STABLE CORONARY ARTERY DISEASE

Definition

Stable coronary artery disease is a non-acute condition due to atherosclerosis of epicardial coronary arteries and/or microcirculation and is diagnosed following a diagnostic ischaemia test or an acute coronary syndrome.

Presentation

Patients with CAD may be asymptomatic or present with angina pectoris or an acute coronary syndrome (unstable angina or MI), congestive heart failure, cardiac arrhythmias, or sudden death. **Angina pectoris** affects almost one-quarter of patients with stable coronary artery disease (Figures 1and 2).[1] Angina is characterized by substernal discomfort, heaviness, or a pressure-like feeling, which may radiate to the jaw, shoulder, back, or arm. It does not resemble localized, stubbing pain. These symptoms are usually brought on by exertion, emotional stress, cold, or a heavy meal and are relieved by rest or nitrates (Table 1). Angina equivalents are SOBOE, epigastric discomfort, fatigue, or faintness, particularly in elderly patients. Pain that is stabbing, positional or reproducible with palpation is usually noncardiac. Differential diagnosis of acute chest pain is discussed in detail in the Chapter of ACS diagnosis.

Physical Examination

May be unremarkable. Hypertension, xanthelasma, decreased peripheral pulses, carotid or renal artery bruits, abdominal aortic aneurysm may be present. History may reveal smoking, diabetes or family history of MI before age of 60 years.

Cardiac auscultation

May reveal S3 or S4 or MR particularly during an episode of chest pain (LV or papillary muscle dysfunction). Crepitations over the lung bases in ischemic heart failure.

Investigations

Initial Investigations

History and basic **biochemistry** are essential (FBC, lipids, glucose, creatinine, markers of myocardial damage, as well as thyroid function tests, lipids, and oral glucose tolerance test (Table 2).[2] In patients with established coronary artery disease, the oral glucose tolerance test identifies the largest number of patients with previously undiagnosed diabetes compared to fasting plasma glucose (*OGTT*) and glycated haemoglobin (*HbA1c*). It has been considered necessary if fasting plasma glucose and HbA1c are inconclusive.[3] However, because people

with OGTT-diagnosed diabetes without diagnostic HbA1c have a risk of cardiovascular disease and chronic kidney disease similar to that of the diabetes-free population, replacement of OGTT with HbA1c-based diagnosis appears justified.[4] High-sensitivity assayed *troponin I,* with values above the limit of detection in up to 80% in the general population is a cardiac-specific marker of global cardiovascular risk.[5] *Lp(a)* should be measured at least once in adults.[6] Young patients with early CAD should be also investigated for the possibility of familial hypercholesterolemia.

12-lead resting ECG is essential. It is normal in approximately half of patients with stable angina, even with severe CAD. ST-T wave changes, Q waves, LV hypertrophy, LBBB, AV block, AF and ventricular arrhythmias may be present, and are associated with worse prognosis. During an episode of angina pectoris, approximately 50% of patients with normal findings on resting electrocardiography develop ECG abnormalities, usually ST-T depression.

Ambulatory ECG monitoring may also be useful in suspected arrhythmias or vasospastic angina.

Chest X-ray may be useful in suspected heart failure, valvular heart disease, pericardial disease or aortic dissection/aneurysm, or clinical evidence of pulmonary disease. In the era of echocardiography and CT scan its clinical importance is diminished.

Chest CT may disclose coronary artery calcification and anatomic cardiac abnormalities. The detection of pulmonary nodules at cardiac computed tomographic angiography results in a small relative reduction in lung cancer mortality of 8% at 3 years, and imaging of the entire thorax might be considered during tomographic imaging of the coronary arteries or coronary calcium, although the cost-effectiveness of subsequent follow-up testing is questionable.[7, 8]

Echocardiography LV function is the major predictor of long-term survival in patients with CAD. MR or other concomitant abnormalities may be seen. Correspondence of LV segments with coronary arteries is presented in Figure 3. [9]

Considerations of the pre-test probability of CAD are presented in Table 3 and Figures 4-6.

Assessment of Myocardial Ischaemia

Diagnostic tests for the detection of myocardial ischemia are most useful in patients with an intermediate pretest probability of CAD (Bayes theorem), and are recommended for all patients with an intermediate or high probability of CAD.

Exercise treadmill test is indicated in all patients with angina or intermediate pre-test probability of CAD. All stress tests are contraindicated within 2 days after acute MI, in symptomatic severe AS, and decompensated heart failure. Exercise treadmill test is nondiagnostic in patients with LBBB, WPW syndrome, paced rhythm, intraventricular conduction delay, and digoxin therapy. Due to low sensitivity and specificity the test is of less prognostic value in low-risk populations such as women, although it might be still be useful

as the initial diagnostic strategy in symptomatic women with suspected CAD.[10] The Duke treadmill score incorporates exercise capacity, ST-segment deviation, and angina as major risk determinants.[11] Stress test-induced ST elevation in lead aVR is highly suggestive of left main or ostial LAD disease.[12] The exercise stress test is terminated before achievement of maximum predicted heart rate for symptoms especially with significant ST-changes (depression >2 mm or elevation >1), or sustained fall in systolic blood pressure >10 mmHg or hypertension (>250 mmHg systolic or >115 mmHg diastolic), or significant arrhythmia.

Stress echocardiography. The most popular test is dobutamine stress echocardiography (DSE) which is more specific but less sensitive than perfusion imaging for detection of ischemia.[13] Both ischemia and myocardial viability can be assessed. Life- threatening events, mainly ventricular arrhythmias, are rare (0.01%),[14] and the prognostic significance of induced VT remains uncertain. In a randomized comparison has resulted in reduced hospitalization, shorter length of stay and less radiation exposure than coronary artery computed tomography, as a chest pain triage method.[15] The diagnostic accuracy of DSE is reduced in patients with poor acoustic window (obese, COPD), severe LV dysfunction, prior cardiac surgery and severe hypertension. Detection of >=3 dobutamine-induced dysfunctional segments indicates high risk. The ABCDE protocol (step A, regional wall motion abnormalities; step B, B lines; step C, left ventricular contractile reserve; step D, Doppler-based coronary flow velocity reserve in left anterior descending coronary artery; and step E, electrocardiogram-based heart rate reserve) allows assessment of multiple different vulnerabilities of the patient, and allows an effective prediction of survival in patients with chronic coronary syndromes.[16]

Myocardial contrast echocardiography is a useful modality for assessment of myocardial perfusion.

Single-photon emission tomography (SPECT) is used for assessment of exercise myocardial perfusion.[17] Technetium or thallium (better for detection of myocardial viability) are used and there is a relatively good correlation of standardized left ventricular segments with each coronary artery.[9] Adenosine or dipyridamole nuclear perfusion imaging is the preferred test for patients with LBBB or ventricular paced rhythm because of increased false-positive findings with exercise or dobutamine echocardiography. In asthmatic patients, adenosine may cause bronchospasm and dipiyridamole is preferred unless if the patient has significant hepatic impairment. Nuclear imaging exposes the patient to a moderate amount of ionizing radiation (approximately 15 mSv). Attenuation artifacts (obese patients and women with large breasts) decrease the specificity of nuclear testing. Global ischemia (left main or severe multivessel disease) may also produce false negative results. Because higher myocyte fraction is needed to maintain contractile reserve than to achieve radiotracer uptake, nuclear imaging has higher sensitivity but lower specificity than dobutamine stress echocardiography

in the detection of viability. However, the predictive accuracy of dobutamine stress echocardiography for functional recovery is higher than SPECT.[18]

Magnetic resonance imaging is an imaging technique that may be used for myocardial perfusion, wall motion imaging, and myocardial viability.[19] It has high spatial and temporal resolution and apart from ischemia identifies non-viable scar tissue, identifies myocarditis, and detects subendocardial ischemia that may be missed by other tests. CMR has greater sensitivity than SPECT.[20] It can be performed in patients with stents and most orthopaedic implants. Patients with pacemakers and defibrillators may also undergo CMR under specific conditions and protocols. Following the intravenous administration of gadolinium, first-pass perfusion sequences can identify myocardial perfusion abnormalities. Low-dose dobutamine, adenosine, or dipyridamole are used, and late gadolinium-enhancement (LGE) protocols are also employed.[21] LGE provides the highest sensitivity (95%) and negative predictive value (90%) to predict improved left ventricular contractility after revascularization, whereas low-dose dobutamine CMR has the highest specificity (91%) and positive predictive values (93%).[13] The transmural extent of infarction on LGE inversely predicts the likelihood of regional contractile recovery after revascularization and is the current CMR standard for myocardial viability assessment.[22] Administration of gadolinium is contraindicated in patients with a creatinine clearance >30 mL/min due to the rare but potentially life-threatening complication of nephrogenic systemic fibrosis. CMR stress T1 mapping can detect ischemia and myocardial blood volume changes without gadolinium, and can accurately distinguish obstructive epicardial CAD from microvascular dysfunction.[23] CMR may show false-positive defects related to transient dark rim artifacts in the subendocardium. If not properly recognized, such artifacts may limit the specificity of CMR perfusion imaging for detecting small subendocardial perfusion defects.[24] The possibility of CMR-induced damage of human lymphocyte DNA integrity has also been raised, but its clinical significance is unknown.[25] CMR requires some of the strongest and fastest switching electromagnetic gradients available in MR, exposing the patients to the highest administered energy levels. Thus, similar restrictions might apply as for X-ray based and nuclear imaging techniques in order to avoid potential carcinogenic effects.

