the ESC Guidelines on Heart Failure,[12] and is not considered in detail in these Guidelines.

3.5 Microvascular dysfunction

A primary dysfunction of the small coronary arteries < 500 μm in diameter underlies microvascular angina. In this case, coronary flow reserve (CFR) is impaired in the absence of epicardial artery obstruction because of non-homogeneous metabolic vasodilation that may favour the 'steal' phenomenon, or by inappropriate pre-arteriolar/arteriolar vasoconstriction, or other by causes for altered cross-sectional luminal area.[13] Conditions such as ventricular hypertrophy, myocardial ischaemia, arterial hypertension and diabetes can also affect the microcirculation and blunt CFR in the absence of epicardial vessel narrowing.[14]

3.6 Assessment of stenosis severity using coronary flow reserve and fractional flow reserve

One pathophysiological consequence of a critical epicardial stenosis is a reduction of CFR. The latter is the ratio of absolute coronary blood flow—during maximal coronary vasodilatation—to resting flow and is an integrated measure of maximal flow through both the large epicardial arteries and the microcirculation. The release of ischaemic metabolites, such as adenosine, within the under-perfused myocardium downstream to the stenotic artery, dilates distal pre-arterioles and arterioles. This favours local perfusion but at the price of 'consuming' part of the normally available flow reserve. Healthy subjects have an absolute CFR of 3.5–5,[15] whereas patients with a relevant epicardial stenosis have a CFR <2–2.5.[16] Patients with a CFR <2 have an adverse prognosis, despite the absence of epicardial disease indicating severe microvascular disease.[17] Flow reserve values between 2.5 and 3.5 are difficult to interpret but may indicate milder forms of coronary microvascular dysfunction, with and without associated epicardial disease.

An atheromatous plaque protruding into an epicardial artery may not only lead to a reduction in CFR but would also cause an associated trans-stenotic pressure fall, from the proximal aorta to the distal post-stenotic coronary segment. When the ratio between distal pressure and aortic pressure during maximal coronary vasodilation—defined as fractional flow reserve (FFR)—becomes ≤0.8,[18] downstream perfusion is limited and may become inadequate when myocardial oxygen demand increases. Major determinants of myocardial oxygen demand are blood pressure (BP), heart rate, contractility and ventricular loading conditions. The severity of angiographic stenosis that causes a critical reduction of FFR is variable. It is influenced by the configuration and length of the stenosis, by the amount and viability of dependent myocardium, by collateral circulation, and by microvascular dysfunction. However, a typical threshold is a stenosis diameter of >50%, although only one-third of all stenoses with a diameter of 50–70% reduce FFR to ≤0.80.[19] Epicardial vasoconstriction can transiently modify the haemodynamic severity of an eccentric stenosis, thus reducing the ischaemic/anginal threshold; this is why FFR is assessed after intracoronary injection of nitrates to obtain maximal stenosis dilation. FFR is discussed in more detail in the main text in section 8.1.2 in the context of revascularization.

6 Diagnosis and assessment

6.1 Symptoms and signs

6.1.1 Distinction between symptoms caused by epicardial vs. functional coronary artery disease

Categorizing the types of angina, as shown in Table 4 of the main text, is clinically useful and one of the cornerstones of estimating pre-test probability for the presence of epicardial CAD. One must be aware, however, that the manifestations of chest pain are so variable—even within a single patient—that a distinction between symptoms caused by an epicardial stenosis and symptoms caused by functional disease at the level of the microvasculature or vasospasm cannot be made with reasonable certainty. Therefore, reliance on ischaemia testing or depiction of the coronary anatomy is often unavoidable. The difficulties associated with distinguishing between functional and anatomical CAD may explain why, even in the early days of coronary angiography, when the indications for this procedure were possibly more strictly handled than today, normal or near-normal coronary angiograms were found in close to 40% of patients,[20] a percentage similar to that found today.[21]

6.1.2 Stable vs. unstable angina

When taking the patient's history it is important to differentiate between stable and unstable angina (UA). The latter significantly increases the risk of an acute coronary event in the short term. The characteristics of UA have been described in the recent ESC Guidelines for the management of ACS in patients presenting without persistent ST-segment elevation.[4] Unstable angina may present in one of three ways: (i) as rest angina, i.e. pain of characteristic nature and location, but occurring at rest and for prolonged periods of up to 20 minutes; (ii) new-onset angina, i.e. recent onset of moderate-to-severe angina (CCS II or III) or (iii) rapidly increasing or crescendo angina, i.e. previously SCAD, which progressively increases in severity and intensity and at lower threshold (at least CCS III) over a short period of 4 weeks or less. The investigation and management of angina fulfilling these criteria is dealt with in Guidelines for the management of ACS.[4]

New-onset angina is generally regarded as UA. However, if angina occurs for the first time with heavy exertion—such as prolonged or fast running (CCS I)—the patient with new-onset angina will fall under the definition of stable, rather than UA.[4]

Moreover, among those with UA it is necessary to distinguish between high-risk, medium-risk and low-risk patients.[4,22] In UA patients identified as being low risk it is recommended that the diagnostic and prognostic algorithms presented in the main text of these SCAD guidelines be applied once the period of instability has subsided.[4] Low-risk UA patients are characterized by the following[4]:

No recurrence of chest pain at rest

No signs of heart failure

No abnormalities in the initial electrocardiogram (ECG) or a second ECG (at 6–9 hours).

No rise in troponin levels (at arrival and after 6–9 hours)

Low risk as defined by the Global Registry of Acute Cardiac Events (GRACE, $\leq$108) or Thrombolysis in Myocardial Infarction (TIMI) (score 0–2) risk scores.

Based on the definition above, many SCAD patients pass through a period of experiencing UA, and there is clear overlap between classifications of stable and unstable angina. For instance, patients with a microvascular problem often complain of a combination of dyspnoea upon exertion and occasional attacks of rest angina. Such attacks of rest angina should not be misinterpreted as UA but—especially when occurring in the early morning hours during or shortly after awakening—are part of the clinical picture of SCAD.[3]

It is often challenging, if not impossible, to distinguish between stable CAD—with superimposed attacks of vasospasm causing chest pain at rest—and true UA, especially when ST-segment shifts are present in the resting ECG. Distinguishing between these two entities is even more difficult in a busy emergency room, which may sometimes result in urgent angiographies showing normal or non-obstructed coronary arteries. This was well documented in the early days of coronary angiography,[23] and has not changed to the present day.[24,25]

6.2.1 Non-invasive cardiac investigations

6.2.1.1 Biochemical tests

Elevated levels of natriuretic peptides are significantly associated with an increased risk for adverse cardiac events in patients with SCAD. In the prevention of events with angiotensin converting enzyme trial, elevated plasma levels of mid-regional pro-atrial natriuretic peptide, mid-regional pro-adrenomedullin and C-terminal pro-endothelin-1 were independently associated with an increased risk of cardiovascular death or heart failure in patients with SCAD and preserved Left ventricular ejection fraction (LVEF).[26] Angiotensin converting enzyme (ACE) inhibitor therapy significantly reduced the risk of cardiovascular death or heart failure in patients with two or more elevated biomarkers. Measuring a combination of biomarkers may hence be helpful in the selection of patients with SCAD who will derive the most benefit from ACE inhibitor therapy. However, it remains unclear whether the increased risk associated with elevated levels of natriuretic peptides is sufficient to change the management or to improve clinical outcomes or cost-effectiveness.[27] Therefore, there is currently insufficient evidence to recommend the routine use of natriuretic peptides in the management of patients with SCAD.

As yet, there is inadequate information regarding how modification of additional biochemical indices can significantly improve current treatment strategies to recommend their use in all patients. Nevertheless, these measurements may have a role in selected patients—for example, testing for haemostatic abnormalities in those with prior MI without conventional risk factors or a strong family history of coronary disease.

A cautious approach is currently also warranted with respect to genetic testing to improve risk assessment in CAD. Studies are currently going on to determine the impact of known and new single-nucleotide polymorphisms detected in genome-wide association studies on risk in combination, and to estimate this impact beyond that of standard coronary risk factors.[28]

6.2.3 Principles of diagnostic testing

Invasive coronary angiography (ICA) remains the 'gold standard' in depicting epicardial CAD. However, the imaging information is only about the lumen, and not the plaque. In most patients, ICA does not address functional abnormalities of the epicardial coronary arteries or the microvasculature. Alternatively, coronary anatomy may be visualized by coronary computed tomography angiography (CTA) or magnetic resonance imaging (MRI) angiography. Both techniques provide additional information about the plaque surrounding the lumen but do not address function of the epicardial coronary arteries or the condition of the microvasculature.

The diagnosis of SCAD may (classically) also be supported by functional testing (exercise ECG or an imaging stress test). These tests give important information about the causal relationship between ischaemia and the occurrence of the patient's symptoms. However, distinction between epicardial lesions and microvascular dysfunction causing ischaemia is difficult.

The choice between the different diagnostic techniques is described in the main text but some important aspects of the choices made there are explained in the following paragraphs.

Guidelines dealing with the diagnosis of chest pain usually recommend pathways that are meant to optimize the diagnostic process (minimizing the number of false positive and false negative tests).[29–31] The recommendations rely heavily on estimates of the prevalence of significant CAD in populations characterized by sex, age and symptoms. However, estimates obtained in the 1970s by Diamond and Forrester,[32] employed in the previous version of these guidelines,[31] may no longer be accurate for today's populations. The declining death rates due to CAD are compatible with a possible decline in today's age-specific prevalence of SCAD.[33,34] This possibility is also suggested by the decreasing prevalence of typical cardiac risk factors.[34] Recent estimates, based on coronary CTA registries,[35] of the prevalence of obstructive epicardial CAD in patients with typical or atypical angina are indeed substantially lower than the Diamond and Forrester estimates from 1979. In contrast, in patients with non-anginal chest pain, the prevalence of obstructive CAD as assessed by coronary CTA may be higher than previously expected. In fact, these coronary CTA data suggest that there may be little difference in the prevalence of obstructive CAD across the three groups of chest pain.[36] This has led to some criticism of these data.[37] However, in these coronary CTA based data, men continue to have higher prevalences than women and prevalence still increases steeply with age. Apart from a true decline in CAD incidence, selection bias and sub-optimal history-taking were mentioned as possible explanations for the lack of correlation between symptoms and significant epicardial coronary stenoses as

visualized by coronary CTA.[37] Using pre-test probabilities (PTPs) from registries with referred patients may overestimate the true PTP in patients presenting in a primary care environment.

One recent study based on ICA registries confirmed the substantially lower prevalence of obstructive CAD found in the coronary CTA registry for women,[36] but found similar prevalences to those of Diamond and Forrester in men.[38] Interestingly, just as in the coronary CTA based study,[36] this ICA-based study also found higher frequencies of CAD in patients with atypical angina,[38] than was expected on the basis of the Diamond and Forrester estimates.[32]

The previous version of these Guidelines[31] contained an algorithm that combined diagnostic and prognostic aspects of non-invasive testing to make recommendations for patient management. In brief, every patient with chest discomfort and/or exercise-related dyspnoea that could not be ascribed to non-cardiac causes, such as pulmonary disease, had to undergo assessment of ischaemia, either using the exercise ECG or—if this was not feasible—either exercise or pharmacological stress imaging. The likelihood of a non-cardiac cause of the chest pain being present was re-assessed after the ischaemia testing. Those in whom the diagnosis of CAD seemed likely were further managed according to the estimated risk of cardiovascular (CV) mortality which rested heavily on the Duke Treadmill Score (DTS). High-risk patients were recommended to undergo coronary angiography, in medium-risk patients, a trial of medical therapy was felt to be appropriate, but coronary angiography was an option in those with severe symptoms. Low-risk patients were recommended to have medical therapy. As detailed in the main text of these Guidelines, this Task Force decided to separate the steps of making a diagnosis and estimating risk in patients with chest pain. This approach is similar to the ones taken in the recent National Institute for Health and Clinical Excellence (NICE) and American Heart Association (AHA)/American College of Cardiology (ACC) guidelines.[22,29]

With regard to the exercise ECG—a completely non-invasive, broadly available and low-cost technique that performs well at intermediate PTPs between 15–65% in patients with a normal resting ECG (no ST–T abnormalities)—this Task Force decided to keep this well-established, time-honoured technique in the algorithm, despite its inferior performance as compared with modern stress imaging techniques. However, the superior diagnostic performance of non-invasive stress imaging was a strong argument for recommending the preferential use of these techniques in all patients where local expertise and availability permit. One must, on the

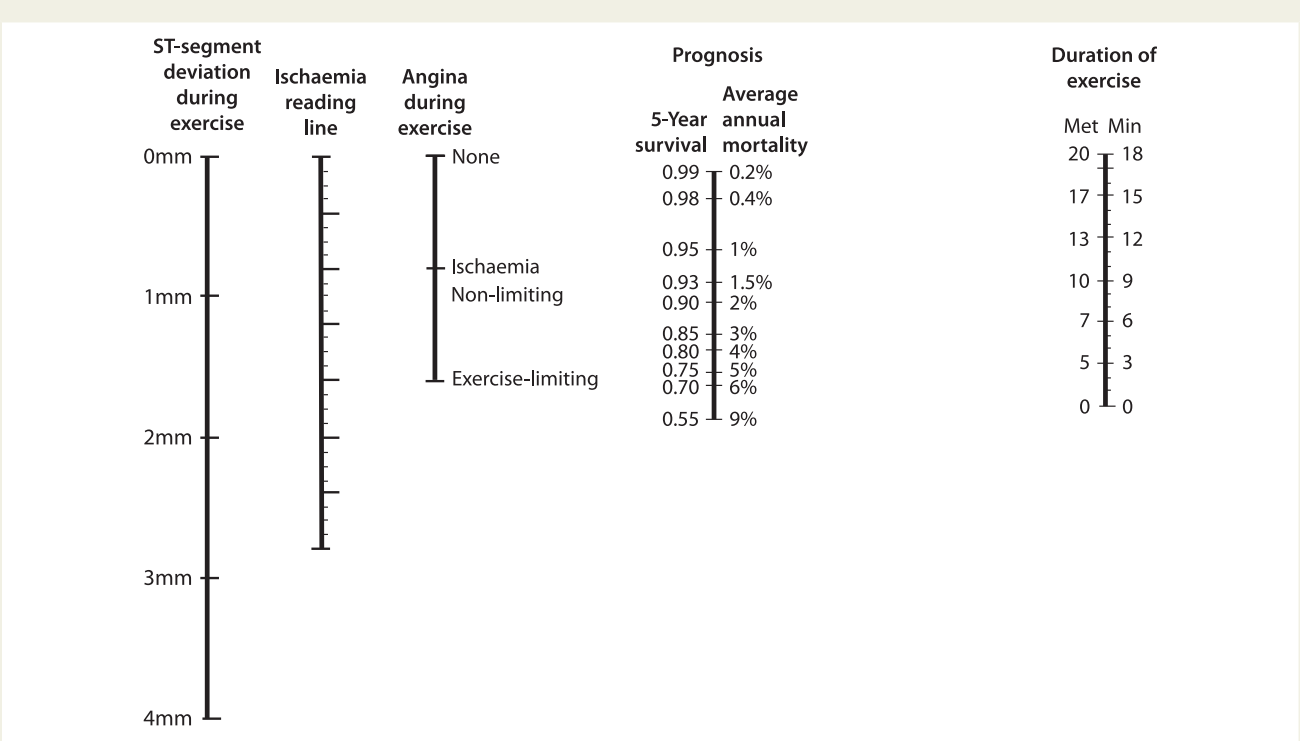

Figure W1 Duke Treadmill Score (DTS) for risk stratification in stable coronary artery disease patients.[40] Nomogram of the prognostic relations embodied in the DTS. Determination of prognosis proceeds in five steps. First, the observed amount of exercise-induced ST-segment deviation (the largest elevation or depression after resting changes have been subtracted) is marked on the line for ST-segment deviation during exercise. Second, the observed degree of angina during exercise is marked on the line for angina. Third, the marks for ST-segment deviation and degree of angina are connected with a straight edge. The point where this line intersects the ischaemia-reading line is noted. Fourth, the total number of minutes of exercise in treadmill testing according to the Bruce protocol (or the equivalent in multiples of resting oxygen consumption (METs) from an alternative protocol) is marked on the exercise-duration line. In countries where a bicycle ergometer is used one may—a rule of thumb—assume the following: 3 METS ~ 25W, 5 METS ~ 75W, 6-7 METS ~ 100W, 9 METS ~ 150W; 13 METS ~ 200W. Fifth, the mark for ischaemia is connected with that for exercise duration. The point at which this line intersects the line for prognosis indicates the 5-year survival rate and average annual mortality for patients with these characteristics.

other hand, acknowledge that there are no prospective, randomized data demonstrating that this superior diagnostic performance translates into superior outcomes.[39] In patients who cannot exercise, an imaging test using pharmacological stress is the best option across the range of PTPs from 15–85%. Patients at pre-test probabilities between 65–85% should be tested using stress imaging. Beyond PTP, the choice of the initial test should be based on the patient's resting ECG, physical ability to perform exercise, local expertise, and available technologies (*Figure 2*, main document).

6.2.4.1 Electrocardiogram exercise testing

The DTC translates the exercise time in minutes, the ST-segment deviation during or after exercise in millimetres, and the clinical symptoms of the patient (no angina, any angina, or angina as the reason for stopping the test) into a prognosis, measured as the annual CV mortality (*Figure W1*). In the original description of this score, in a population with suspected CAD, two-thirds of patients had scores indicating low risk.[40] These patients had a 4-year survival rate of 99% on medical therapy (average annual mortality rate 0.25%). In contrast, the 4% of patients who had scores indicating high-risk had a 4-year survival rate of only 79% (average annual mortality rate 5%). In order to be able to classify patients with an annual mortality of >3%, which identifies patients whose prognosis could be improved by performing coronary angiography and subsequent revascularization, it is necessary to enter the values for maximum ST depression, the metabolic equivalents (METs) achieved, and the clinical symptoms into the nomogram shown in *Figure W1* or a programme available at http://www.cardiology.org/tools/medcalc/duke/. This calculation will give a value for annual mortality, facilitating the decision on whether the patient is a high risk (annual mortality >3%) or not. This can be used for decision-making according to *Figure 3* in the main document.

6.2.4.2 Stress imaging or exercise electrocardiogram? Which form of stress imaging?

Stress imaging techniques have several advantages over conventional exercise ECG testing, including superior diagnostic performance (*Table 12* in the main document) for the detection of obstructive coronary disease, the ability to quantify and localize areas of ischaemia, and the ability to provide diagnostic information in the presence of resting ECG abnormalities. Moreover, stress imaging can also be used in conjunction with pharmacological tests in patients with inadequate exercise ability. Stress imaging techniques are also preferred to stress ECG testing in patients with previous percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), who often have pre-existing ECG abnormalities and in whom the diagnosis of CAD is already known. The superior ability of stress imaging, compared with exercise ECG, to localize and quantify ischaemia may translate into more effective risk stratification, thus avoiding unnecessary invasive procedures.[41] In patients with

Table W1 Advantages and disadvantages of stress imaging techniques and coronary CTA

Technique	Advantages	Disadvantages
Echocardiography	Wide access Portability No radiation Low cost	Echo contrast needed in patients with poor ultrasound windows Dependent on operator skills
SPECT	Wide access Extensive data	Radiation
PET	Flow quantitation	Radiation Limited access High cost
CMR	High soft tissue contrast including precise imaging of myocardial scar No radiation	Limited access in cardiology Contra-indications Functional analysis limited in arrhythmias Limited 3D quanfification of ischaemia High cost
Coronary CTA	High NPV in pts with low PTP	Limited availability Radiation Assessment limited with extensive coronary calcification or previous stent implantation Image quality limited with arrhythmias and high heart rates that cannot be lowered beyond 60–65/min Low NPV in patients with high PTP

CMR = cardiac magnetic resonance; CTA = computed tomography angiography; NPV = negative presictive value; PET = positron emission tomography; PTP = pre-test probability; pts = patients; SPECT = single photon emission computed tomography.

angiographically confirmed intermediate coronary lesions, evidence of anatomically appropriate ischaemia may be predictive of future events, whereas a negative stress imaging test can be used to define—and reassure—patients with a low cardiac risk.[42] FFR measurements appear to be a useful complement to imaging techniques when the proof of ischaemia has not been obtained before the angiogram, but their relative role is still under debate.[43] The indications for performing stress imaging in patients with suspected SCAD were recently expanded when NICE recommended that stress imaging, rather than exercise ECG, should be employed in patients with an intermediate PTP of disease if testing for myocardial ischaemia was indicated.[29] *Table W1* summarizes the advantages and disadvantages of the various stress imaging techniques and coronary CTA.

Exercise testing, as compared with pharmacological stress, better reflects the physical capacities of the patient. In many patients, higher levels of stress can be achieved when exercise is used to provoke ischaemia. One also gets a better impression about the level of exercise that provokes angina in daily life, plus additional information from the ECG that is always registered in parallel. Therefore, exercise stress testing in combination with imaging is preferred over pharmacological stress testing, although the reported sensitivities and specificities are similar (see table 12 of the main text).

6.3 Intravascular ultrasound and optical coherence tomography for the diagnostic assessment of coronary anatomy

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) require the introduction of a small catheter inside the artery via a 6 French guiding catheter, with the additional need for contrast injection during the 3 seconds of image acquisition for OCT. IVUS demonstrates the full thickness of the plaque, the only exception being in the presence of extensive sub-intimal calcification, but the resolution of IVUS is insufficient to measure cap thickness. Plaque characterization relies on the application of 'virtual histology', a technique still lacking extensive clinical validation and fraught with methodological limitations. OCT penetration is much more limited (1 mm) but its greater resolution allows reliable identification of sub-intimal lipidic plaques and precise measurement of the fibrous cap, the two key elements characterizing vulnerable plaques. Both techniques have greatly added to our understanding of the natural history of coronary atherosclerosis. Recently, an IVUS study using virtual histology analysis of plaque composition in 697 patients has shown that thin cap fibro-atheroma plaques and segments with large plaque burdens in non-critically stenosed vessels at the time of PCI are associated with higher risks of events.[44] However, while these results are promising, their practical value is limited by the lack of safe therapeutic measures, potentially deliverable locally at the time of identification with IVUS and OCT, to reduce the risk of plaque destabilization and rupture. Therefore, these continue to be used in highly specific clinical settings and for research purposes, rather than being widely applied as first-line investigations for diagnostic and prognostic purposes in patients with coronary disease.

6.4 Risk stratification

Several independent lines of evidence indicate that revascularization will improve prognosis only in high-risk patients. Although there are no randomized data proving this, it is known from large registries that only patients with documented myocardial ischaemia involving >10% of the LV myocardium have a lower CV and all-cause mortality when revascularization is performed.[42,45] In contrast, revascularization may increase mortality in patients with ischaemia involving <10% of the myocardium (*Figure W2*). Medically treated patients with an area of ischaemia involving >10% of the left ventricular (LV) myocardium have an increased annual risk of CV death >2%[45] and all-cause death >3%,[42] whereas this risk in those patients with less ischaemia is <3%.[42,45] Hence, high-risk patients are characterized by a large area of ischaemia by imaging and an annual all-cause death rate >3%.

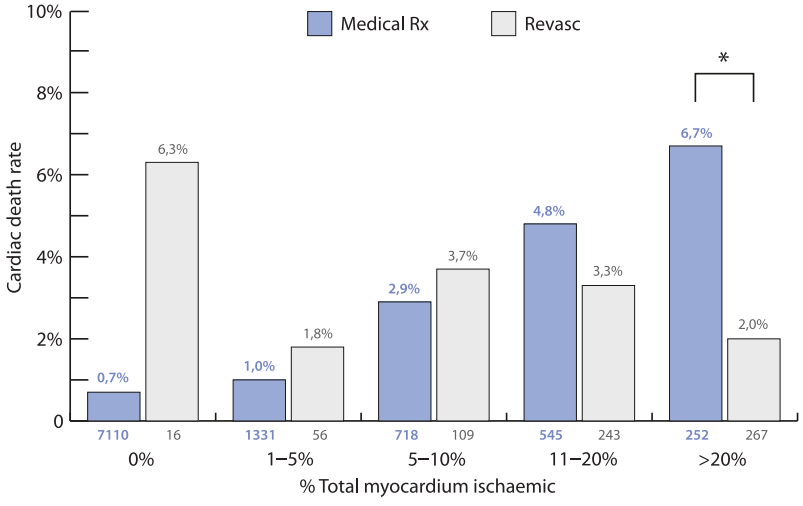

Figure W2 Relationship between cardiac mortality and extent of myocardial ischaemia, depending on type of therapy.[45] Numbers below columns indicate numbers of patients in each group. *$P < 0.02$. Medical Rx = medical therapy; Revasc = revascularization.

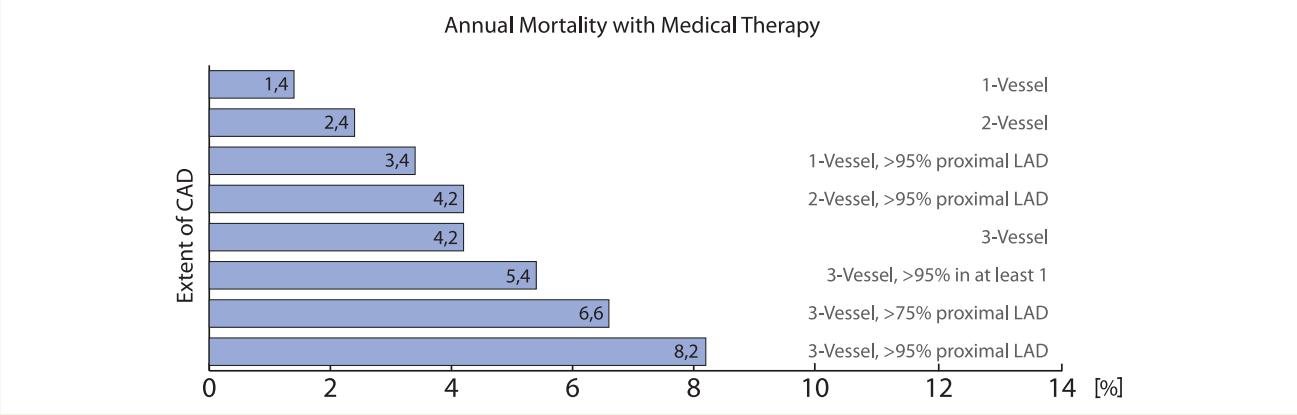

Figure W3 Cardiac death rates in patients on medical therapy with different extents of angiographically defined coronary artery disease. LAD = left anterior descending.[46]

Another line of evidence comes from a large prospective angiography registry with >9000 patients.[46] In this registry, patients with high-risk angiographic findings, such as left main (LM) stenosis, proximal left anterior descending (LAD) disease and proximal triple-vessel disease, who are known to benefit in terms of prognosis from revascularization, had an annual death rate >3% on medical treatment (*Figure W3*). Patients with an observed annual mortality <3% on medical therapy had lower-risk coronary lesions, and revascularization did not improve their prognosis.