In patients with known CAD, **stress CMR** perfusion imaging can effectively reclassify patient risk beyond CV risk factors and LV function. Absence of ischemia on stress CMR indicates a low (<2%) annual risk for nonfatal MI/CV death.[26, 27]

CCT-derived FFR, and **CT perfusion imaging** are now available.[28, 29] In the SYNTAX III REVOLUTION Trial in patients with complex CAD, optimal CCT with FFR_{CT} availability (ie deriving FFR from coronary CT images), led to almost similar therapeutic recommendations as conventional coronary angiography.[30]

Anatomical Imaging

Coronary artery computed tomography angiography (CCT) with multidetector scanners may visualize the coronary artery lumen, detect calcification and provide functional assessment of coronary lesions.[28, 31] In patients with acute chest pain, CT angiography in an experienced center is faster to obtain than a stress test and improves diagnostic ability. The radiation dose from CCT has decreased progressively over the past years 15–17 18 with a typical mean effective radiation dose of 3 mSv and reaching <1 mSv with the latest technologies.[31] The latest innovation is photon-counting detector CT (PCD-CT) technology, which combines the advantages of DSCT with high temporal resolution with new matrix technology that allows a spatial resolution up to 0.2 mm.[31] Limitations of CCT are high image noise in obese patients, interference by severe calcification and coronary stents, and the need of a slow sinus rhythm that usually requires beta blockade.

CCT has a high diagnostic accuracy to rule out clinically significant coronary artery disease in patients with ***acute coronary syndrones***.[32] However, the routine use of early CT coronary angiography in intermediate risk patients with acute chest pain and suspected acute coronary syndrome is not recommended.[33] In ***asymptomatic*** patients with type 1 or type 2 diabetes, use of CCT to screen for CAD did not reduce the composite rate of all-cause mortality, nonfatal MI, or unstable angina requiring hospitalization at 4 years.[34] Contemporary ***chest pain*** populations referred for testing have a low burden of obstructive coronary artery disease and myocardial ischemia, and CCT, by visualizing nonobstructive coronary artery disease, identifies additional at-risk patients, and in the context of the Framingham Risk Score improves the prognostic value of functional assessment.[35] In trials on patients with symptomatic coronary disease, the results of CCT-guided referral for invasive angiography and revascularization and reduced the risk of MI,[36] CCT predicted the 3.5 year composite risk of late revascularization, myocardial infarction, and all-cause death mortality,[37] and in patients undergoing evaluation for suspected CAD, CCT was associated with a lower risk of MI but similar risk of mortality and at higher costs than functional testing.[38, 39] Clinical outcomes did not improve in the PROMISE and SCOT-HEART trials, but follow-up was relatively short (20-22 months).[40] However, in the 5-year follow-up of the SCOT-HEART trial, the use of CCT in patients with stable chest pain resulted in a significantly lower rate of death from coronary heart disease or nonfatal myocardial infarction at 5 years, without resulting in a significantly higher rate of coronary angiography or coronary revascularization.[41] It seems that the totality of the evidence does not support endorsing CCT as the noninvasive test of choice in evaluating patients with stable chest pain,[42] and stress echocardiography is preferable to CCT as a chest pain triage method.[15]

In patients with suspected acute coronary syndrome in whom myocardial infarction had been ruled out, and high-sensitivity cardiac troponin testing indicated an

intermediate risk of a cardiovascular event, routine CT coronary angiography–guided management did not result in a lower incidence of subsequent myocardial infarction or death from a cardiac cause than standard care.[43]

Positron emission tomography has high sensitivity for detection of ischemia and myocardial viability and perhaps characterization of atherosclerotic plaques.[17] Disadvantages are the high cost and lack of clinical verification studies for its prognostic ability. In clinical practice, the use of positron emission tomography may not offer additional information on myocardial viability compared to conventional methods,[44] but it may be used for calculation of the coronary flow capacity in order to guide therapy.[45]

Coronary angiography is indicated for diagnostic and risk stratification purposes in patients with significant angina on medical therapy, high-risk clinical characteristics and non-diagnostic invasive testing criteria, LV dysfunction (LVEF<45%), aborted sudden death or VT/VF. Serious complications of coronary angiography such as death, MI or stroke, and aortic dissection or aortic valve avulsion had been previously reported in the order of 0.1%,[46] but are less in modern catheter labs. Fasting is no longer considered necessary prior to the procedure (SCOFF RCT).[47] For coronary lesion assessment see section on risk stratification. Recommendations are provided in Tables 4 and 5, and Figure 7.

Differential Diagnosis

Coronary causes of angina-like pain

Apart from epicardial coronary artery stenosis, other conditions that may cause myocardial ischemia are:

Congenital coronary abnormalities

Myocardial bridging involves a segment of a coronary artery, usually the LAD, embedded within the myocardium in a way that arterial compression occurs with systole.[48] With intense symptoms and documented ischemia, myotomy or CABG may be required. The value of stenting is debated. Fistulas, anomalous origins of coronary arteries, compression by the PA as may happen with ASD are other relevant anomalies (see the relevant Chapter in ACHD for a detailed discussion).

Ischemia and Non-obstructive Coronary Arteries (INOCA)

Up to 70% of patients presenting to the cardiac catheterization laboratory with angina (ANOCA) may have no angiographic evidence of coronary artery disease.[49, 50] In these patients, the prevalence of demonstrable ischaemia (INOCA) varies, depending on the stress test performed, between 10% and 30%.[2] The condition is more common in women,[51] and may be associated with an adverse prognosis regardless of sex.[52, 53] However, half of the patients have resolution of stress-induced wall motion abnormalities on repeat stress echocardiography

at 1 year and symptoms improve in 43%.[54] Recommendations are provided in Table 6 and Figure 8.

Myocardial bridge, endothelial dysfunction (a decrease in luminal diameter of >20% after intracoronary acetylcholine), ***epicardial spasm*** (>90% coronary spasm with acetylcholine) ***microvascular dysfunction*** (diminished coronary flow reserve in response to pharmacological vasodilatation: index of microcirculatory resistance ≥ 25 and CFR<2-2.5), and ***microvascular spasm*** (ESG changes with acetylcholine without epicardial spasm) constitute the pathophysiology of the condition. An explanation for their angina may not be found in approximately 23% of patients presenting with angina and angiographically normal coronary arteries.[55]

Syndrome X is an old term referring to exercise-induced angina-like symptoms in the context of ischemic changes on treadmill stress testing and normal coronary arteries on angiography. *Prinzmetal's angina* refers to chest pain at rest associated with ST elevation and was thought to be due to epicardial or microvascular spasm.