The major focus in non-invasive risk stratification is on subsequent patient mortality, with the rationale of identifying patients in whom coronary arteriography and subsequent revascularization might decrease mortality, namely those with three-vessel disease, LM CAD, and proximal left anterior descending CAD. The difficulties in getting ICA to correctly estimate the haemodynamic relevance of disease,[47] however, suggest that additional functional testing by FFR may be useful, even in patients to be sent for bypass surgery on the basis of the coronary angiogram.[48]

6.4.5. Invasive assessment of functional severity of coronary lesions

Coronary angiography is of limited value in defining the functional significance of stenosis. Yet the most important factor related to outcome is the presence and extent of inducible ischaemia.[49] This—and alleviation of angina symptoms caused by significant stenosis—is the rationale for revascularizing such lesions. If, on the other hand, a stenosis is not flow-limiting, it will not cause angina and the prognosis without coronary intervention is excellent, with a 'hard' event rate of <1% per year.[50] Although non-invasive ischaemia testing is very precise in determining the functional implications of single-vessel disease, this is more difficult and complex in multi-vessel disease. Therefore, interventional guidance by non-invasive ischaemia testing through imaging techniques may be sub-optimal under such circumstances.[43]

The functional severity of coronary lesions visualized angiographically may be assessed invasively, either by measuring coronary flow velocity (CFR), or intracoronary artery pressure (FFR). The CFR is the ratio of hyperaemic to basal flow velocity and reflects flow resistance through the epicardial artery and the corresponding myocardial bed. Measurements depend on the status of the microcirculation, as well as on the severity of the lesion in the epicardial vessel. For practical and methodological reasons, measurement of CFR is not widely used in catheterization laboratories today and hence does not play any role in patient management.

In contrast, FFR is considered nowadays as the 'gold standard' for invasive assessment of physiological stenosis significance and an indispensable tool for decision making in coronary revascularization.[50,51] FFR provides guidance to the clinician in situations when it is not clear whether a lesion of intermediate angiographic severity causes ischaemia. Such situations are encountered in practice when non-invasive ischaemia testing was not performed before catheterization or multi-vessel disease is found at coronary angiography. Use of FFR in the catheterization laboratory accurately identifies which lesions should be revascularized and improves the outcome in most elective clinical and angiographic conditions, as compared with the situation where revascularization decisions are simply made on the basis of angiographic appearance of the lesion. Recently, the use of FFR has been upgraded to a Class IA classification in multi-vessel PCI in the ESC Guidelines on coronary revascularization.[18]

Fractional flow reserve is calculated as the ratio of distal coronary pressure to aortic pressure measured during maximal hyperaemia. A normal value for FFR is 1.0, regardless of the status of the microcirculation, and stenoses with a FFR >0.80 are hardly ever associated with exercise-induced ischaemia.[50]

6.5 Diagnostic aspects in the asymptomatic individual without known coronary artery disease

The following is the list of key messages from the recent ESC Guidelines on prevention of the cardiovascular disease (CVD),[52] to be considered when dealing with asymptomatic individuals in whom the risk of having silent CAD needs to be estimated. Based on such

estimations, further diagnostic testing may be indicated or not (list of recommendations in the main text of the Guidelines).

In apparently healthy persons, risk is most frequently the result of multiple interacting risk factors.

A risk estimation system such as Systematic Coronary Risk Evaluation (SCORE) can assist in making logical management decisions, and may help to avoid both under- and over-treatment (www.heartscore.org).

Certain individuals are at high CVD risk without needing risk scoring and require immediate intervention for all risk factors. These include all patients with diabetes, especially those with signs of end-organ damage with one or more CV risk factors, patients with chronic kidney disease [glomerular filtration rate (GFR) $<$60 mL/min] and those with markedly elevated single risk factors, such as familial dyslipidaemias or severe hypertension.

In younger persons, a low absolute risk may conceal a very high relative risk, and use of the relative risk chart or calculation of their 'risk age' may help in advising them of the need for intensive lifestyle efforts.

While women appear to be at lower CVD risk than men, this is misleading as risk is deferred by 10 years, rather than avoided.

All risk estimation systems are relatively crude and require attention to qualifying statements.

Additional factors affecting risk can be accommodated in electronic risk estimation systems such as HeartScore (www.heartscore.org).

Early-onset manifestation of CVD or of major risk factors (high BP, diabetes mellitus, or hyperlipidaemia) in a family member mandates counselling of first-degree relatives.

Low socio-economic status, lack of social support, stress at work and in family life, depression, anxiety, hostility, and the type D personality contribute both to the risk of developing CVD and the worsening of clinical course and prognosis of CVD.

These factors act as barriers to treatment adherence and efforts to improve lifestyle, as well as to promoting health and wellbeing in patients and populations.

Novel biomarkers have only limited additional value when added to CVD risk assessment with the SCORE algorithm.

High-sensitivity C-reactive protein (Hs-CRP) and homocysteine may be used in persons at moderate CVD risk.

Imaging methods such as carotid ultrasound or calcium scoring using computed tomography (CT) can be relevant in CVD risk assessment in individuals at moderate risk by reclassifying them as either high- or low-risk individuals. Measurement of the ankle-brachial index (ABI) should also be considered in this patient group. An exercise ECG may be considered in the same patient group, particularly when attention is paid to non-ECG markers, such as exercise capacity.

6.7 Special diagnostic considerations: angina with 'normal' coronary arteries

The clinicopathological correlation of symptoms with coronary anatomy varies widely, from typical symptoms of angina due to significant coronary lesions causing transient ischaemia when myocardial demand is increased, to clearly non-cardiac chest pain with normal coronary arteries. Spanning the extremes of this spectrum are a number of clinicopathological correlates, which may overlap to a greater or lesser extent with each other. These range from atypical anginal symptoms with significant coronary stenosis—which would fall under the umbrella of the conventional diagnosis of angina pectoris—to typical anginal symptoms with angiographically normal coronary arteries, which would fit the clinical picture of microvascular angina.[53] Vasospastic angina—caused by dynamic coronary obstruction in coronary arteries, which may be either angiographically smooth or diffusely diseased without or even with significant stenosis—is a further factor to be considered in the interpretation of symptoms.

6.7.1 Microvasular angina

6.7.1.1 Clinical picture

The morbidity of patients with microvascular angina remains high and the condition is frequently associated with continuing episodes of chest pain and hospital re-admission,[54,55] As many of the patients with coronary microvascular disease have atherosclerotic risk factors, it is not surprising that epicardial atherosclerotic coronary disease may develop later in the course of the disease.[56]

Some of the confusion over the clinical manifestations and implications of coronary microvascular disease may result from the fact that previously different patient groups were studied and all were said to suffer from what used to be called 'cardiac syndrome X'. However, the definition of syndrome X varied from study to study,[57] which may explain the different results found in many of them. Although coronary microvascular disease and ischaemia cannot be confirmed in all patients previously felt to have syndrome X, the consensus today is that coronary microvascular disease is the unifying pathogenetic mechanism in most of the patients described above.

In patients with microvascular angina, chest pain occurs frequently and is usually provoked by exercise in a stable pattern. Therefore, microvascular angina very much resembles 'classical' chronic SCAD caused by severe epicardial vessel narrowing. However, coronary microvascular disease is more likely if chest pain persists for several minutes after effort is interrupted and/or shows poor or slow response to nitroglycerin.[13] The clinical presentation of patients with coronary microvascular disease is highly variable and angina at rest is often encountered in addition to exercise-provoked chest pain.[58] These attacks of angina at rest imply that an element of vasospasm is present in some patients with coronary microvascular disease.[59] Severe attacks of resting angina may prompt recurrent emergency presentations and hospital admissions, based on the supposition that the patient has UA due to plaque instability, leading to unwarranted diagnostic and therapeutic procedures.

6.7.1.2 Pathogenesis and prognosis

The mechanism of chest pain in patients with coronary microvascular disease continues to be discussed. Functional abnormalities of the coronary microcirculation during stress, including abnormal dilator responses and a heightened response to vasoconstrictors, have been considered as potential mechanisms of chest pain and ischaemic-appearing ST-segment depression during exercise. Endothelial dysfunction is most probably only one of the components.[13] Enhanced cardiac pain perception, coupled with a minor impairment of CFR, has been proposed as an explanation of the presence of (sometimes severe) angina, in spite of modest signs or even absence of myocardial ischaemia.[13]

In previous studies in small series of well-characterized patients with microvascular angina, the outcome was found to be good with the exception of re-admissions for angina.[60] However, in a recent

large study, the event rate in terms of combined adverse CV events (CV death, MI, stroke or heart failure, and all-cause mortality) was found to be higher in patients with SCAD and normal coronary arteries [hazard ratio (HR) 1.52] or diffuse non-obstructive CAD (HR 1.85) as compared with a reference population without CAD [5-year event rate 2% for women (0.4% per year) and 6% for men (1.2% per year)].[61]

6.7.1.3. Diagnosis and management of coronary microvascular disease

Invasive measurement of CFR using a Doppler wire is complex, time consuming, and carries a small risk. Therefore, objective evidence of microvascular disease may alternatively be obtained by measuring diastolic coronary blood flow in the LAD at peak vasodilatation (following intravenous adenosine) and at rest using transthoracic echocardiographic Doppler recordings.[62] A CFR <2.0 strongly suggests coronary microvascular disease. However, CFR may be preserved in mild forms of coronary microvascular disease. Positron emission tomography (PET) can also measure CFR and detect coronary vasomotor abnormalities caused by microvascular disease.[17,63] However, availability of PET is limited. There is no consensus on whether contrast stress echocardiography or cardiac magnetic resonance (CMR) can reliably quantify perfusion abnormalities caused by coronary microvascular disease. An explanation other than microvascular disease for angina may be found in patients with diffuse epicardial disease but without relevant proximal stenosis. In such patients, who may have evidence of ischaemia by non-invasive imaging, FFR with a distal position of the flow wire may indeed demonstrate FFR values indicating ischaemia, whereas a proximal position of the flow wire may indicate no relevant disease.[64] Therefore, excluding the haemodynamic relevance of obvious coronary plaque—yet without the appearance of stenosis—by FFR may be helpful in selected patients before making a diagnosis of microvascular disease as the cause of the patient's symptoms.

6.7.2 Vasospastic angina

6.7.2.2 Pathogenesis and prognosis

The pathogenesis of vasospasm is not entirely clear (see Section 3.3 of this web document for further information). It may occur in response to smoking, electrolyte disturbances (potassium, magnesium), cocaine use, cold stimulation, auto-immune diseases, hyperventilation or insulin resistance. It is related to smooth muscle cell hyper-reactivity, probably caused by alteration of intracellular mechanisms, leading to calcium overload or to enhanced myosin sensitivity to calcium.[10] The prognosis of vasospastic angina depends on the extent of underlying CAD. Death and MI are not frequent in patients without angiographically significant obstructive disease,[65] but those with spasm superimposed on stenotic lesions,[66] or those with focal occlusive spasm,[67] do significantly less well. Prognosis also depends on disease activity (frequency and duration of spastic episodes), the amount of myocardium at risk, and the presence of severe ventricular tachyarrhythmias or advanced atrioventricular (AV) block during ischaemia.

8.2 Coronary artery bypass surgery

8.2.2 On-pump vs. off-pump surgery

Off-pump surgery was initially proposed almost three decades ago.[67] Despite scepticism by some over its technical feasibility in achieving optimal revascularization in terms of numbers and quality of grafts, this approach was promoted by others, who argued that the avoidance of cardiopulmonary bypass could substantially reduce the adverse clinical consequences of extracorporeal circulation. These polarized views have remained essentially unchanged in Europe and the USA, with off-pump coronary artery bypass surgery (CABG) plateauing at around 20% of all CABG operations. However, it should be recognized that this statistic is derived from the practice of a relatively small number of surgeons who perform almost all their CABG off-pump and the majority who rarely use this technique. This is also in marked contrast to Asian countries, where off-pump CABG is performed in 60–100% of the whole CABG population. Numerous randomized trials and meta-analyses of these have confirmed that off-pump surgery does not increase operative mortality and leads to a reduction in many aspects of post-operative morbidity, especially stroke. A current meta-analysis, covering almost 9000 patients from 59 randomized trials,[68] reported non-statistically significant lower post-operative mortality (1.6 vs. 1.9%) and MI (3.4 vs. 3.9%) in the off-pump group but a clinically and statistically significant one-third reduction in the incidence of stroke from 2.1% in the on-pump group to 1.4% in the off-pump group (relative risk 0.7; 95% CI 0.49–0.99).

In a recent large, randomized trial, there was no significant difference between off-pump and on-pump CABG with respect to the 30-day rate of death, MI, stroke, or renal failure requiring dialysis. The use of off-pump CABG resulted in reduced rates of transfusion, re-operation for peri-operative bleeding, respiratory complications, and acute kidney injury, but also resulted in an increased risk of early revascularization from 0.2% in the on-pump group to 0.7% in the off-pump group.[69]

Several registries of tens of thousands of propensity-matched patients, reflecting a wider spectrum of clinical practice and often containing higher-risk patients, have consistently reported significant reductions in mortality, stroke, and all aspects of major post-operative morbidity.[70–72] In arguably the most powerful single study of this issue in over 120 000 propensity-matched patients, Kuss and colleagues reported highly clinically and statistically significant benefits for mortality [odds ratio (OR) 0.69; 95% CI 0.60–0.75) and stroke (OR 0.42; 95% CI 0.33–0.54), as well as major reductions in the incidence of renal failure, prolonged ventilation, intra-aortic balloon pump and inotropic support ($P = 0.05$), wound infection ($P < 0.001$), and red blood cell transfusion ($P < 0.0001$) with off-pump surgery.[72]

However, as alluded to earlier, off-pump surgery may result both in fewer numbers of grafts (at least during the 'learning curve') and in reduced vein graft patency rates, possibly due—at least in part—to the loss of the 'protective' antiplatelet effect of cardiopulmonary bypass.[73] In some studies, this has led to a late increase in the need for repeat revascularization and the loss of the early mortality benefit of off-pump surgery.

8.2.3 General rules for revascularization

The decision to revascularize a patient on prognostic grounds should be based on the presence of significant obstructive coronary artery stenoses and the amount of ischaemia induced by the stenosis (*Figure 9* of the main document). There are several anatomical conditions that, *per se*, may imply the need for revascularization to improve prognosis regardless the presence of symptoms [e.g. (i) significant left

main disease with or without significant stenoses in the three other vessels; (ii) last remaining vessel or (iii) multi-vessel disease with left ventricular dysfunction). Additionally, the presence of large areas of ischaemia (>10% by SPECT, for instance) in the territory supplied by the stenosed artery or a FFR ≤0.80 also indicate the need for revascularization (*Table 11* of the main document). Having settled the indication for revascularization, technical feasibility should be assessed. Feasibility should not anticipate or substitute a definitive indication.

In the event that a prognostic benefit of revascularization is not anticipated (ischaemia <10% of the left ventricle), or that revascularization is technically not possible or potentially difficult, or would be high-risk, the patient should remain on optimal medical therapy (OMT). According to residual symptoms or the presence of a large burden of ischaemia, additional therapies can be used (see Section 9.7 on refractory angina).[74]

When the benefit of revascularization can be anticipated and when it is technically feasible (*Figure 9* of the main document), revascularization can be performed for relief of pain and disability or to prolong or save lives. As shown in *Figure 9*, the decision-making process can be based on the anatomical scenario (e.g. single-vessel vs. multi-vessel vs. left main disease), then on a few additional anatomical factors (e.g. Chronic total occlusions (CTO) vs. non-CTO, ostial vs. non-ostial, bifurcation vs. non-bifurcation, angiographic scores, etc), clinical conditions (diabetes, low EF vs. normal EF, renal impairment, co-morbidities, age, gender, prior revascularization, concomitant medication, etc.), operator- or centre-related factors, and logistical factors (availability, cost of the procedure, etc). The vast number of possible combinations makes absolute recommendations difficult to mandate in every situation. In this regard, for a given patient in a given hospital, clinical judgement with consensual—rather than individual—decision-making (at best, heart team discussion) should prevail.

8.3 Revascularization vs. medical therapy

8.3.2.1 The randomized studies

Among the older studies that investigated revascularization vs. OMT, a few are selectively reviewed below.

The Angioplasty Compared to Medicine (ACME) study ($n = 328$) demonstrated superior control of symptoms and better exercise capacity in patients managed with percutaneous transluminal coronary angioplasty, when compared with OMT, at 6-month follow-up. Death or MI were similar in both groups. Results were confirmed at 2 years.[75]

The Atorvastatin Versus Revascularization Treatment (AVERT) study ($n = 341$) randomly assigned patients with SCAD with normal LV function and Class I and/or II angina to PCI and standard medical treatment, or to OMT with high dose atorvastatin. At 18 months follow-up, 13% of the medically treated group had ischaemic events, as opposed to 21% of the PCI group ($P = 0.048$). Angina relief was greater in those treated with PCI.[76]

The Asymptomatic Cardiac Ischaemia Pilot (ACIP) study ($n = 558$) compared PCI or CABG revascularization with an angina-guided drug strategy or angina-plus-ischaemia-guided drug therapy in patients with documented CAD and asymptomatic ischaemia identified by stress testing and ambulatory ECG monitoring. At 2-year follow-up, death or MI had occurred in 4.7% of the revascularization patients, compared with 8.8% of the ischaemia-guided group and 12.1% of the angina-guided group ($P < 0.01$ in favour of the revascularized group). The benefit was almost entirely confined to those who underwent CABG as opposed to PCI. The results of the ACIP trial suggest that higher-risk patients, who are asymptomatic but have demonstrable ischaemia and significant CAD, may have a better outcome with revascularization than with simple OMT.[77]

The Medical, Angioplasty, or Surgery Study (MASS) ($n = 611$) randomized patients with SCAD and isolated disease of the left descending coronary artery to medical treatment, PCI, or CABG. At 5 years, the primary combined endpoint of cardiac death, MI, and refractory angina requiring repeat revascularization occurred in 21.2% of patients who underwent CABG, compared with 32.7% treated with PCI and 36% receiving medical therapy alone ($P = 0.0026$). No statistical differences were observed in overall mortality among the three groups. The 10-year survival rates were 74.9% with CABG, 75.1% with PCI, and 69% with medical therapy ($P = 0.089$). The 10-year rates of MI were 10.3% with CABG, 13.3% with PCI, and 20.7% with medical therapy ($P < 0.010$).[78]

The Second Randomised Intervention Treatment of Angina (RITA-2) trial ($n = 1018$) showed that PCI resulted in better control of symptoms of ischaemia and improved exercise capacity compared with OMT, but this is associated with a higher rate of the combined endpoint of death or MI after 2.7 years of follow-up (6.3 vs. 3.3%; $P = 0.02$), a difference driven by peri-procedural MI. Twenty-three per cent of the OMT patients required a revascularization procedure during this initial follow-up. This crossover rate increased to 43% at 7-year follow-up with finally no difference for death or MI (14.5% with PCI vs. 12.3% with OMT, NS).[79,80]

The Trial of Invasive versus Medical therapy (TIME) ($n = 301$) compared, in elderly patients (age >75 years) with severe angina, a strategy of immediate invasive therapy or continued OMT. Of those randomized to invasive therapy, 52% received PCI and 21% had CABG. Invasive therapy was associated with a significant improvement in symptoms at 6 months, but the difference was not maintained at 1 year, partly due to a 48% delayed revascularization rate in the OMT arm. Death and MI were not significantly different between the two treatment strategies. However, at 4-year follow-up, patients who had been revascularized within the first year of the study had a significantly better survival than those receiving drug therapy (76 vs. 46%; $P = 0.0027$).[81,82]

In the Japanese Stable Angina Pectoris (JSAP) study, Japanese patients with SCAD and multi-vessel disease in one third of the population were randomized to PCI + OMT ($n = 192$) or OMT only ($n = 192$). Over a 3.3-year follow-up, there was no significant difference in the cumulative death rate between PCI + OMT (2.9%) and OMT only (3.9%). However, the cumulative risk of death or ACS was significantly smaller with PCI + OMT, leading to premature interruption of the follow-up of this study.[83]

8.3.2.2 Limitations of the randomized studies

A number of limitations relate directly to the study designs and populations as shown in *Table X* for the two larger and most recent trials [Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) and Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D)]. A small proportion of screened patients were actually randomized in the study and this may have

implications on the general applicability of the results. Some of the commonly encountered clinical syndromes were also poorly represented in these studies, and the amount of evidence may appear insufficient or even contradictory to the other studies, as also referred to in *Table W2*.[84,85]

Other limitations relate to the results themselves: for example while, in the sample size calculation of the COURAGE trial, it was expected that crossover would occur in 5% over 5 years in patients randomized to OMT, it actually occurred in 33%.[86] This high rate of crossover to revascularization in the OMT group was also found in other trials (42% in BARI 2D), suggesting that revascularization was merely deferred in 33–42% of patients randomized to a conservative approach. The COURAGE nuclear-imaging sub-study showed that patients with moderate-to-severe ischaemia benefited more through PCI than OMT.[87] With this in mind, it is noteworthy that documented ischaemia was not mandatory for enrolment in COURAGE like in BARI 2D, while, in contrast, many high-ischaemic-risk patients underwent *ad hoc* PCI revascularization after the angiogram, without having a chance eventually to be randomized to OMT-only in these studies . Bare metal stents (BMS) were mostly used, as drug-eluting stents (DES) were not available when the studies started, although this would probably have had an impact on symptoms but not death/MI. OMT was particularly well managed, with the implementation of aggressive nurse case management, lifestyle changes, and the provision of most medications without cost—a favourable strategy that may not reflect current practice in many places, although such care management should be promoted.

Finally, there are some limitations in the interpretation of the studies.[88,89] The most debated interpretation applies to the two neutral studies, COURAGE and BARI 2D, which had superiority statistical hypotheses that were not met, suggesting that revascularization had no impact on 'hard' outcomes in stable CAD patients. However, other smaller studies and meta-analyses have evaluated the role of revascularization (PCI or CABG) vs. medical therapy in patients with SCAD, with somewhat different conclusions. A meta-analysis of 17 randomized trials, comparing a PCI-based treatment strategy with medical treatment in 7513 patients with chronic

Table W2 Clinical situations not corresponding to COURAGE and BARI 2D populations

	Exclusion criteria in COURAGE	Exclusion criteria in BARI-2D	Contradictory or insufficient evidence
CLINICAL SITUATIONS			
Acute coronary syndromes		✓	
Post-MI angina or silent ischaemia or CHF	✓		✓
CCS Class IV angina or markedly positive stress test	✓	✓	
Moderate-to-severe ischaemia			✓
Large area of viable plus jeopardized myocardium with LV dysfunction			✓
Refractory HF or shock or EF <30%	✓	✓	
EF 30-50%			✓
Uncontrolled hypertension (200/100mmHg)	✓		
Creatinine > 177 mol/L		✓	
Alanine aminotransferase >2 times the ULN		✓	
Ventricular arrhythmia	✓	✓	
Concomitant valvular heart disease likely to require surgery	✓		
Need for concomitant major vascular surgery		✓	
Limited life expectancy	✓	✓	
AFTER ANGIOGRAPHY			
No coronary angiogram available	✓	✓	
FFR guided revascularization	✓		✓
Multi-vessel disease CAD			✓
Left main disease >50%	✓	✓	
Revascularization within prior 6/12 months	✓	✓	
Definite need for invasive coronary intervention	✓	✓	

CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; CHF = congestive heart failure; EF = ejection fraction; FFR = fractional flow reserve; HF = heart failure; LV = left ventricular; MI = myocardial infarction; ULN = upper limit of normal.

stable angina, suggested that the PCI-based strategy might improve long-term survival.[90] This meta-analysis was criticized for its heterogeneity, as it included groups of patients with recent MI, and for the variable medical strategies used. Another meta-analysis of 28 trials performed over 30 years, comparing revascularization with medical therapy, and which excluded patients with ACS, drew similar conclusions.[91] Obviously these findings go against those of most individual trials, except TIME, Swiss Interventional Study on Silent Ischemia Type II (SWISSI I)I and ACIP, which suggested reductions in mortality with revascularization. These studies were also those with the populations at higher ischaemic risk. However, none of the studies, with the exception of BARI 2D, were powered for mortality, limiting the validity of individual studies with regard to this endpoint. A recent meta-analysis examined contemporary studies only, but *included* studies of Q-wave MI patients without residual angina or ischaemia, and *excluded* studies with acute patients or patients revascularized with CABG: no benefit was found with PCI.[92] Another limitation of the studies and meta-analyses is the rapid evolution of revascularization techniques (e.g. DES for PCI and arterial grafts for CABG) and antiplatelet, anticoagulant, hypolipidaemic and anti-ischaemic drugs, which render many of the studies obsolete and difficult to interpret in the contemporary era. Finally, the conclusions of these trials are based upon the minority of highly selected patients who are undergoing angiography, among whom there is clinical equipoise.[93]

Limitations of the randomized studies rely not only on the selection of the patients, but also on the type of intervention applied to the selected population. The difficulties of implementing OMT and lifestyle intervention in daily practice, as performed in the COURAGE study, must not been overlooked. It takes enormous effort, dedication, cultural change, and commitment to expect the benefits observed in the randomized trials to manifest in 'real' practice. A recent example has been the work published by Hannan and colleagues, which looked at patients with stable CAD who were candidates for PCI after angiography.[94] They derived 933 propensity-matched pairs of patients on routine medical treatment, with an individual patient who underwent PCI being matched with another who remained on routine medical treatment—the matching being based on a long list of potential confounders. Medical treatment was not optimal but followed routine practice in terms of drug prescription and lifestyle intervention, and PCI was performed with DES in 71% of cases; another major difference from the COURAGE study. At 3-year follow-up, outcomes, including mortality, were significantly improved with PCI. This contradictory result from a non-randomized study outlines the gap between 'optimal' and 'real' practice, highlighting the issues of implementing therapy at the physician level and of adherence to these therapies at the patient level.

8.3.2.2.1 Applicability. Cardiologists and surgeons should be more conservative with regard to decisions over revascularization in stable CAD patients, especially in the case of technical difficulties or in mildly symptomatic patients or in patients without extensive provocable ischaemia, when a period of OMT has not been adequately conducted. On the other hand, OMT should not be considered an alternative but a synergistic approach to revascularization. In low-risk stable CAD patients, after careful clinical and angiographic selection, the strategy of deferring PCI is safe and this applies probably to 50–60% of patients. The fact that a significant proportion of patients will subsequently undergo revascularization does not alter the fact that the majority will not need revascularization. The major benefit of revascularization is the relief of symptoms and, in low-risk patients, the price to be paid by an initial conservative strategy is not that of death or MI. Patient preference and collegiate review (involving a heart team wherever possible) are important factors in the initial treatment decision. Such a strategy is not only medically wise but also cost-effective.[95] An initial OMT strategy does not preclude regular re-evaluation of the patient and a subsequent change in strategy according to symptoms, drug side-effects or limited quality of life. It should be emphasized that the success—or lack of success—of an initial trial of OMT should be manifest within a relatively short period of time, thus avoiding a prolonged process if drugs are ineffective or not tolerated. The modern management of SCAD places revascularization as an integral component of strategies incorporating pharmacological therapy, to control symptoms and risk factors, and aggressive lifestyle management.