The term *microvascular angina* is used to characterize anginal symptoms and evidence of myocardial ischemia triggered by coronary microvascular dysfunction.[56, 57] The coronary microcirculation, constituted by pre-arterioles (lumen diameter 100–500 μm), arterioles (lumen diameter <100 μm), capillaries, and venules, is responsible for most part of the resistance to flow that modulates blood pressure (BP) and tissue perfusion.[57] Functional abnormalities leading to coronary microvascular dysfunction include impaired dilatation or excessive coronary microvascular constriction. Impaired vasodilatation may be because of abnormalities in endothelium-dependent mechanisms (frequently associated with diabetes mellitus, obesity, smoking, and other cardiovascular risk factors), endothelial-independent mechanisms, or both. Inflammation is another potentially important cause of coronary microvascular disease. Coronary microvascular spasm, similarly to epicardial coronary spasm, may cause myocardial ischemia in the absence of increased myocardial demand and trigger rest angina.[56] However, most patients have coexisting obstructive or nonobstructive macrovascular atherosclerosis.[58] Mainly depending on resting microvascular resistance (coronary pressure divided by flow velocity) functional and structural distinct endotypes of microvascular dysfunction have been identified with differing degrees of systemic disease involvement.[59]

Measurement of microvascular resistance at rest and during pharmacologically induced hyperaemia identifies 2 types of coronary microvascular dysfunction, functional and structural, with normal and elevated minimal microvascular resistance, respectively.[60]
Coronary reactivity testing may be helpful in establishing the diagnosis of coronary spasm, microvascular dysfunction or abnormal cardiac nociception (Figures 9-11). Vasoreactivity testing, and measurement of coronary flow reserve and microcirculatory resistance can be

used to guide medication therapy in patients with angina who have no obstructive epicardial coronary disease (CorMicA trial).[61] Acetylcholine is administered in a stepwise manner into the left coronary artery (20-200 μg) or into the right coronary artery (20–80 μg) over a period of 3 min with an interval of 2–3 min between injections. Ergonovine is administrated as a bolus in a stepwise manner into the left coronary artery (8–60 μg) and right coronary artery (8–40 μg) with an interval of 2–3 min between each injection.[62] A positive response to achetylcholine or ergonovine spasm provocation testing is defined as symptom reproduction, ischemic ECG changes, and subocclusive/estimated ≥90% narrowing focal (within a single coronary segment) or diffuse (involving ≥2 segments) coronary diameter reduction compared with the relaxed state after intracoronary nitroglycerin (*epicardial spasm)*. Lack of epicardial coronary spasm by angiography in the presence of ischaemic ECG changes and angina suggests *microvascular spasm* that may not respond to nitrates.[63, 64] Coronary artery spasm may be inducible in up to 27% of patients myocardial infarction and non-obstructive coronary arteries (MINOCA).[65] Provocations tests are safe without reported deaths, and coronary provocative testing with intra-coronary ACh is a safe procedure, with no death and a pooled incidence of major complications such as VT/VF of 0.5%, but up to 4.9% in some studies, which however has been considered comparable to that during spontaneous angina events. [62, 66] Arrhythmic complications are more often with acetylcholine than with ergonovine. These tests, however, have technical shortcomings.

Cardiac positron emission tomography and adenosine stress perfusion using CMR are the most accurate non-invasive tests for the detection of microvascular dysfunction.[50]

Continuous themodilution,[67] and ***microvascular resistance reserve***[68] are other methods for assessing microvascular dysfunction and vasodilator reserve capacity of the coronary microcirculation.

Abnormal cardiac nociception

The term indicates increased perception of pain centrally mediated or due to changed sensitivity of chemical and mechanical atrial and ventricular receptors.

Non-coronary causes of angina-like pain

Oesophageal reflux, oesophagitis, and abnormal oesophageal motility have similar distribution with cardiac pain but are not related to exercise. These findings are common in patients presenting with chest pain but not necessarily the causative factor.

Duodenal ulcer and **gallbladder pain**.

Pericardial pain. Retrosternal or epigastric, precipitated by inspiration and relieved by sitting forward. May radiate to left shoulder.

Aortic stenosis, hypertension and **LV hypertrophy** (reduced coronary blood flow)

Aortic dissection. Tearing pain radiating to the back. Aortic aneurysms may also produce chronic pain.

Painful LBBB syndrome

Clinical suspicion for painful LBBB syndrome may be raised in individuals whose chest pain paroxysms correlate temporally with intermittent LBBB after ruling out myocardial ischemia, although it rarely coexists with coronary artery disease. Additional ECG features that may be associated with painful LBBB syndrome are an inferior axis and low S/T wave ratio in the precordial leads (<1.8).[69]

Pulmonary embolism is usually associated with sudden onset shortness of breath rather than pain.

Costochondritis. There is tenderness on palpation.

A full list of conditions that may cause chest pain is presented in the Chapter on ACS Diagnosis.

Risk Stratification

Risk stratification is essential for the choice of appropriate mode of therapy (Table 7). It seems that the anatomic extent and severity of coronary atherosclerosis, as well as the LV function are more important than the severity of angina or documented ischaemia. In low-risk patients who present with atypical symptoms and negative high-sensitive troponin testing, further investigations with provocative testing or CCT may not be needed.[70]

Severity of angina

The severity of angina has been traditionally considered a risk factor in patients with coronary artery disease. However, in an analysis of the STICH trial, the occurrence of angina pectoris was not a predictor of mortality in medically treated patients with coronary artery disease and left ventricular systolic dysfunction. CABG, that was more effective than medical therapy in relieving angina, lowered mortality to a similar extent in those with and without angina.[71] In the prospective observational CLARIFY registry on patients with stable coronary artery disease, angina did carry adverse prognostic significance but only in patients with a prior MI.[72] In a subsequent analysis of the same registry, resolution of angina within 1 year with conservative management predicted outcomes similar to lack of angina, whereas persistence or occurrence was associated with worse outcomes.[1] However, most probably due to the development of ***collateral circulation***, as an adaptive response to ischemia, there is no linear relationship between stenosis severity, ischemia, and symptom burden.[73]

Coronary Anatomy Indices

The extent of significant lesions on the coronary arteries has been correlated with long-term mortality,[74, 75] and risk stratification can be based on coronary anatomy (see also Indications

for Revascularization). The clinical importance of angiographic extensive coronary disease has been verified by subanalyses of the COURAGE and STICH trials.[76, 77] The angiographic **diameter percent stenosis** is also of clinical significance. In the COURAGE trial, the only angiographic predictor of myocardial infarction or acute coronary syndrome was the number of lesions originally ≥50% diameter stenosis that had not been revascularized.[78] Coronary stenoses have been considered hemodynamically significant when >50% diameter stenosis of the left main and >70% diameter stenosis of the other epicardial arteries.[79] However, both visual assessment and quantitative coronary angiography methods have limited accuracy for risk stratification purposes.

The **SYNTAX score** is an angiographic grading tool calculated as the sum of the points assigned to each lesion identified in the 16 segments of the coronary tree with greater than 50% diameter narrowing in vessels with a diameter greater than1.5 mm (www.syntaxscore.com) (Figure 13). The clinical SYNTAX score (***SYNTAX score II***) combines the angiographic SYNTAX Score with a clinical risk score incorporating age, ejection fraction, and creatinine clearance. It is calculated as:
Clinical SYNTAX score = SYNTAX score **x [** (Age/LVEF) **+** 1 point for each 10 ml creatinine clearance <60 ml.min/1.73 mm^2)]. It predicts major cardiac and cerobrovascular events and mortality better than the angiographic score and in patients with multivessel disease.[80, 81] Incorporating ***functional*** assessment by considering coronary lesions with FFR measurements < 0.80, improves its clinical usefulness.[82] The SYNTAX score II 2020 incorporates 8 prognostic factors (age, creatinine clearance, LVEF, COPD, peripheral vascular disease, diabetes, insulin therapy, and smoking) together with disease type and anatomical SYNTAC score, and has been found useful to predict 10-year deaths and 5-year MACE.[83] It should be noted that the SYNTAX score was created as an ad hoc synthesis of prior angiographic risk scores and expert judgment, and the weights are not strictly based on empirical evidence.[84] Many important comparative revascularization studies have used these scored to define therapeutically heterogeneous subgroups, but they all demonstrate modest discrimination in predicting adverse clinical events after revascularization.[79]

The presence of **coronary artery calcification** is an established cardiovascular risk marker.[85, 86] Coronary artery calcification is assessed on an ECG-gated non-contrast-enhanced CT scan. Alternatively, the presence of CAC can be evaluated qualitatively by visually inspecting the coronary arteries on a previous non-cardiac chest CT scan, if available.[2] The final **coronary artery calcium score CACS,** or Agatston score, results from the sum of all plaque areas along the complete coronary artery circulation. Algorithms for calculating calcium scoring (CACS) has been devised such as the Agaston and Weston score. The absence of coronary artery calcium has been reported to have a very high negative predictive value (>95%) for obstructive CAD.[87] A CACS of 0 indicates low risk, whereas a CACS >

100 (or ≥ 75th percentile) upgrades the risk. Incorporation of coronary calcium into the MESA risk score has also been proposed for risk stratification purposes,[88] and coronary calcium score of 0 has resulted in the greatest downward shift risk.[89] Of note, however, in the CONFIRM and PROMISE trials, a score of 0 did not rule out the presence of significant coronary disease, and the presence of calcium score did not add incremental prognostic information to that provided by clinical risk factors, severity of CAD, or functional tests.[90, 91] Coronary artery calcium density may also be considered. The relationship between coronary calcification and the susceptibility of a plaque to provoke a thrombotic event remains incompletely understood. Although some studies have highlighted microcalcification and spotty calcification as definable components of vulnerable plaque, others have suggested that sheet calcification may render a plaque less likely to rupture.[92]