8.3.2.3 Ongoing studies for management of stable coronary artery disease patients with demonstrated ischaemia

Several studies have suggested that patients with more extensive ischaemia benefit from revascularization therapy, and this benefit could translate into a long-term survival benefit if the ischaemia is severe and the reduction of ischaemia is significant. This hypothesis has been poorly investigated prospectively, although the positive randomized trials ACIP and SWISSI II strongly suggest that ischaemia plays a key role in the benefit of revascularization.[96,97] The hypothesis of deciding upon an invasive approach prior to angiography—and not

Table W3 Decision making according to severity of symptoms/ischaemia

Severe: Angina CCS III–IV or ischaemia >10% ➡	catheterization laboratory.
Moderate-to-severe: Angina CCS II or ischaemia 5–10% ➡	OMT[a] only or catheterization laboratory.
Mild-to-moderate: Angina CCS I or ischaemia <5% ➡	OMT[a] first and defer catheterization laboratory.

[a]If symptoms and/or ischaemia are markedly reduced/eliminated by OMT, then OMT may be continued; if not, catheterization should follow. CCS = Canadian Cardiovascular Society; OMT = optimal medical therapy.

after, as in COURAGE and BARI 2D—on the basis of documented clinically meaningful ischaemia during stress testing, certainly needs re-evaluation. This hypothesis is currently being evaluated in randomized trials, *viz.* the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA). The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME 2) is the first approach of a revascularization strategy decided in patients with demonstrated functional stenosis (see main manuscript).[98] The primary endpoint was reduced significantly, without significant impact on death or MI. In the ongoing ISCHEMIA trial, patients are randomized before coronary angiography for a conservative OMT strategy or an invasive strategy when they have documented myocardial ischaemia, the primary endpoint being death or MI.

While waiting for more information, the decision to refer patients to the catheterization laboratory will depend mainly on a thorough assessment of risk, the presence and severity of symptoms, and the extent of ischaemia *(Table W3)*. In a number of situations, patient preference should prevail and a second opinion from colleagues not directly involved (ideally agreement by the heart team) may help to reach a decision.

8.4 Percutaneous coronary intervention vs. coronary artery bypass graft

8.4.1 Target populations of the randomized studies

Over the last two decades there have been approximately 20 trials of PCI vs. CABG, which have consistently reported no overall difference in survival between the two interventional techniques, but a reduction in the need for repeat revascularization with CABG. These trials have, however, been criticized on the basis that they often only enrol a small percentage of the potential eligible population, often $<10\%$, and were mainly populated by patients with one- or two-vessel coronary disease and normal left ventricular function—a population in which it could be predicted that there was no survival benefit of CABG.

In contrast, several propensity-matched registries have consistently demonstrated a survival benefit for CABG, of around 5 percentage points by 3–5 years after intervention, accompanied by a marked reduction in the need for repeat intervention.[99–101] However, despite propensity matching, registries may still be susceptible to confounding by both known and unknown factors. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) trial has at 3 years reported similar findings to the propensity-matched registries, most likely on the basis that it is also relatively an 'all comers' trial, and emphasizes that both forms of evidence have strengths and weaknesses that should be used in a complementary fashion.

8.5 Scores and decisions

8.5.1 Scores

SYNTAX scores are a measure of the anatomical severity of CAD,[102,103] and have been arbitrarily classified as low (SYNTAX score 0–22), intermediate (SYNTAX score 23–32), and high severity (SYNTAX score >32), to produce three approximately similar-sized groups. For three-vessel CAD with low scores, there was no difference in major adverse cardiac and cerebrovascular events (MACCE) between CABG and PCI, but for intermediate (17 vs. 29%; $P = 0.003$) and high (18 vs. 31%; $P = 0.004$) scores, there were much better outcomes with CABG.

For left main stem (LMS) disease there was a higher mortality for CABG than PCI in both the lower (6 vs. 2.6%; $P = 0.21$) and intermediate score groups (12.4 vs. 4.9%; $P = 0.06$) whereas, for the highest SYNTAX scores, the mortality was 13.4% for PCI and 7.6% for CABG ($P = 0.10$), with a tripling of repeat revascularization with PCI (28 vs. 9%; $P = 0.001$).

These outcomes broadly indicate that, with the increasing complexity of CAD, CABG offers a survival benefit and marked reduction in MACCE, largely driven by a lower incidence of MI and repeat revascularization. However, both SYNTAX and the 'Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease' (PRECOMBAT)[104] study suggest that, for lower- and intermediate-risk LMS disease, PCI is at least equivalent to CABG. These LMS patients with SYNTAX scores <33 are now the subject of the 'Evaluation of XIENCE PRIME or XIENCE V versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization' (EXCEL) trial, which is currently recruiting 2600 patients in a randomized trial and 1000 patients into a parallel registry to establish definitively what the optimal revascularization strategy is in this pattern of disease.[105]

The surgically-derived EuroSCORE[106] (EuroSCORE II: pending final validation and publication) and the SYNTAX score may now be fitted in the Global Risk Classification.[102,107] Recently, the Global Risk Classification has been validated in the context of LM revascularization.[108] The levels of recommendation and levels of evidence regarding PCI vs. CABG have been reported in the previous ESC revascularization guidelines.[18] In order to translate the reported evidence into the clinical arena, a summary of recommendations, which include several conditions that decisively influence the indication, is presented in *Table W4*. In general, PCI is initially recommended in patients with single-vessel disease (with or without diabetes mellitus) or in those with multi-vessel disease and low SYNTAX score (<22) and high risk for surgery (EuroSCORE >6). Besides, PCI is also initially recommended in those conditions where surgery may be contra-indicated or at high risk (severe lung impairment, bilateral carotid stenoses, prior mediastinal irradiation, prior CABG with patent left internal mammary artery, prior cardiac non-CABG surgery, age >80 years or frail patients). Frailty should be well assessed eventually by means of currently available indices.[109–111] Conversely, CABG is initially recommended in multi-vessel disease (especially if diabetes mellitus is present) with SYNTAX score >22 or LM disease with SYNTAX score ≥ 33. Other factors swaying the decision towards CABG are intolerance of, or lack of compliance with, dual antiplatelet therapy (DAPT), recurrent in-stent re-stenosis involving the proximal-mid LAD or concomitant structural or valve abnormalities that require surgery. The 'grey zone' when deciding upon the preferred method of revascularization (PCI, CABG, or hybrid treatment) remains in the following conditions: multi-vessel disease with SYNTAX score <22 and EuroSCORE <6, LM disease with SYNTAX score <33, impaired left ventricular function, severe renal insufficiency or dialysis, and peripheral vascular disease. Under those conditions, either option may be recommended. Additional factors relate to centre experience and results, patient/operator/physician preference, availability, and the costs of the procedures (*Figure 5* and *Table W4*).

Table W4 Indications to perform CABG or PCI in stable CAD

Clinical conditions	Type of preferred revascularization[a]
Single-vessel disease, non-proximal LAD, with or without diabetes mellitus.	PCI
Multi-vessel disease with SYNTAX score <22 and high surgical risk (e.g. EuroSCORE >6).	PCI
Revascularization in patient with contra-indication to surgery (severely impaired lung function, prior mediastinal irradiation, prior CABG or non-coronary cardiac surgery, bilateral carotid artery stenoses).	PCI
Elderly patient (>80 years) and co-morbidities or frailty [b]	PCI
Left main disease with SYNTAX score ≥33.	CABG
Multi-vessel disease (with or without diabetes) with LAD involvement and SYNTAX score >22.	CABG
Recurrent in-stent re-stenosis after DES implantation in proximal-mid LAD.	CABG
Revascularization in patients with concomitant significant structural heart disease also requiring surgery.	CABG
Multi-vessel disease or left main disease with SYNTAX score <22 and low surgical risk (e.g. EuroSCORE <6)	CABG or PCI
Left main disease with SYNTAX score <33.	CABG or PCI
Impaired LV function.	CABG or PCI
Renal insufficiency or dialysis.	CABG or PCI

[a]Decision to be taken in a Heart Team meeting.
[b]Frailty defined by means of validated scores (Charlson, Barthel, Frailty scores[10–12])
CABG = coronary artery bypass graft; CAD = coronary artery disease; DES = drug eluting stent; LAD = left anterior descending; LV = left ventricular; PCI = percutaneous coronary intervention.

Finally, new versions of the EUROSCORE and SYNTAX score have been developed (EUROSCORE II and SYNTAX score II) that deserve now prospective validations.

8.5.2 Appropriate utilization of revascularization

The determination of 'optimal' utilization is difficult, both in regard to revascularization and other procedures. Appropriateness criteria are based upon expert consensus as to when a procedure is appropriate, but do not address at all the issues of under-utilization.[112] This is, however, an important and complex area of concern as the cost of imaging and revascularization comes under increasing but appropriate scrutiny,[113,114]

Several studies have looked at the appropriateness of coronary bypass surgery, and in the Northern New England database, 98.6% of procedures were considered appropriate.[115] With regard to PCI in the USA, Chan *et al.* demonstrated a high rate of appropriateness for acute indications, but fewer procedures were considered appropriate in the non-acute setting.[112] Using the Euro Heart Survey on Coronary Revascularization, the conclusion was that treatment decisions in patients with SCAD were largely in agreement with professional guidelines and determined by multiple factors.[116] On the other hand, a study from the National Health Service in the UK, of 1375 patients with suspected stable angina pectoris, demonstrated considerable inequity of access to coronary angiography, with race, income, and gender being prominent determinants.[117]

Several studies from the USA and Europe draw attention to the marked geographical variability in the use of coronary angiography and revascularization procedures and, in some studies, this was independent of age, sex, and income.[118–122] Moreover, conclusions from a study of 3779 patients in the Euro Heart Survey demonstrated evidence to suggest that revascularization rates were strongly influenced by non-clinical-, in addition to clinical factors.[119]

To what extent variability is due to over-utilization vs. under-utilization is not really known, but there is a widespread perception that PCI is over-utilized in patients with chronic SCAD. The reasons underlying this are multifactorial, including the availability of cardiologists and catheterization facilities, the frequency of angiography, the lack of a 'heart team approach', financial considerations, and defensive medicine.[123] Irrespective of these factors, the onus of responsibility rests upon the shoulders of the CV community and the appropriate rates of use are a major concern with important socio-economic implications. What is needed is to establish whether use is appropriate (and if not—why not?) and to be sure that, as a community, evidence-based medicine dominates clinical practice. How we as cardiologists implement coronary angiography and revascularization is integral to the credibility of our profession.

9 Special groups or considerations

9.1 Women

9.1.1 Introduction

Coronary heart disease develops 5–10 years later in women than in men. Nevertheless, CVD is responsible for 42% of premature deaths in women under the age of 75 and for a high proportion of lost disability-adjusted life years, in particular in low- and lower-middle income countries.[124] Recent studies indicate that the decline in mortality from CAD does not extend to younger women, in whom it has remained constant.[125] CVD guidelines in general are based on research conducted primarily in men, the mean percentage of women enrolled in clinical trials since 2006 being 30%.[124]

CAD in women has been a neglected area until about two decades ago, when reports of lower awareness and a less aggressive treatment of CAD in women began to be published.[126–131] These data suggest that stable angina remains under-investigated and under-treated in women.

9.1.2 Risk factors

The considerable decline in mortality from CAD in recent years is mainly caused by population-level improvements in risk factors and by improvements in primary and secondary prevention.[132–134]

CAD risk factors in women and men are the same, although their distribution differs over time and between regions. Smoking seems to be associated with a higher relative risk in women,[135,136] and systolic blood pressure (SBP) increases more with age in women, resulting in higher rates of stroke, LVH and diastolic heart failure. Hypertriglyceridemia is a more important risk factor for CAD in women,[137] and type II diabetes is associated with a higher risk of CAD in women than in men.[138] Women who develop hypertension or impaired glucose tolerance/diabetes during pregnancy are at higher risk of subsequent CAD.

For decades, evidence from epidemiological and laboratory studies led us to believe that circulating oestrogens had a beneficial effect on the risk of CAD. Results from large randomized trials have not supported this; in contrast, HRT increased the risk of CAD in women above the age of 60.[139] The mechanisms are unclear and the possibility remains that HRT may be beneficial if instituted at an earlier age, i.e. at the time of menopause, in women with intact vascular endothelium and few CV risk factors.[140,141] However, at present HRT is not recommended for primary or secondary prevention of CVD.

9.1.3 Clinical presentation

Stable angina is the most common initial presentation of CAD in women and more common than in men.[142] There is a widespread understanding that women with CAD present with symptoms that are different from those in men. Some of this is due to women presenting at older ages and symptoms becoming less specific with advancing age. Thus it is important for physicians to investigate women who present with symptoms suggestive of cardiac ischaemia, and not dismiss them as non-cardiac in origin.[143–145]

9.1.3.1 Angina with obstructive coronary artery disease

Women and men of every age presenting with stable angina have increased coronary mortality relative to the general population.[146] Women with angina who were younger than 75 years, however, had higher standardized mortality ratios due to CAD than men; among those aged 55–64 years, for example, it was 4.7 in women and 2.4 in men.[147] Thus the contemporary prognosis of patients with stable angina is not uniformly favourable. These sex differences are important as they may reflect pathophysiological differences between men and women in the development of CAD.