The simultaneous presence of three **vulnerability features** (thin-cap fibroatheroma, as determined by grey-scale and radiofrequency ***IVUS***, large plaque burden, and small luminal area) were associated to a 3 years increase of a combined endpoint including cardiac death, target-vessel MI, and re-hospitalization due to ischaemia (PROSPECT study). However, such a combination of features is uncommon.[93] In the PREVENT RCT, Preventive PCI of vunerable lesions significantly reduced major cardiac events (see Therapy).[94] ***Near-infrared spectroscopy (NIRS)*** intravascular ultrasound imaging can detect lipid-rich plaques (LRPs). Preliminary evidence has detected an association between maximum 4 mm Lipid Core Burden Index ($maxLCBI_{4mm}$) and non-culprit major adverse cardiovascular events.[95] ***Optical coherence tomography (OCT)***, with its capability of visualizing superficial plaque components at a high resolution is potentially capable of identifying high-risk plaques.[96, 97]

Extent of Ischemia

In longitudinal studies in patients with known or suspected coronary artery disease, detection of ischemia predicts a significantly higher overall mortality, cardiac death or MI, even in the absence of angina, whereas normal scintigraphy studies identify patients with a good prognosis at a low risk for future cardiac events.[98-100] However, in the COURAGE and ISCHEMIA RCTs, ischemia severity, as opposed to the angiographic extent of CAD, was not associated with increased risk after adjustment for CAD severity in patients with preserved LV function. [101, 102]

Acute myocardial ischemia is an established cause of polymorphic ventricular tachycardia or fibrillation and sudden cardiac death, with an incidence ranging from 1.5 to 7.6% in ACS.[103] The majority of sudden deaths due to ischemic heart disease are not associated with an acute MI, but transient acute ischemia is an important trigger preceding 35 to 80% of deaths due to a ventricular tachyarrhythmia.[104] The presence of extensive ischemia has been considered useful in identifying patients who would benefit from revascularization, but this is now controversial and probably depending on the LV function (see also Indications

for Revascularization for a detailed discussion). Imaging tests such as exercise scintigraphy results do not correlate well with angiographic findings, both in patients with and without angina, and they may not identify the culprit lesion(s) with certainty in the presence of multivessel disease.[105]

Haemodynamic significance of coronary stenoses

Fractional flow reserve (**FFR**) is a means of assessing the haemodynamic significance of a particular stenosis. Initially, the FFR cut-off value for revascularization was 0.75, with FFR values <0.75 having >99% positive predictive value for inducible myocardial ischaemia. Subsequent studies have reported that in a minority of patients, FFR between 0.75 and 0.80 is associated with flow-limiting stenosis, and currently, FFR of 0.80 is used as revascularization threshold. However, FFR values between 0.75 and 0.80 are still considered as being in the grey zone in revascularization decision-making, and intervention may not be result in improved clinical outcomes.[106] Meta-analyses and other trials of stable patients in which PCI was based upon fractional flow reserve (FFR) measurements demonstrated a reduction in death and late and peri-procedural MI,[107, 108] and FFR assessment is also valid in patients with a low LVEF (<=40%).[109] In another meta-analysis of 79 prospective, observational studies that evaluated the association between abnormal coronary flow and clinical outcomes in patients with established cardiovascular disease, impaired coronary flow was strongly associated with an increased hazard of death and major adverse coronary events.[110] FFR shows modest concordance with imaging tests such as perfusion scintigraphy and dobutamine stress echocardiography, and quantitative coronary angiography particularly with 30% to 70% diameter stenosis,[111] but may be a more important determinant of the natural history of coronary stenoses than anatomy.[112] Approximately one third of patients may show discordance between ≥50% diameter stenosis, especially of the left main stem, and FFR ≤0.8 thresholds of stenosis severity,[113] and in diabetic patients its predictive ability may be limited.[114, 115] Its role in patients with aortic stenosis is also not established. In patients with STEMI undergoing complete revascularization, an FFR-guided strategy did not have a significant benefit over an angiography-guided strategy.[116] FFR is an objective means to assess the severity of coronary stenosis and FFR-guided intervention is currently recommended, but in all relevant trials the composite endpoint was driven largely by repeat revascularization, and FFR-guided intervention has not been shown to reduce total or cardiac mortality (see Indications for Revascularization). Calculation of FFR may be hampered by induction of complete heart block, especially when used in the right coronary artery.

The **pressure pullback gradient (PPG)** is a method to quantitate the pathophysiologic pattern of coronary artery disease called The PPG index ([maximal Δfractional flow reserve [FFR] units/20 mm of arterial length]/total vessel ΔFFR, corrected for relative disease length to total vessel length) quantifies the degree of purely focal

(PPG=1), diffuse (PPG=0), or mixed atherosclerotic disease.[117] PPG has showed a predictive capacity for optimal revascularization and demonstrated added value compared with an FFR measurement.[118]

The **Instantaneous Wave-Free Ratio (iFR)** is an index based on resting coronary pressure measurement during diastole. Both FFR and iFR are recommended to guide revascularization,[79] but iFR has proven inferior to FFR for this purpose.[119]

Coronary angiography–derived FFR (FFR_{angio}) is a computational method for measuring FFR on CT coronary angiograms or 3-dimensional (3D) reconstructed conventional angiograms, without a coronary pressure wire or hyperemic agent. It compares well with pressure wire-derived FFR In the FAST III RCT, vessel fractional flow reserve (vFFR), derived from three-dimensional quantitative coronary angiography was noninferior to pressure-wire–based FFR.[120] In the ALL-RISE RCT, FFR derived from coronary angiographic images alone was also noninferior to pressure-wire–based FFR.[121]
In a large nationwide cohort in the US, but a binary stenosis-specific threshold of 0.67 identified individuals at increased risk for future MI and cardiovascular death.[122] In the P4 RCT, a CCTA-guided PCI strategy (with FFR-CT) was noninferior to IVUS-guided PCI with respect to target-vessel failure at 12 months.[123]

Quantitative flow ratio (QFR or FFRct) is a novel method for evaluating the functional significance of coronary stenosis by computation of FFR in the vessel based on 3-dimensional angiographic reconstruction and fluid dynamics algorithms. However, the FAVOR III Europe trial did not support the use of QFR if FFR is available to guide revascularisation decisions in patients with intermediate coronary stenosis. [124]

Resting distal coronary to aortic pressure (Pd/Pa), as measured by the FFR wire shows very good agreement with iFR and may be used as a simple measure of stenosis severity (threshold <=0.91) without induction of hyperaemia with adenosine.[125] There has been some evidence that contemporary thresholds (0.80 for FFR and 0.89 for iFR) may provide suboptimal diagnostic accuracy compared with an FFR threshold of 0.75 and iFR threshold of 0.86.[126]

Coronary flow reserve (CFR) provides combined physiologic information on epicardial stenosis plus microvascular function. However, measurement of invasive CFR with the present techniques remains technically more challenging and less reproducible than FFR, and its clinical value is not established.[127]

Global coronary flow reserve, calculated by positron emission tomography as the ratio of stress to rest absolute myocardial bold flow (mL/min/gr) for the whole left ventricle has been associated with revascularization outcomes independently of angiographic CAD.[128]

Coronary flow velocity reserve assessed by echocardiography may also be useful for risk stratification.[129]

Intravascular ultrasound (IVUS) is useful to define left main stem lesion severity.[79] Deferral of intervention recommended for a minimum lumen area of ≥6 to 7.5 mm^2 is safe, although a smaller cutoff (4.5–4.8 mm^2) may be more appropriate in patients of Asian descent.[79]

CMR Perfusion

Myocardial-perfusion cardiovascular magnetic resonance imaging is a noninvasive test for the detection of coronary artery disease that has a high concordance with FFR for ischemia detection. In the MR-INFORM randomized trial, on patients with stable angina and risk factors for coronary artery disease, myocardial- perfusion cardiovascular MRI was associated with a lower incidence of coronary revascularization than FFR and was noninferior to FFR with respect to major adverse cardiac events.[130]

LV function

Echocardiographic LVEF<50% is considered abnormal. LVEF<35% denotes patients at high risk and is an independent predictor of mortality. Dobutamine stress echocardiography, myocardial perfusion tests, cardiac magnetic resonance, and positron emission tomography are used for assessment of viability of apparently scarred ventricular tissue.[131] In patients with multivessel disease, ischemic heart failure, and LVEF<35%, the value of CABG over medical therapy is now established, following substudies and long-term results of the STICH trial (see also Indications for Revascularization). [77, 132-134]

Myocardial viability

The demonstration of viable myocardium in patients with coronary artery disease and LV dysfunction has been traditionally considered as a prerequisite for potential revascularization.[131, 135] However, it did not identify patients with a survival benefit from revascularization in both a substudy of the STICH and the smaller HEART trial, [136, 137] whereas results of the PARR trial have been controversial [138] (see Revascularization). The presence of severe LV dysfunction with extensive scar and remodeling, and the fact that medical therapy may also restore the viable myocardium,[139] are probably responsible for these results that are not necessarily generalizable. Viability testing may still be useful for the detection of hibernating myocardium that should benefit from revascularization in selected patients.[140]

Biomarkers

A model combining patient age, clinical variables (smoking, diabetes, and peripheral artery disease), and levels of biomarkers (NT-proBNP, hs-cTnT, and LDL-C) can also be used to predict adverse CV outcomes including death.[141] Ceramides and phospholipids are lipids that have been used for prediction of CVD events through a simple score. Initial results are promising.[142]

ECG

An ECG score for the risk of sudden arrhythmic death has been validated over o 5-year follow-up (PREDETERMINE).[143]

Genetic risk scores

Genetic (polygenic) risk scores can be calculated from thousands to millions of genetic variants, weighted by variant-level strength of association with disease, and can integrate information about the underlying genetic relationships between variants. These scores may capture residual risk left unaccounted by traditional risk factors, and predict recurrent cardiovascular events in patients with CAD.[144]

Clinical decision pathways for the management of patients with suspected or established chronic coronary syndromes are presented in Figures 14-16.

Therapy

Therapy of patients with CAD is aimed at alleviating ischemia and affecting the natural history of the disease by improving endothelial function, stabilising atherosclerotic plaques, and modifying risk factors. Life-style modification is essential for risk reduction and symptomatic relief (Tables 8 and 9, and Figures 17 and 18). A detailed discussion of general measures and desirable dietary habits is provided in Chapter 28 on CVD prevention.

Antiplatelets and anticoagulants

Aspirin should be continued indefinitely unless contraindicated. Similar outcomes and better long-term adherence occur with an 81mg compared to a 325 mg dose of aspirin.[145] In high risk patients it reduces arterial thrombosis by 25%, by inhibiting platelet cyclooxygenase-1 and decreasing synthesis of thromboxane A^2.

P2Y12 inhibitors may replace aspirin if aspirin is contraindicated. According to the PANTHER Collaboration meta-analysis and an individual patient meta-analysis, they are superior to aspirin, due mainly to a lower risk of myocardial infarction and fewer adverse events.[146, 147] In stable patients with a previous MI or ACS long-term therapy with an antiplatelet added to aspirin may be beneficial (Figure 10). In patients with CAD and moderate risk of ischaemic events but without a high risk of bleeding it is optional (ESC 20121 GL on CVD prevention, IIb A).[148] In patients receiving DES, clopidogrel 75 mg daily should be added to aspirin.[149] In the THEMIS trial, in patients with stable coronary artery disease and type 2 diabetes who did not have a history of myocardial infarction or stroke, **ticagrelor** plus aspirin was associated with a lower incidence of ischemic events than placebo plus aspirin at the expense of a higher incidence of major bleeding, including intracranial hemorrhage.[150] A subanalysis of this trial detected a benefit in patients with a previous PCI, but at the cost of increased bleeding.[151] Thus, the value of added ticagrelor is not established

in this setting. Compared with aspirin monotherapy, $P2Y_{12}$ inhibitor monotherapy is associated with a lower risk of myocardial infarction and a comparable risk of stroke.[152] In patients with symptomatic peripheral artery disease, ticagrelor and clopidogrel, as monotherapy, are equally effective in reducing cardiovascular events.[153] The CHADS-P2A2RC score may particularly identify low-risk patients with limited benefit from treatment.[154] The optimum duration of antiplatelet therapy following stenting is not established with RCTs having provided controversial results regarding the value of extended dual antiplatelet therapy (see also Chapter on Revascularization).[155-158]

Long-term anti-Xa therapy is under consideration in patients with stable CAD. Low-dose **rivaroxaban** (2.5 mg twice daily) plus aspirin 100 mg od had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone in patients with stable CAD (COMPASS trial),[159, 160] and previous PCI (Compass-PCI).[161] In the AFIRE trial on patients with AF and stable coronary artery disease more than 1 year after revascularization, monotherapy with rivaroxaban (10 mg once daily for patients with a creatinine clearance of 15-49 ml/min or 15 mg od for patients with a creatinine clearance of ≥50 ml/min) was noninferior for efficacy and superior for safety compared to combination therapy with rivaroxaban plus an antiplatelet agent.[162] Addition of low-dose rivaroxaban to aspirin may be also considered in patients at high-risk of ischemic events (ESC 2021 GL on CVD prevention, IIa A, and ACC 2026 Statement).[148, 163] However, in the AQUATIC RCT, among patients with chronic coronary syndrome at high atherothrombotic risk who were receiving an oral anticoagulant, the addition of aspirin led to a higher risk of cardiovascular and total mortality and major bleeding.[164]

In patients with **AF** and chronic coronary disease OAC monotherapy, compared with OAC plus single antiplatelet therapy, is not associated with a statistically significant increased risk of ischemic events but results in a significantly reduced risk of bleeding.[165] Following PCI, combination therapy of OAC and single APT (aspirin or P2Y12 inhibitor) is not recommended beyond 12 months to decrease the risk of major bleeding (ACC/AHA/ACCP/HRS 2023 GL on AF, 1 B-R, (ESC 2024 GL on AF, III B).

Recommendations are provided in Table 10, and Figures 19-21.

Anti-anginal Δrugs

The medical therapy of angina should be personalized (Table 11, and Figure 22). There is no evidence to support the use of first and second line treatments for the management of angina.[166]

β-Blockers should be given in patients with a recent past MI, acute coronary syndrome, or LV dysfunction in the context of coronary artery disease unless contraindicated (severe asthma, sick sinus syndrome, AV block). Beta blockers, and especially metoprolol and bisoprolol, have been shown to reduce adverse effects in stable patients even in the absence of

a recent MI or heart failure,[167, 168] but this has not been verified by all studies.[169, 170] They are not recommended in stable patients after complete revascularization by the 2021 ACC/AHA/SCAI GL on revascularization (III-C-LD).[79] Beta blockers are contraindicated in patients with coronary spasm.[171]

Beta blockers are essential for symptomatic **myocardial bridging**, and nebivolol due to its highly B1 selective nature and possible beneficial effects on endothelial dysfunction may be preferable.[172]

Calcium channel blockers are given for angina if beta blocker treatment is unsuccessful or contraindicated. Long-acting nondihydropyridines can be used instead of beta blockers. When dihydropyridines are used they should be preferably combined with a beta blocker.

Nitrates are useful for immediate angina relief. Short acting nitrates are preferred. They might be also considered for long-acting therapy if beta blocker treatment is unsuccessful or contraindicated but with adequate nitrate-free interval to decrease nitrate tolerance. However, prolonged exposure to nitrates induces endothelial dysfunction and oxidative stress, and long-term therapy may worsen the prognosis of patients with CAD or vasospastic angina.[173, 174]

Ranolazine for chronic angina relief usually in addition to or instead of beta blockers. Ranolazine is a sodium ion channel inhibitor that does not affect heart rate or blood pressure. It does not affect the incidence of cardiac mortality or MI (MERLIN-TIMI 36). There had been evidence suggesting that it may suppress re-entrant and EAD-induced ventricular fibrillation,[175] but in the RAID trial in high-risk ICD patients, treatment with ranolazine did not significantly reduce the incidence of the first VT or VF, or death, despite a modest benefit on a pre-specified secondary endpoint of recurrent ICD therapies for VT and VF events.[176] In patients with incomplete revascularization following PCI, ranolazine does not reduce the rate of ischaemia-driven revascularization.[177]

Nicorandil is an anti-ischemic and cardioprotective agent that as adjunct therapy may reduce major coronary events in stable patients. [178]

Although no single pharmacological mechanism has been established, **trimetazidine** targets deranged cellular energetics particularly in ischaemic myocardial tissue,[179] and may be useful for angina relief in drug-refractory patients.