Several studies have indicated gender-related bias in care of both acute and chronic CAD. In the Euro Heart Survey of Stable Angina, women were less likely to undergo an exercise ECG or coronary angiography and women with confirmed coronary disease were less likely to be re-vascularized, to receive antiplatelet and statin therapy, and less likely to be free of symptoms at follow-up.[130] Some of this difference was due to higher age and co-morbidity. After age-adjustment, women and men had a similar overall prognosis,[148] but among women with confirmed CAD, the multivariable adjusted survival was poorer; they had twice the risk of death or non-fatal MI of their male counterparts during a 1-year follow-up period. Differences in revascularization rates and use of secondary pharmacological prevention did not explain the increased risk in women, indicating that potential treatment bias is not the (sole) cause of higher risk in women with confirmed CAD.

9.1.3.2 Angina with no obstructive coronary artery disease

More than half of women reaching invasive angiograms for stable angina have either no signs of atherosclerosis or $<50\%$ stenotic arteries.[61,149] This condition, which includes a heterogeneous group of patients including 'syndrome X', microvessel disease, and vasospastic angina[150–152] (see sections 6.7.1 and 6.7.2), is much more common in women than in men.[153] Many continue to have recurrent chest pain despite maximal anti-ischaemic treatment; they are substantially limited in everyday life and consume a great deal of healthcare resources.[154] Importantly, these women do not have as benign a prognosis as previously thought; risk of CVD is considerably higher than the background population.[55,155,156] Furthermore, the notion that these women have 'normal' coronary arteries should be reconsidered in the light of the IVUS sub-study from the Women's Ischemia Syndrome Evaluation (WISE), showing that, among a sample of 100 such women, $\sim$80% had definite coronary atherosclerosis which was concealed by positive remodelling.[157] Furthermore, patients with angina and no obstructive coronary disease who have evidence of myocardial ischaemia or impaired CFR have a particularly poor outcome.[55,158] The diagnosis of CAD in women therefore poses unique challenges. Future outcome studies should include well-characterized cohorts where the mechanisms for microvascular angina have been thoroughly studied. In the clinical setting, additional invasive testing aimed at determining the type of coronary dysfunction: for example, acetylcholine or adenosine testing during coronary angiography is required to assess the aetiological mechanisms of chest pain. Further studies are needed to identify appropriate therapeutic strategies but, until sufficient trial-based evidence is available, women with chest pain and no obstructive coronary disease should be screened for CVD risk factors and treated according to risk stratification as described in CVD prevention guidelines,[52] supplemented by individualized symptomatic treatment for angina (see sections 7.5.1 and 7.5.2). In the future, objective demonstration of microvessel disease may identify a group at increased risk that requires more intensive pharmacological treatment to improve prognosis.

9.1.4 Clinical management

9.1.4.1 Diagnostic strategies

The diagnostic accuracy of the exercise electrogram is lower in women (sensitivity and specificity ranging from 60–70%) compared with men (reaching about 80%),[159] which is in part related to functional impairment, precluding women from performing adequate exercise stress tests.[160] Additional reasons leading to diminished accuracy of stress ECG testing in women include ST-segment abnormalities due to menstrual cycle or other hormonal changes, such as peri-menopause and lower QRS voltage.[161–163]

Single photon emission computed tomography (SPECT) is the most commonly used nuclear-based technique for the investigation of women presenting with angina.[164] The diagnostic accuracy is higher than for exercise ECG testing and reaches a sensitivity of 85% and specificity of 70%.[154,160] The accuracy is, however, lower in women with limited exercise capability. For this reason, pharmacological stress using adenosine or dipyridamole is often recommended. In addition, in order to reduce soft tissue attenuation artefacts (due to voluminous breast tissue or obesity) the higher energy technetium (Tc-99m) radioisotope is preferred in women.[165] Computer algorithms for attenuation correction of

SPECT imaging have also resulted in a dramatic improvement in diagnostic accuracy for women with chest pain. Another challenge with the use of SPECT imaging in women is due to their smaller heart size and, consequently, potentially smaller myocardial areas with reduced perfusion that may be missed by currently available SPECT cameras with limited spatial resolution.

Exercise echocardiography is a highly accurate technique for the detection of CAD with a sensitivity of 85% and a specificity of 75%,[160,165] but can be sub-optimal in women due to decreased exercise tolerance, obesity and lung disease limiting acoustic windows; use of pharmacological stress testing (using dobutamine or dipyridamole) may be preferred in women with reduced exercise capacity.

The use of cardiac MRI in detection of ischaemia is described in detail elsewhere. Accuracy in ischaemia detection is superior to SPECT imaging and viability detection is similar to PET imaging.[166] Indeed, cardiac MRI was recently used to demonstrate subendocardial hypoperfusion during the intravenous administration of adenosine in women with chest pain without obstructive CAD.[167] Cardiac MRI therefore has the potential to identify certain subgroups of patients with syndrome X who have subendocardial ischaemia.[168]

Functional testing during angiography may provide a better understanding of the mechanisms that account for chest pain in patients with normal or near-normal angiography.[144,145,153,169] Coronary artery function is most commonly assessed by intracoronary infusion of acetylcholine, which can be done safely.[9] Reduced vasodilatory response of the coronary microcirculation and/or paradoxical vasoconstriction of the epicardial coronary vessels are signs of coronary artery dysfunction. The diagnosis of coronary artery dysfunction is highly rewarding, both to the patient and the physician.

9.1.4.2 Treatment strategies

Pharmacological management recommendations are similar in men and women. Psychosocial and socio-economic factors are increasingly recognized as markers of increased risk of CAD. Women twice as often report depression and anxiety and have a lower socio-economic status that may negatively affect their lifestyle behaviour and medical compliance. Small-scale studies of medical or behavioural intervention have reported varied results and no clear picture emerges regarding improvement in CAD prognosis following treatment of anxiety and depression. Limited evidence suggests that group-based intervention programmes may improve survival in women with CAD but this needs to be confirmed in further studies.[170] Thus current recommendations are to screen for depression and anxiety and refer to specialized care.

Women tend to attend cardiac rehabilitation to a lesser extent than men, presumably due to age, co-morbidity and more often being without a supportive network or a healthy spouse—all important factors in determining uptake of treatment. These factors should be taken into consideration to ensure uptake of cardiac rehabilitation in all groups. Home-based cardiac rehabilitation may be a preferred option in women not able or willing to attend outpatient cardiac rehabilitation.

9.1.4.3 Revascularization procedures

Women have higher procedural complication rates, including mortality, stroke, and vascular complications.[171–174] Part of the difference is due to higher age and frequency of co-morbidities, such as diabetes and hypertension, but higher risk is also related to smaller body size; adjustment for body surface area almost eliminates gender differences in some,[175] but not all, studies,[176,177] emphasizing the importance of other, yet unknown, factors.[178] The gender-based difference in complication rates seems to be greatest among younger women.[176]

Trial data indicate that overall benefit of revascularization is similar in men and women. The Bypass Angioplasty Revascularization Investigation (BARI)[179] showed no sex differences in either early or late mortality after PCI and CABG. Other recent studies focusing on newer treatment strategies,[180–182] such as the use of DES, have reported improved outcomes in women, with results similar to men. In the COURAGE study, there was a trend for interaction with respect to sex toward better effect of PCI in women,[183] but only 15% of the study population were women and, due to power issues, no firm conclusions could be drawn. Nonetheless, it may be prudent to adopt a more conservative approach in undertaking PCI and CABG in women.

9.2 Patients with diabetes mellitus

Mortality due to CVD is increased threefold in diabetic men and two- to fivefold in diabetic women, compared with age- and sex-matched non-diabetic persons.[184] The control of CV risk factors appeared to be efficacious in preventing or slowing CVD in people with diabetes mellitus. Large benefits are seen when multiple risk factors are addressed globally.[185,186] In terms of clinical prevention, recent European Guidelines on CVD prevention[187] consider the sole presence of diabetes mellitus as high risk for the patient. Furthermore, if diabetes mellitus is accompanied by other coronary risk factors or target organ damage, the patient is considered to be at very high risk. In such conditions, CVD prevention should be applied. This must include a target glycated haemoglobin (HbA1c) below 7% (<53 mmol/mol) and target blood pressure <140/80 mmHg. The use of ACE-inhibitors or a renin-angiotensin receptor blocker is recommended for blood pressure control. Metformin should be indicated as first-line therapy if tolerated and not contra-indicated, and statins are recommended to reduce cardiovascular risk in diabetes. Hypoglycemia and weight gain must be avoided and antiplatelet therapy with aspirin is not recommended for people with diabetes, who do not have clinical evidence of atherosclerotic disease. Conversely, both in the acute phase of an acute coronary syndrome and in the chronic phase (>12 months) aspirin is recommended for secondary prevention. Currently, aspirin and clopidogrel are the standard treatments in diabetic patients with SCAD, since the use of new P2Y12 inhibitors has not yet been tested in this scenario. Favourable results were reported with prasugrel in ACS patients undergoing coronary stenting over 15 months of follow-up.[188] However any use of prasugrel or ticagrelor in SCAD diabetic patients would be 'off-label', as no trial has so far been performed in this population.

The clinical manifestations of CVD in diabetic subjects are similar to those in non-diabetic patients. In particular, angina, MI, and heart failure are the most prominent and tend to occur at an earlier age. The cardiac assessment of symptomatic ischaemia in diabetic patients should follow the same indications as for patients without diabetes. It is agreed that the prevalence of silent ischaemia is higher in diabetic patients. However, routine screening for CVD in asymptomatic

patients is not recommended as it does not improve outcomes as long as CVD risk factors are treated.[189] This statement is based on various premises. Firstly, intensive medical therapy may provide equal outcomes to invasive revascularization.[183,190] There is also some evidence that silent myocardial ischaemia may reverse over time.[191] Finally, the recent randomized observational Detection of Ischaemia in Asymptomatic Diabetic (DIAD) trial demonstrated no clinical benefit in routine screening of asymptomatic patients with type 2 diabetes mellitus and normal ECGs.[192] The role of new non-invasive CAD screening methods—such as CT angiography—in asymptomatic diabetic patients has been addressed in several studies.[193–195] The role of these tests beyond risk stratification is not clear. Their routine use leads to radiation exposure and may result in unnecessary invasive testing, such as coronary angiography and revascularization procedures. The ultimate balance of benefit, cost, and risks of such an approach in asymptomatic patients remains controversial, particularly in the context of optimal antidiabetic and coronary risk factor therapy.[183,186,191]

Coronary artery revascularization of diabetics remains a challenge, morbidity and mortality being increased in diabetic patients undergoing PCI or CABG, as compared with non-diabetic patients.[196,197] At the point of deciding the need for revascularization in stable CVD, one should keep in mind the results of the BARI 2D trial (see above)[191], with its comparable outcomes with medical treatment or revascularization (PCI or CABG). Patients treated with CABG showed much greater atherosclerotic burden and more lesions than the PCI stratum. Prompt revascularization significantly reduced the major adverse cardiac events (MACE) rate in those patients treated with CABG, largely because of a reduction in MI events, but not among those selected to undergo PCI, as compared with OMT. The Design of the Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM)[198] trial of 1900 patients with multi-vessel disease (triple-vessel disease in 87%) demonstrated a significant reduction on the primary outcome of death, non-fatal MI, and non-fatal stroke at 5 years in patients treated with CABG vs. PCI (18.7 vs. 26.6%; $P = 0.005$). This is primarily driven by a reduction in the rates of MI and all cause death ($P = 0.049$) with a higher rate of stroke in the CABG group (5 year rates of 5.2 vs. 2.4 %; $P = 0.03$). The benefit of CABG over PCI was observed independently of the SYNTAX score, which could not discriminate patients preferentially for one or the other technique of revascularization.

When taken into conjunction with the results of the BARI 2D trial,[191] the diabetes subgroup in SYNTAX and subset analyses of patients at higher risk in the BARI 2D trial, there is now clear evidence that, in diabetics with complex multi-vessel disease—and in particular 3 vessel disease—there is a significant mortality benefit from bypass surgery over. PCI and also a reduction in the rates of non-fatal MI, but the rate of non-fatal stroke, although relatively low in both groups, is doubled in the CABG population.

The decision to use either PCI or CABG as preferred mode of revascularization should be based on anatomical factors (see above), together with clinical factors and other logistical or local factors (*Figure 10*). As a rule, PCI is recommended in diabetics with single-vessel disease. Conversely, CABG should be performed in diabetics with multi-vessel disease but both strategies may be performed, always after discussion in a heart team meeting, especially for the patients with double-vessel disease or without LAD involvement where FREEDOM does not bring definite conclusion.[199–201] If PCI is decided upon, the use of DES has been demonstrated to be more efficacious, as compared with BMS, in preventing restenosis.[202,203] Additional issues should be taken into account when performing PCI in a diabetic patient. Diabetes mellitus *per se* represents a high risk for contrast-induced nephropathy, and risk evaluation should be performed and adequate measures of prevention taken before contrast administration (hydration, interruption of metformin, choice of contrast media, etc.).

9.3 Chronic kidney disease

Chronic kidney disease (CKD) is a risk factor for—and strongly associated with—CAD and has a major impact on outcomes and therapeutic decisions. CVD mortality is increased by a factor of five in patients with end-stage renal disease and, even in patients not on dialysis, impaired renal function is an independent predictor of CAD.[204,205] Hence, patients with CKD should be closely monitored for symptoms suggestive of CAD. While MPI carries prognostic value in end-stage renal disease patients who are asymptomatic for CAD,[206] no data exist that demonstrate a clinical benefit in 'screening' perfusion imaging, followed by revascularization, in such patients.[207,208]

The work-up of suspected CAD in symptomatic patients with renal disease follows the same patterns as in patients with normal renal function. Two issues merit consideration: the presence of impaired renal function increases the PTP of CAD in patients who report chest pain, and non-invasive test results need to be interpreted accordingly; also, the use of iodinated contrast agent should be minimized in patients with pre-terminal renal failure and in dialysis patients with preserved urine production, in order to prevent further deterioration of kidney function. Decisions regarding diagnostic modalities should be made accordingly. Similarly, special attention should be paid to the drugs that are renally cleared and may need dose down-adjustment or substitution.

Upon demonstration of CAD, the same treatment options are available for patients with renal failure as for patients with normal renal function. Medical treatment for risk modification should be intensive.[209] Revascularization options include PCI and bypass surgery. Data regarding the choice of one over the other in patients with renal failure are conflicting. In general, coronary bypass surgery is associated with higher procedural mortality and a greater likelihood of haemodialysis in non-haemodialysis-dependent patients after revascularization,[210] while available studies suggest a trend towards better long-term survival, as compared with PCI.[211]

9.4 The elderly

There is a growing elderly population with stable CAD that cumulate the risks discussed above (gender, diabetes, renal insufficiency) and other morbid conditions. This specific population has been dramatically under-represented in recent randomized trials in stable CAD. In the elderly, there is an equal prevalence of CAD in men and women,[212] and CAD has specific characteristics in this population, with a more diffuse and severe disease that incudes higher prevalence of LM stenosis, multi-vessel disease, and impaired LV function. The evaluation of chest pain syndromes is also more difficult because

atypical complaints or situations related to co-morbid conditions may less easily orient towards angina pectoris.[213]

In stable CAD, stress imaging, as well as stress ECG, might be challenging in the elderly, while functional capacity often is compromised from muscle weakness and deconditioning. The higher prevalence of disease means that exercise tests more frequently result in false-negatives;[214] false-positive test results may also be more frequent because of the higher prevalence of confounders, such as prior MI or left ventricular hypertrophy (LVH). The number of false-positive test results could be limited by excluding patients who have a borderline or non-interpretable resting ECG. Despite these differences, exercise stress testing remains important in the elderly and should remain the initial test in evaluating elderly patients with suspected CAD unless the patient cannot exercise, in which case it may be replaced by pharmacological stress imaging. If a stress test is feasible (which is the case in about 50% of patients), it provides important prognostic information: a negative test on medical therapy indicates a good 1-year prognosis, such that these patients can be managed medically.[215] Elderly patients with objective evidence of significant ischaemia at non-invasive testing should have the same access to OMT or coronary arteriography as younger patients. However, side-effects, intolerance and overdosing of drugs are more frequent,[216] as are procedure-related complications (compared with younger patients) including access-site bleeding or contrast-induced nephropathy.[217,218] Accordingly, radial access should also be encouraged in elderly patients undergoing elective angiography in experienced centres and measures undertaken to prevent contrast-induced nephropathy.[219] After discharge, these patients have a higher chronic bleeding risk on prolonged DAPT, more frequently have an indication for anticoagulation (e.g. atrial fibrillation) and have a higher risk of poor compliance to treatment.

Revascularization decisions are also more challenging in elderly patients. In patients with multivessel disease and/or LM stenosis, age might have a great impact on whether to choose PCI or CABG. Scores, as described earlier, do not take into consideration the frailty of the elderly patient, which may be evaluated in some cases by dedicated geriatric consultation. Despite high risk scores, patients are more frequently referred for PCI revascularization; the choice of stent is also a matter of great debate. Indeed, elderly patients might benefit from DES to avoid repeat hospitalization or revascularization related to re-stenosis, but these patients also have a higher bleeding risk on prolonged DAPT, more frequently have an indication for anticoagulation (e.g. atrial fibrillation), have a higher probability of invasive procedure within months following stent implantation, and have a higher risk of poor compliance to treatment. Thus, decision should be made on an individual basis and new-generation DES, allowing shorter duration of DAPT, might extend the use of DES in this population.

The TIME study, which randomized patients with SCAD despite standard therapy to an invasive vs. an OMT strategy, showed that patients aged $\geq$75 years (mean 80 years) benefited from revascularization over OMT in regard to faster symptom relief and better quality of life (QoL).[81] The invasive approach carries a small early intervention risk, while medical management poses an almost 50% chance for later hospitalizations and revascularizations for increasing or refractory symptoms. This resulted in a similar mortality, symptom status and QoL after 1 year for both groups,[220] but after 4 years, non-fatal events occurred more frequently in OMT patients and survival was better for patients who were revascularized within the first year (on treatment)[82]. Elderly women differed from men in disease presentation, perception and outcome; despite similar angina at baseline and lower disease severity they had a lower QoL and worse survival.[221]

9.5 The patient after revascularization

Secondary prevention and cardiac rehabilitation are essential parts of long-term management after revascularization because such measures reduce future morbidity and mortality.[18,222–224]

Therapy and secondary prevention should be initiated during hospitalization when patients are highly motivated. Cardiac rehabilitation includes comprehensive patient education in addition to structured rehabilitation and exercise programs in a variety of medical institutional and community settings. Adherence to lifestyle and risk factor modification requires individualized behavioural education and can be implemented during exercise-based cardiac rehabilitation. Education should be interactive, with full participation of patient care providers, providing an explanation for each intervention, while early mobilization and physical conditioning should vary according to individual clinical status.[222,225,226]

Follow-up strategies should focus on the assessment of the patients' symptoms, functional status and secondary prevention, and not only on the detection of re-stenosis or graft occlusion. Although the rate of re-stenosis has somewhat diminished in the DES era, a sizeable proportion of patients are still treated with BMS or balloon angioplasty, with higher recurrence rates. Likewise, the durability of CABG results has increased with the use of arterial grafts, and ischaemia stems mainly from saphenous vein graft attrition and/or progression of CAD in native vessels. Recent studies emphasized the importance of progression of CAD in up to 50% of non-revascularized vessels after 3–5 years of follow-up, presenting as sudden cardiac death, MI, ACS, SCAD or silent ischaemia (silent perfusion defects in 70% of 5-year scintigraphic studies in unselected patients).[227,228]

Computed tomography angiography can detect occluded and stenosed grafts with very high diagnostic accuracy.[229,230] However, assessment should not be restricted to graft patency but should include evaluation of the native coronary arteries. This will often be difficult because of advanced CAD and pronounced coronary calcification. Furthermore, it is acknowledged that anatomical imaging by CT angiography does not assess ischaemia, which remains essential for therapeutic decisions. CT angiography can detect in-stent re-stenosis, depending on stent type and diameter, yet the aforementioned limitations equally apply. Patients who have undergone unprotected LM PCI may be scheduled for routine control CT or invasive angiography within 3–12 months. Otherwise, routine invasive control angiography is not recommended.

9.6 Repeat revascularization of the patient with prior coronary artery bypass grafting revascularization

Repeat revascularization in the patient who has undergone prior CABG poses a clinical challenge. The large numbers of patients who have undergone prior bypass surgery in the developed world, the aging of the population, and the high attrition rate of saphenous

vein grafts results in a growing number of such patients requiring management of recurrent angina.[231–233]

The indications for repeat revascularization are in general based upon similar indications determining the primary procedure. Nonetheless these may need to be tailored to whether the return of symptoms is due to re-stenosis, progression of disease in native vessels or in bypass grafts and to the extent of LV dysfunction and the suitability of target vessels and conduits. Considerations in determining the preferred modality of revascularization include the age of patients, co-morbidities and diffuseness of coronary disease, as well as the potential for damage to patent grafts, intraluminal embolization in saphenous vein grafts, lack of suitable arterial and venous conduits, and instability of a graft independent circulation. With regard to survival, the critical factor is patency of the LAD system. In patients with graft disease of the right coronary and circumflex systems, the target of revascularization is symptom relief.[234–236]

PCI may be preferred in patients with discrete lesions in grafts and preserved LV function, native vessel disease, saphenous vein graft disease more than 3 years post-CABG, and patients without available conduits for a new CABG. Repeat bypass surgery may be preferred when the vessels are unsuitable for PCI, when there is a large number of diseased bypass grafts, when there are chronically occluded native arteries, and when there are good distal vessel targets for bypass graft placement and available graft material. PCI is not recommended for chronic total vein graft occlusions, for multiple target lesions plus multi-vessel disease, for failure of multiple saphenous vein grafts, or in patients with severe LV dysfunction, unless repeat CABG poses excessive risk due to severe co-morbidities and poor distal vessels.[237] The use of distal embolic protection devices is strongly recommended in saphenous vein graft interventions, although often not utilized. Any revascularization strategy needs to be accompanied by optimizing medical therapy with anti-anginal drugs and risk factor reduction.

9.7 Chronic total occlusions

Chronic total occlusions are identified in 15–30% of all patients referred for coronary angiography.[238–240] In theory, the indications for revascularization of a CTO should be the same of a sub-total stenosis provided that viability, ischaemia of a sufficiently large territory and/or anginal symptoms are present.[241] In reality, only a very small percentage of all occlusions are treated percutaneously or with CABG, and guidelines have wrongly contributed to this unfair discrimination by applying the results of the Occluded Artery Trial (OAT),[242] conducted in sub-acute and often sub-total occlusions post-ST elevation myocardial infarction (STEMI).

While this trial is relevant in confuting the 'open artery hypothesis', the opportunity to open the culprit artery post-Q wave MI also if no viability or ischaemia are present, its results cannot be applied to CTOs which have no previous STEMI in 60% of cases and must, by definition, have proof of viability or ischaemia or be the cause of symptoms refractory to medical treatment.[243–246] In fact, patients with CTO are among the few stable angina subgroups with strong indirect evidence that a successful outcome may lead to a mortality benefit.[247–251] The comparison of surgical vs. PCI registries identifies the presence of a persistent occlusion of one or more arteries in the PCI arm as one of the most powerful predictors of worse outcome, in comparison with complete surgical revascularization.[99,252] Also among patients treated with PCI, failure to recanalize an occlusion is a powerful predictor of increased mortality and subsequent need for further revascularization. Previous cohort studies have rather consistently reported improved survival with successful vs. failed CTO PCI.[253–257] A recent meta-analysis on mortality with successful vs. failed CTO PCI in 13 non-randomized cohort studies, showed a significant 44% reduction in mortality with successful CTO PCI.[258] This may at least in part be a result of a less-favourable clinical profile of patients with failed PCI, rather than the beneficial effect of recanalizing a CTO, and two randomized trials have been promoted to confirm this hypothesis. The mechanism of the mortality benefit is probably multifactorial, with improvement of regional wall motion in hibernating segments playing a role.[259–261] The untoward consequences of disease progression in patients with a pre-existing CTO probably play the main role in the worse outcome patients with isolated CTO have when compared with other SVD patients. The presence of a CTO in a non-infarct-related artery is an independent predictor of mortality after STEMI and a multicentre randomized trial is currently in progress to investigate the clinical benefit of opening a CTO in a non-culprit vessel within one week after an acute STEMI.[262–264]

Percutaneous coronary intervention of CTOs is technically challenging and requires familiarity with advanced techniques and specialized equipment. The complexity of percutaneous treatment of CTOs is illustrated by the relatively low procedural success rates observed in CTOs (60–85%) compared with sub-total stenoses (>98%).[253,265,266] The wide range of success rates varies with the operators' experience and familiarity with techniques such as bilateral injection to visualize the distal artery via contralateral collaterals, anchoring of the guiding catheter, guide extension with telescopic daughter guides, standard use of over-the-wire technique, often via dedicated microcatheters (Corsair, Tornus, Finecross, etc.), balloon trapping, IVUS guided re-entry or identification of entry point in stumpless occlusions, retrograde approach, wire knuckling, wire externalization, etc.[267–287] Familiarity with these techniques influences not only the success rates but also the complexity of the CTO cases attempted, with large centres documented as accepting less than 2% of all the CTOs studied for PCI. Treatment denial, avoiding referral to dedicated centres and operators, appears particularly cruel in symptomatic patients who experience major symptom relief and quality of life improvement post-procedure.[288] The long-term success of percutaneous CTO recanalization has been improved by the introduction of DES, which have dramatically reduced re-stenosis rates, compared with BMS.[289–294] A recent meta-analysis showed that DES use in CTO recanalization is associated with lower target vessel revascularization (TVR).[294–303]

Surgical treatment with the implantation of a distal bypass graft is a valid alternative, especially with a left internal mammary artery (LIMA) on the LAD,[91,304] and is technically easier. There are challenges related to the incomplete filling of the distal vessels, which may conceal diffuse disease or post-anastomotic stenoses. Recent studies show that CABGs are implanted in approximately two-thirds of the CTOs initially planned. Obviously CABG has limited indications in non-LAD single-vessel CTOs and might not be feasible because of co-morbidities or in the frequent scenario of patients with previous CABG and late occlusion of the SVGs on occluded right coronary artery/left circumflex with LIMA still patent.

9.8 Refractory angina

The term 'refractory angina' is defined as "a chronic condition caused by clinically established reversible myocardial ischaemia in the presence of CAD, which cannot be adequately controlled by a combination of medical therapy, angioplasty or coronary artery bypass graft".[74] For this patient group, a number of treatment options have emerged, including some new pharmacological options (see section 7.1.3.2 on drugs) and non-pharmacological treatments such as enhanced external counterpulsation (EECP), neurostimulatory techniques [transcutaneous electrical nerve stimulation (TENS); spinal cord stimulation (SCS)], and angiogenesis through non-invasive techniques (extracorporeal cardiac shock wave therapy) or invasive techniques such as transmyocardial laser revascularization (TMR), percutaneous myocardial laser revascularization (PMR) or stem cell/gene therapy (preclinical or investigational).

Enhanced external counterpulsation (EECP) consists of the application of three pairs of pneumatic cuffs placed on the lower extremities, at the levels of the calves and lower and upper thighs. Cuff inflation and deflation are synchronized with the ECG. ECG-synchronized sequential cuff inflation and deflation increases venous return and (analogous to intra-aortic balloon pump) decreases afterload. The early diastolic pressure is increased beyond the systolic, resulting in hyper perfusion of coronary, cerebral and other proximal vascular beds. A typical course consists of 35 hour-long sessions over 7 weeks. Among contra-indications are abdominal aortic aneurysm >5cm, uncontrolled hypertension, severe aortic regurgitation and severe peripheral artery disease (PAD).