Lipid Therapy

A detailed discussion on pharmacotherapy for dyslipidemia in greneral is provided in the Chapter on CVD prevention. Specific recommendations for dyslipidemia in this setting are also provided in Table 12 and Figure 23.

Other therapies

ACE inhibitors should be given indefinitely in patients with LVEF<40%, hypertension, diabetes or chronic kidney disease (Table 11). **Angiotensin II receptor blockers** may be used in patient's intolerant of ACE inhibitors. However, ACEIs and ARBs are not beneficial in stable patients with CAD in the absence of mentioned comorbidities and, especially, heart failure.[180] **Aldosterone blockers** are recommended in all patients with LVEF<40% and diabetes or heart failure but without renal dysfunction or hyperkalemia.

Vorapaxar, an inhibition of the protease-activated receptor PAR-1 through which thrombin activates platelets, reduced the risk of cardiovascular death or ischemic events in patients with stable atherosclerosis (a history of myocardial infarction, ischemic stroke, or peripheral arterial disease) who were receiving standard therapy, but also increased the risk of moderate or severe bleeding, including intracranial hemorrhage.[181] Subsequently, reduction of late stent thrombosis and ischemic stroke in patients without prior stroke were reported.[182, 183] Vorapaxar has been also found effective for long-term secondary prevention in patients with diabetes and a prior MI in the absence of a prior stroke or TIA.[184]

Colchicine 0.5 mg od has been found beneficial in patients with stable (and unstable) CAD.[185, 186]

Ivabradine has been found rather promising in heart failure, but in patients with stable CAD did not improve outcomes (SIGNIFY trial).[187]

Proton pump inhibitors are given in patients on dual antiplatelet therapy and a high-risk of GI bleed (advanced age, warfarin, steroids, NSAIDs, peptic ulcer). Routine use is not recommended (ACC/AHA 2011 on PCI, III-C). Co-administration of PPIs with clopidogrel is discussed in ACS Therapy.

NSAIDs, both non-selective and, especially, selective COX-2 inhibitors that spare COX-1 in the gut, are associated with an increased thrombotic risk and should be used only if necessary and at the lowest dose for the shortest possible duration. COX-1 and COX-2 are isoforms of the COX enzyme that catalyses the conversion of arachidonic acid to prostaglandins (such as prostacyclin) and thromboxane A_2. The inhibition of COX-1-mediated production of prostaglandins in the gastric mucosal cells increases the risk of gastrointestinal toxicity, and COX-2 selective inhibitors, such as diclofenac, nimesulide and celecoxib, are associated with lower gastrointestinal side effects. However, they confer a higher risk for cardiovascular events by interfering with generation of vascular prostacyclin without affecting the COX-1 generation of thromboxane A_2 both at the endothelium and the platelets that contain only COX-1. The relatively safer agents are drugs with higher COX-1 selectivity such as naproxen (≤500 mg /day) and ibuprofen (≤1200 mg /day). [188] These drugs they may reduce the irreversible antiplatelet effect of aspirin by interfering with aspirin acetylation of the COX-1 binding site on plateles,[188] and, especially at higher doses, confer the same risk as low-dose celecoxib (100 mg bd).[189, 190]

Anti-inflammatory therapy targeting the interleukin-1β innate immunity pathway with the human monoclonal antibody **canakinumab**,150 mg subcutaneously every 3 months, has resulted in a significantly lower rate of high-sensitivity C-reactive protein (hsCRP) and recurrent cardiovascular events over a period of 48 months, independent of lipid-level lowering, in patients with a prior MI and CRP>2mg/L (CANTOS trial). [191]

Influenza vaccine annually is indicated for all patients with CAD.[192]

Herpes zoster vaccination also appears to be beneficial.[193]

Ecologic studies have shown lower rates of death from cancer and cardiovascular disease in regions with greater sun exposure than in areas with less sun exposure, but **vitamin D** supplementation has not resulted in reduced cardiovascular events (VITAL study).[194]

However, In DANCODE (Danish Coronary Decalcification), **vitamin K_2** and **D_3** supplementation reduced 24-month coronary artery calcification progression by 52 Agatston units (21%) compared with placebo in patients with baseline CAC ≥400 Agatston units.[195]

A positive dose–response association between **gout** and CVD mortality has been found,[196] and xanthine oxidase inhibition maintains an important role in lowering serum uric acid concentrations to prevent the risk of gout exacerbations, but **allopurinol** does not improve cardiovascular outcomes in patients with stable IHD.[197] Benzbromarone that exerts pleiotropic effects, might be superior in this respect.[198]

Hormone therapy either with oestrogen plus progestin, or oestrogen alone should not be given (ESC 2019 GL on CCS, III-C), and the value of antioxidant vitamin supplements (vitamins E, C, or beta carotene) or folic acid, with or without B6 and B12 is not proven.

Metabolic surgery (sleeve gastrectomy, gastric bypass, gastric banding, duodenal switch) emerges as a potentially useful option for grossly overweight patients with CAD.[199]

Chelation therapy (ethylenediamine tetraacetic acid or EDTA) is not indicated and may be harmful because of its potential to cause hypocalcaemia, although it might be beneficial in combination with high-dose vitamins in post-MI patients.[200]

All patients should be screened for **depression**, particularly following an ACS.

Specific Conditions

INOCA

In INOCA, nitrates, beta blockers ACE inhibitors, and calcium channel blockers nay be used but with variable success. Ivabradine, ranolazine and other therapies such as hormones and adenosine antagonists may also be tried.[201] Detailed recommendations have been provided in Table 6 and Figure 12.

Diabetes mellitus

In diabetic patients, intensive glycemic control reduces the risk of coronary event by 15% but without affecting mortality,[202] and at a risk of increased major hypoglycaemia. Thus, a ***HbA1c*** < 6.5-***7***% is recommended, [203, 204] but changes in life-style and dietary measures rather than strict adherence to HbA1c reduction are emphasized (Tables 11 and 13).

Heart Failure

Recommendations are provided in Table 14 as well as in the relevant chapters on heart failure.

Other conditions

In patients with **atrial fibrillation** and stable coronary artery disease (defined as coronary artery disease previously treated with revascularization or managed medically), edoxaban monotherapy has been found superior to dual antithrombotic therapy (edoxaban plus a single antiplatelet agent) at 12 months (Table 15).[205]

Recommendations for the **elderly**, patients with **chronic kidney disease**, and for patients with **cancer** are also provided in Table 15.

Revascularization

Indications

Revascularization is appropriate in certain settings for prognostic or symptomatic relief (Tables 16-18, and Figures 24 and 25). The earliest trials of coronary artery bypass grafting (CABG) vs medical therapy in patients with chronic stable angina were conducted in the 1970s and 1980s.[206-209] Symptomatic relief was better with CABG; however, no overall difference was observed in survival or freedom from MI with CABG vs medical therapy, except in patients with left main disease (a substudy of the VA trial), multivessel disease plus LV dysfunction but not overt heart failure (35%<LVEF<50%) (VA and CASS trials), and probably proximal LAD disease in conjunction with multivessel disease, severe angina and LVEF>=50% (European trial). Major advances in medical therapy (especially aggressive lipid-lowering and anti-platelet therapy), and intervention (2nd generation drug-eluting stents) surgical techniques (including the use of the internal mammary artery), has rendered these trials rather obsolete, and the potential benefit of revascularization varies among different patient groups. [210] In patients with stable coronary artery disease, meta-analyses have shown that revascularization with CABG or PCI reduces cardiac death and spontaneous MI,[211] but not total mortality.[212, 213] CABG reduces total mortality only in high-risk groups (especially significant left main disease).[214] No mortality benefit has been shown with PCI alone in stable patients, with the probable exemption of patients with significant left main stem disease amenable to PCI.[215] In current clinical practice the following factors should be considered.