Evidence on the performance of EECP comes from non-randomized studies and international registries involving approximately 15 000 patients and several small randomized, controlled trials.[305–307] The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP)[308] randomized trial ($n = 139$ patients) demonstrated a 15% rise in the time to the onset of 1 mm ST-depression and 25% fewer angina episodes per week. In the prospective evaluation of EECP in heart failure trial,[309] 187 patients with chronic heart failure (70% with ischaemic background) were randomized to conventional treatment or EECP therapy, which was shown to improved exercise tolerance, quality of life, and New York Heart Association (NYHA) functional classification. Possible mechanisms of action included improved LV diastolic filling, improved endothelial function, increased collaterals, neurohormonal and cytokine changes and a peripheral training effect. These mechanisms were identified in small randomized studies.[310–315] The effect of EECP on invasively measured collateral development was studied in two randomized trials. Gloekler *et al.*[310] randomized 20 SCAD patients to 30 sessions of active EECP or sham therapy. A total of 34 vessels without coronary intervention were studied with intracoronary haemodynamics. The invasive collateral flow index changed from 0.125 at baseline to 0.174 in the EECP group ($P = 0.006$), and from 0.129 (0.122) to 0.111 (0.125) in the sham group ($P = 0.14$), while the change of coronary collateral conductance (mL/min/100 mm Hg) was from 0.365 to 0.568 in the EECP group ($P = 0.072$), and from 0.229 to 0.305 in the sham group ($P = 0.45$). The effects of EECP on coronary collateral function was also investigated by Buschmann *et al.*,[311] who randomized 23 SCAD patients (2:1 ratio of EECP to control) who underwent invasive measurement of coronary haemodynamics at baseline and after 35 EECP sessions. The collateral flow index increased significantly in the EECP group, from 0.08 ± 0.01 to 0.15 ± 0.02; ($P < 0.001$) and FFR from 0.68 ± 0.03 to 0.79 ± 0.03; ($P = 0.001$) while, in the control group, no significant change was observed. The effects of EECP on large and small artery properties were also investigated in recent randomized studies. Casey *et al.*[312] randomized (on a 2:1 ratio) 42 patients to active EECP or sham treatment and assessed arterial stiffness and aortic wave reflection. In the EECP group, augmentation index decreased significantly from $29.1 \pm 2.3\%$ to $23.3 \pm 2.7\%$ ($P < 0.01$) and PWW decreased from 11.5 ± 0.5 m/sec to 10.2 ± 0.4 m/sec ($P < 0.01$) while there was no significant change in the sham group. They also measured exercise capacity and peak oxygen uptake (VO_2 max), in mL/kg/min, increased in the EECP group from 17.0 ± 1.3 to 19.4 ± 1.5, whilst it remained unchanged in the sham group (16.5 ± 1.3 to 16.6 ± 1.4) ($P < 0.05$). Levenson *et al.*[313] randomized 30 SCAD patients to 35 sham or real EECP sessions and found a significant reduction in β stiffness index and carotid vascular resistance in the EECP group, as assessed by carotid ultrasound. The effects of EECP treatment on endothelial function and the release of vasoactive agents and cytokines were studied in some recent RCTs. Braith *et al.*[314] randomized 48 patients 2:1 to real or sham EECP and showed that EECP significantly increased FMVD in brachial (+51 vs. +2%) and femoral (+30 vs. +3%) arteries, whereas it decreased endothelin-1 (−25 vs. +5%) and the asymmetric dimethylarginine (-28 vs. +0.2%) and improved angina symptoms. In a study by Casey *et al.*,[315] 30 patients with SCAD were randomized 2:1 to a full 35 h sessions of either active or sham EECP. The EECP group had a significant reduction in TNF-α (6.9 ± 2.7 vs. 4.9 ± 2.5 pg/mL, ($P < 0.01$) and MCP-1 (254.9 ± 55.9 vs. 190.4 ± 47.6 pg/mL, ($P < 0.01$). Levenson *et al.* also investigated the effect of a single 1 h session of EECP treatment on plasma and platelet cyclic guanosine monophosphate (cGMP) in a sham-controlled randomized clinical study in 55 subjects (30 with proven SCAD and 25 asymptomatic with high CVD risk)[316]: The counterpulsation-induced cGMP increase was twice as large in subjects receiving active EECP treatment, compared with those serving as a sham group. EECP increased platelet cGMP content, which suggests nitric oxide synthase activation. In a meta-analysis of 949 patients, anginal class was improved by one CCS Class in 86% of patients.[317] Older registries have suggested similar functional improvements.[318] The results of these studies proving the concept and clinical effects of EECP treatment lead to the recommendation that EECP therapy should be considered for symptomatic treatment in patients with invalidating refractory angina. Larger RCTs with stronger clinical endpoints are required to define the precise role or EECP.

Transcutaneous electrical neural stimulation (TENS) involves applying a low voltage electrical current via pads placed on the skin in the area of pain. The technique primarily works via the 'gate control' theory of pain. Stimulating large-diameter afferent fibres inhibits input from small diameter fibres in the substantia gelatinosa of the spinal cord.[319] The activation of an endogenous opioid pathway or an increased endorphin concentration in blood and cerebrospinal fluid may also be involved.[320] This technique may induce mild secondary effects, such as skin irritation, paraesthesiae, and pacemaker interaction. In a small series of patients with pacing-induced angina,[321] TENS demonstrated an increased tolerance to pacing, improved lactate metabolism, and less-pronounced ST-segment depression. No data on the long-term efficacy have been reported. The benefits of TENS are

that it is a passive, non-invasive, non-addictive modality with no potentially harmful side-effects. It may be used as a test method for planned SCS implantation, to determine whether myocardial ischaemia is really the cause of the patient's pain and to evaluate whether the patient shows good enough compliance to handle a spinal cord stimulator.[322] Thus, TENS is a potentially harmless technique that may be useful to ameliorate symptoms, although efficacy in the long term is unknown.

Spinal cord stimulation (SCS) consist of the antidromic activation of the dorsal column fibres, which activate the inhibitory interneurons within the dorsal horn by means of positioning an electrode epidurally between levels C7 and T1. Implantation of the SCS is performed under local anaesthesia. The electrode is positioned by puncturing the epidural space at T6–7, so that paresthesia is produced in the region of anginal pain radiation. The patient carries the pulse generator in a subcutaneous pouch below the left costal arch. The pulse generator is connected to the epidural lead with a subcutaneous connection wire. The efficacy of SCS is supported by several randomized trials and small controlled studies. A recent meta-analysis of seven randomized trials,[323] including 270 patients with refractory angina, demonstrated that SCS improved outcomes (specifically exercise capacity, health-related QoL and a trend in ischaemic burden) when compared with 'no-stimulation'. Few adverse events were reported. These included infection (1%) and lead migration/fracture (7.8%). In a recent multicentre European registry including 235 patients (110 finally receiving SCS), the implanted patients reported fewer angina attacks, reduced nitroglycerin consumption, improved CCS class, and improved QoL in all dimensions of Short Form (SF)-36 and the Seattle Angina Questionnaire, up to 1 year follow-up.[322] A few small randomized trials have been performed.[324] Larger randomized trials with longer follow-up are clearly needed. Thus, SCS is a reasonable therapeutic alternative in patients with refractory angina pectoris that has the potential to ameliorate symptoms and improve QoL. Evidence regarding reduction in both ischaemia burden and mortality is currently lacking.

Transmyocardial laser revascularization (TMR) and PMR have been evaluated by NICE.[325] The evaluation of TMR included 10 randomized, controlled clinical trials, involving a total of 1359 patients. Seven of the trials compared TMR with continued medical management and, in two trials, CABG was compared with a combination of TMR and CABG. It was demonstrated that while there was an improvement in the more subjective outcome measures (including exercise tolerance testing, angina score, and QoL) this was counterbalanced by a higher risk of post-operative mortality and morbidity (including MI, heart failure, thrombo-embolic events, pericarditis, acute mitral insufficiency, and neurological events). In the same way, the evaluation of PMR included five randomized trials. As a conclusion, overall mortality was not increased. However, morbidity (MI, ventricular perforation and tamponade, cerebrovascular events, and vascular complications) was also increased by PMR. Thus current evidence on both TMR and PMR for refractory angina pectoris shows no efficacy and may pose unacceptable procedural-related risks. Therefore, these procedures should not be used.

Extracorporeal shockwave myocardial revascularization is under investigation. This technology uses low-intensity shockwaves (one-tenth the strength of those used in lithotripsy) that are delivered to myocardial ischaemic tissue. Shockwaves, created by a special generator, are focused using a shockwave applicator device. The treatment is guided by standard echocardiography equipment. The shockwaves are delivered in synchronization with the patient's R-wave to avoid arrhythmias. At first, the patient undergoes stress SPECT testing to identify the ischaemic areas. Following that, the same area is localized by the ultrasound device and the shockwaves are focused on the ischaemic area. Several treatments are required for optimal results. A small study ($n = 9$ patients) has reported an improvement in symptoms and in functional class score.[326] More data are needed before establishing a potential recommendation.

9.9 Primary care

The treatment objectives in SCAD are to improve:

- patient symptoms, and hence QoL
- prognosis by preventing MI and death.

Primary care physicians have a key role in ensuring that patients understand the benefits of medical therapy, together with any potential intervention, and that medication, together with positive lifestyle measures, are reviewed and optimized to ensure improved outcomes.[327]

In order to achieve this, there need to be systems in place to ensure regular surveillance and evaluation of patients' therapy—together with re-appraisal of their risk factors and any change in clinical status—at appropriate intervals.

To improve prognosis, physicians need to ensure that all patients are prescribed appropriate antithrombotic therapy. Single antiplatelet therapy (SAPT) (aspirin or clopidogrel) is recommended in the long term for all those with established CAD.[328,329] DAPT is recommended, for up to 1 year, in those patients undergoing PCI with a DES. In those receiving a BMS, 4 weeks of DAPT is recommended.[330,331]

All patients with CAD require lipid-modification therapy, in line with current guidelines and targets. Those with diabetes, post-MI, LV systolic dysfunction, renovascular disease and hypertension should also be prescribed ACE inhibitors to improve their long-term prognoses.

Particular attention needs to paid to optimal control and management of co-morbidities, including hypertension, diabetes mellitus, dyslipidaemia, and renovascular disease. Intensifying management of these conditions, together with addressing adverse lifestyle factors—including smoking—is important in modifying the atherosclerotic disease process.

Those patients identified with symptoms suggestive of ongoing myocardial ischaemia, despite optimal medical and lifestyle intervention, represent a high-risk cohort, with increased morbidity and mortality. They require early re-assessment and consideration of referral for further evaluation, to exclude high-risk coronary anatomy that may be suitable for revascularization.

9.10 Gaps in evidence

These Guidelines suffer from the absence of conclusive evidence on many of the recommendations issued, as reflected by the large number of recommendations having type C evidence. Risk stratification suffers from the small size of the existing registries and the variability of the inclusion criteria, skewing the population studied towards the high-risk patients treated in tertiary referral academic centres. The prevalence of SCAD in the elderly, often not seeking medical attention or only evaluated by their primary care physicians,

is probably underestimated. While the 'leitmotif' of these Guidelines is the warning against the excessive use of redundant diagnostic tests and unnecessary interventions, we must caution the reader that stable coronary syndromes are still under-diagnosed and under-treated, especially in terms of secondary prevention. The evidence supporting the use of specific imaging modalities often comes from small, uncontrolled, single-centre observational studies. This explains the caution used in these Guidelines in prompting the use of expensive and sophisticated imaging modalities that are still of limited availability, with great emphasis on clinical findings and risk factors. The technical progress allowing high-quality imaging of the coronary arteries with multislice CT has clinical implications not yet clarified by longitudinal studies. The concept of plaque characterization and vulnerability remains a challenge for the future. Modern pharmacology and rapid myocardial revascularization are well established therapeutic modalities in ACS, but most trials with new antiplatelet and antithrombotic agents have excluded stable CAD patients, with very few pharmacological or revascularization trials focusing on stable CAD either in progress or expected.[332–335] The indications for myocardial revascularization in stable CAD come from very old studies and the universal use of statins, β-blockers, and ACE inhibitors—as well as the major epidemiological changes of the last two decades (reduction of the smoking habit; attention to healthy diet)—may have improved the results of medical treatment. The revascularization techniques have also greatly improved, with better long-term results with the use of the internal mammary artery in surgery and DES in interventional cardiology. The net effect of these changes cannot be assessed without large, repeated, randomized trials of contemporary medical therapy and revascularization. The existing trials deal with an angiographically selected low-risk population, with outcomes skewed by a high percentage of crossover from medical treatment to angioplasty. Bare metal stents and 'eyeballing' lesion severity led to opposite conclusions to those of the FAME 2 trial with universal use of FFR and DES, but the difference is only caused by different end-point selection, with no changes in either trial on 'hard' endpoints, such as mortality. The only indirect evidence that angioplasty can have prognostic benefit in patients with stable CAD comes from comparative studies with surgery in three-vessel and LM disease. With first-generation DES there is still an advantage for surgery in complex disease and diabetic patients.[336] The equivalence shown in simpler cohorts, including patients with LM disease, is under investigation in new trials exploiting the reduction in re-stenosis and stent thrombosis offered by second generation DES and new antiplatelet agents.

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CME questions for this article are available at: European Heart Journal http://www.oxforde-learning.com/eurheartj and European Society of Cardiology http://www.escardio.org/guidelines.

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