Angiographic extent of coronary artery disease

A subanalysis of the STICH trial[77] supports the results of the three major CABG trials,[206-209] according to which revascularization with CABG is generally favored in the presence of ***triple vessel (≥70% diameter stenosis) disease*** or in the presence of significant ***left main stem disease (≥50%)***.[216, 217] Left main minimum diameter <4.5 mm^2 by intracoronary imaging mandates revascularization. Subanalyses of the COURAGE trial have also verified the adverse effect of the number of coronary arteries diseased on survival, although they have failed to identify it as an indicator for revascularization with PCI .[77, 218] Factors that particularly identify the potential for better long term outcomes with CABG include ***significant proximal LAD stenosis, and a high complexity of coronary atherosclerotic disease*** (multiple significant lesions, presence of chronic total occlusions). In such high-and medium-risk patients, CABG decreases mortality compared to medical therapy, whereas in low-risk patients there is no benefit.[135, 214] CABG also offers improved survival and reduced MI in specific subsets of ***diabetic patients with multivessel disease***. In the BARI 2D trial in patients with diabetes mellitus and stable ischemic heart disease, a strategy of prompt coronary artery bypass graft surgery, but not percutaneous coronary intervention (PCI), significantly reduced the rate of death/myocardial infarction (MI)/stroke in those at high risk as determined by the extent of coronary artery disease, myocardial jeopardy index, impaired left ventricular function (LVEF<50%), and the Framingham score.[219] CABG was also beneficial in diabetic patients with reduced LV function LVEF<50%, but not class III or IV heart failure, as well as in diabetic patients with a high SYNTAX score.[220] A patient-level meta-analysis (COURAGE, FREEDOM and BARI PCI/CABG) has also confirmed the benefit of CABG over optimal medical therapy, as well as PCI, in patients with type 2 diabetes and multivessel coronary disease,[221] but no incremental benefit for PCI vs OMT. The presence of ***vulnerable plaques*** may also be an indication for preventive PCI. In the PREVENT RCT, vulnerable plaques were defined as lesions possessing at least two of the following four characteristics: a minimal lumen area of less than 4.0 mm² by intravascular ultrasonography or optical coherence tomography; a plaque burden > 70% by intravascular ultrasonography; a lipid-rich plaque by near-infrared spectroscopy (defined as maximum lipid core burden index within any 4 mm pullback length [maxLCBI4mm] >315); or a thin-cap fibroatheroma detected by radiofrequency intravascular ultrasonography or optical coherence tomography (defined as a ≥10% confluent necrotic core with >30° abutting the lumen in three consecutive frames on radiofrequency intravascular ultrasonography or as a lipid plaque with arc >90° and fibrous cap thickness <65 μm on optical coherence tomography).[94] Following preventive PCI of vulnerable lesions with an FFR>0.8, the primary outcome (a composite of death from cardiac causes, target-vessel myocardial infarction, ischaemia-driven target-vessel revascularization, or hospitalisation for unstable or progressive angina) at 2 years, occurred in three (0·4%) patients in the percutaneous coronary intervention group and in 27 (3·4%)

patients in the medical therapy group (absolute difference –3·0 percentage points [95% CI –4·4 to –1·8]; p=0·0003). The effect of preventive percutaneous coronary intervention was directionally consistent for each component of the primary composite outcome.[94]

The PREVENT suggested that sealing such plaques may prevent future acute coronary events, particularly in high-risk patients with multivessel disease. However, these benefits were driven mainly by softer endpoints observed in an open-label design, and were not accompanied by significant reductions in mortality or hard outcomes.[222] Concerns remain regarding the procedural risks and cost-effectiveness of preventive PCI, and the impact of novel and more intensive lipid-lowering therapies in this clinical setting has not been adequately explored.

Coronary lesion severity

In the BARI 2D trial, diabetics with more extensive coronary disease and greater myocardial jeopardy had less cardiac death or MI when treated with CABG (but not PCI) and optimum medical therapy than medical therapy alone.[223]

In the FAME II trial, 888 patients with stable coronary artery disease and at least one stenosis with fractional flow reserve (FFR) ≤0.80 were randomly assigned to FFR-guided PCI plus the optimal medical therapy or optimal medical therapy alone. At five years, the primary endpoint, a composite of death, MI, or urgent revascularization, was lower in the PCI group than in the medical-therapy group (13.9% vs. 27.0%; P<0.001). The difference was driven by urgent revascularizations, which occurred in 6.3% of the patients in the PCI group as compared with 21.1% of those in the medical-therapy group (hazard ratio, 0.27; 95% CI, 0.18 to 0.41). There were no significant differences between the PCI group and the medical-therapy group in the rates of death or myocardial infarction.[224] Similar results were derived a 2-year follow-up.[225] Thus, lesions with FFR≤0.80 may be treated with PCI,[226 227] whereas coronary lesions with fractional flow reserve (FFR) > 0.8 can be left on medical therapy (DEFER, FAME, and FAME II trials).[228 107, 224, 225, 229]

Routine FFR assessment of at least ambiguous lesions at time of diagnostic angiography should be considered,[230-232] although reservations have been raised.[233] The interim results of the FUTURE trial in 933 patients with multivessel stable or unstable coronary artery disease showed a non-significant excess of mortality trend in the FFR-guided revascularization group and no clinical benefit of FFR in comparison with standard angiographically guided revascularization.[234] Furthermore, it should be noted that in all relevant trials the composite endpoint differences favoring FFR were driven largely by repeat revascularization, and FFR-guided intervention has not been shown to reduce total or cardiac mortality. The long-term significance of FFR measurements depends on the rate of disease progression, and FFR may be less relevant in patients with diabetes or plaques with unstable features.[235, 236]

Detection of ischemia

The clinical significance of detected ischemia is still controversial, particularly in patients with mild or absent symptoms.[210] Small RCTs,[237-240] and several registry analyses [241, 242] have provided evidence that revascularization by CABG or PCI may offer a greater survival benefit than medical therapy in patients with significant inducible ischemia (>10% of LV myocardium), but this has not yet been verified by adequately sized RCTs in the presence of preserved LV function.[243-245]

Several trials have demonstrated that PCI has reduced major cardiac events, defined as a composite of death, myocardial infarction and repeat revascularization without an effect on mortality: the ACIP trial in patients with ischemia during stress testing and ambulatory ECG monitoring,[237] the TIME trial in elderly patients with severe symptoms,[239] and the SWISSI 2 trial of asymptomatic post –infarct patients with a positive stress test.[240] In a small trial in stable, low-risk patients with inducible ischemia, revascularization by PCI was also found to be superior to medical therapy using the combined end-point of mortality and incidence of an acute coronary syndrome (JSAP trial).[246] The MASS-II trial in patients with proximal multivessel coronary stenoses of more than 70% by visual assessment and documented ischemia compared 10-year survival of medically treated patients with to those treated with PCI or CABG. Medical therapy was associated with a significantly higher incidence of combined events of cardiac death, subsequent MI, and additional revascularization compared to CABG.[238] However, the medical therapy used in that trial was not optimal by contemporary standards. In the large observational series of Cedars-Sinai Medical Center, revascularization compared with medical therapy offered a greater survival benefit (absolute and relative) in patients with moderate to large amounts of inducible ischemia. In contrast, the survival of patients with minimal ischaemia was superior with medical therapy without revascularization.[241, 242]

The COURAGE trial enrolled 2287 patients with 70% or greater diameter stenosis in at least one proximal epicardial coronary artery, preserved LV function, and evidence of myocardial ischemia or angina. For the composite primary endpoint of death and nonfatal MI, no significant difference was found between PCI plus optimal medical therapy (OMT) versus OMT alone after a mean follow-up of 4.6 years. Rates of angina were consistently lower in the PCI group than in the medical therapy group during the first several years of follow-up but were no longer statistically significantly different at 5 years. Rates of subsequent revascularization were also lower in the PCI group.[247] No difference in mortality was detected during an extended follow-up up to 15 years.[101] In the COURAGE nuclear substudy, more PCI patients exhibited significant ischemia reduction (33% versus 19% for OMT; P=0.0004), especially patients with moderate to severe pretreatment ischemia (78% versus 52%; P=0.007). Patients with ischemia reduction had lower unadjusted risk for death or myocardial

infarction (P=0.037 [risk-adjusted P=0.26]), particularly if baseline ischemia was moderate to severe (P=0.001 [risk-adjusted P=0.08]).[248] However, in subsequent analyses of the COURAGE database, the presence of ischaemia did not identify subjects with greater benefit from PCI.[218, 249] In another subset analysis of this trial, the anatomic burden of atherosclerosis was a consistent predictor of death, MI, and NSTE-ACS, whereas ischemic burden was not.[76] The presence of inducible ischemia did not identify patients with worse prognosis or those who would benefit from revascularization in the STICH trial.[244] The ORBITA randomized trial, of only 200 patients, compared treatment of stable angina with percutaneous coronary intervention and intensive optimal medical therapy versus a sham procedure and medical therapy in 200 patients with ischemic symptoms. After a short follow-up period of 6 weeks, there was no statistically difference in the primary end-point of exercise time increment between groups although there were trends in favour of PCI which may have reached statistical significance in a larger trial.[250] However, among patients who were receiving little or no antianginal medication and had objective evidence of ischemia, PCI resulted in a lower angina symptom score than a placebo procedure.[251] In a meta-analysis of 5 RCTs (including the MASS II and COURAGE) involving 5286 patients with documented myocardial ischemia by exercise stress testing, nuclear or echocardiographic stress imaging, or fractional flow reserve, PCI plus medical therapy was not associated with a reduction in death, nonfatal MI, unplanned revascularization, or angina compared with medical therapy alone.[245]

The ISCHEMIA trial randomized 5179 patients with moderate or severe ischaemia, (>5% ischemia on imaging at low levels of exertion, ≤ 7 METS, or ≥2 segments with dobutamine- or exercise-induced severe hypokinesis or akinesis), and preserved LV function to optimum medical therapy versus PCI or CABG. At 6 months, the cumulative event rate of the primary outcome (a composite of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest) was 5.3% in the invasive-strategy group and 3.4% in the conservative-strategy group (95% CI 0.8 to 3.0, mainly due to more procedural infarctions); at 5 years, the cumulative event rate was 16.4% and 18.2%, respectively (difference, −1.8 percentage points; 95% CI, −4.7 to 1.0). Results were similar with respect to the key secondary outcome. There were 145 deaths in the invasive-strategy group and 144 deaths in the conservative-strategy group (hazard ratio, 1.05; 95% CI, 0.83 to 1.32). [252] Invasive management also did not lower all-cause mortality at 5.3 years of follow-up. However, cardiovascular mortality was significantly lower, whereas non-cardiovascular mortality was higher.[253] Ischemia severity was not associated with CV outcomes, but coronary anatomic severity was associated. In the subgroup of patients with the most severe CAD based coronary CT angiography, revascularization was associated with a reduction in CV death or MI but not in all-cause death.[102] In a further analysis, when the prespecified secondary MI definition was applied, the conservative strategy had significantly

lower composite event rates for the primary and major secondary trial end points because of an increased number of procedural MIs in the invasive strategy. Spontaneous type 1 MI events, associated with increased risk of cardiovascular death, were reduced with an invasive strategy (percutaneous coronary intervention or coronary artery bypass grafting).[254] In another subanalysis of the ISCHEMIA trial, complete percutaneous or surgical revascularization of all obstructed major coronary arteries reduced the composite incidence of cardiovascular death or MI.[255] Quantitative CCTA parameters of stenosis severity and atherosclerotic burden have been found independently associated with cardiovascular death and MI in a patient population with advanced CAD and moderate or severe myocardial ischaemia. However, these parameters offered only modest improvement in prognostic value beyond clinical risk characteristics.[256] The invasive strategy confers higher early risks such as peri-procedural MI (mainly with CABG) whereas it lowers long-term risks such as spontaneous MI.[257] Revascularization provided significantly greater angina relief physical functioning and quality of life than medical therapy.[258, 259] In the small, high-risk subgroup with HF and LVEF 35% to 45%, an initial invasive approach was associated with better event-free survival.[260] Patients with diabetes also did not derive incremental benefit from routine invasive management compared with initial medical therapy alone.[261] The ISCHEMIA-CKD trial on 777 patients with stable coronary disease, advanced chronic kidney disease, and moderate or severe ischemia, also did not find evidence that an initial invasive strategy, as compared with an initial conservative strategy, reduced the risk of death or nonfatal myocardial infarction.[262] Angina and quality of life were also similar in the two groups.[263] In a further analysis of the ISCHEMIA, both PCI and CABG were associated with better 3-year health status than conservative management.[264]

In the prospective observational CLARIFY registry (32 691 patients with stable coronary artery disease), anginal status was mapped each year in patients without new coronary revascularization or new myocardial infarction. The effect of 1-year changes in angina status on 5-year outcomes was analyzed using multivariable analysis. Angina affected almost one-quarter of patients with stable coronary artery disease but resolved without events or coronary revascularization in most patients.[1] However, the CLARIFY population had a high rate of previous MI and revascularization procedures suggesting that most of the dangerous coronary lesions already revascularized or having caused MI.

In another large cohort of 43,443 patients, early myocardial revascularization was associated with a significant reduction in mortality among both patients with normal LVEF and severe inducible myocardial ischemia and patients with low LVEF and moderate or severe inducible myocardial ischemia.[265]

It seems, therefore, that ischemia is important as a criterion for revascularization in the presence of reduced LV function.

Left ventricular function

In patients with ***multivessel disease, symptomatic heart failure, and LVEF<35***%, the value of CABG over medical therapy is now generally accepted, despite initial apparently neutral results by the HEART and STICH trials (see also Chapter 33).[137, 266] In a substudy of the STICH trial on patients with extensive disease and at least 2 of three prognostic factors such as presence of 3-vessel CAD, LVEF below the median (27%), and end-systolic volume index (ESVI) above the median (79 ml/m^2), but not with significant left main stenosis or class II or greater angina, CABG did reduce mortality compared to medical therapy alone.[77] In the 10-year follow-up report of the STICH extension trial (STICHES), in patients with LVEF≤35%, total and cardiovascular mortality were significantly lower among patients who underwent CABG in addition to receiving medical therapy than among those who received medical therapy alone.[132] The beneficial effect of revascularization in this group has also been verified in a meta-analysis on revascularization by CABG or PCI.[134] In the STICH Trial, younger patients had greater benefit for all-cause mortality than older subjects, but effects were equal when measured as cardiovascular mortality.[133] In a network meta-analysis, CABG appeared to be the best therapy for ischaemic LV dysfunction compared to medical therapy and PCI, although mainly based on observational data.[267] In the REVIVED-BCIS2 RCT, PCI was not associated with lower all-cause mortality, aborted sudden death, or sustained ventricular arrhythmias in patients with ischemic left ventricular dysfunction (LVEF <=35%) compared with optimal medical therapy alone.[268]

Myocardial viability

Assessment of myocardial viability did not identify patients with a survival benefit from CABG as compared with medical therapy alone, in either a substudy of the STICH or the smaller HEART trial. [136, 137] In the nonrandomized substudy of the STICH trial, detection of myocardial viability by SPECT or dobutamine echocardiography did not identify patients who would benefit with CABG over a 5-year follow-up, although considering crossovers and hospitalization for cardiovascular causes it favored revascularization.[136] However, in the 10-year follow-up study of the STICH, the presence of substantial amounts of viable myocardium was not associated with a long- term beneficial effect of CABG. The presence of viable myocardium was associated with improvement in left ventricular systolic function, irrespective of treatment, but such improvement was not related to long-term survival.[269] In the REVIVED RCT involving patients with severe left ventricular systolic dysfunction, extensive coronary disease, and dysfunctional but viable myocardium who received optimal medical therapy, the addition of revascularization by PCI did not result in a lower incidence of death from any cause or hospitalization for heart failure or incremental improvement in the left ventricular ejection fraction at a median of 3.4 years.[270] Similar results were produced by

the REVIVED-BCIS2 that failed to demonstrate a reduction in all-cause mortality or aborted sudden death following PCI in patients with reduced LVEF and viable myocardium.[268]

Despite the lack of clear evidentiary support and given the limitations in the available studies, viability testing provides prognostic information that might help predict the potential for benefit from revascularization in selected patients with CAD and LV dysfunction.[140] The ESC/EACTS 2018 GL on revascularization give a IIb-B recommendation for non-invasive imaging to access myocardial ischaemia and viability before the decision for revascularization in patients with heart failure and reduced LVEF.[217]

CABG vs PCI

In the absence of an acute coronary syndrome or recent MI, elective percutaneous coronary intervention with balloon, bare metal stents (BMS) or drug-eluting stents (DES) has not been shown to improve survival or decrease the risk of MI compared to medical therapy alone, even in the presence of proven ischemia.[245, 271-274] PCI outcomes may be better following the advent of new-generation drug eluting stents,[275] and studies comparing PCI to CABG provide indirect evidence that in several clinical scenarios percutaneous intervention may not be inferior to open heart surgery.[276] However, data from RCTs demonstrate a superiority for surgery in higher risk subsets with more extensive triple vessel disease and LV dysfunction.[210]

A number of trials have compared PCI with medical therapy in stable CAD, largely in patients with single vessel disease or less complex multivessel disease.[210] Because of low event rates in these lower risk patients, primary endpoints shifted from survival to composites of death, myocardial infarction and revascularization and even intermediates such as exercise treadmill time.[229, 237, 239, 240] In the absence of an acute coronary syndrome or recent MI, elective PCI has not been shown to improve survival or decrease the risk of MI compared to medical therapy alone.[245, 271, 272, 274] However, in patients with stable single-vessel coronary disease, PCI reduces ischemia and restores a normal hemodynamic response to exercise.[277] In an analysis of the ISCHEMIA trial, etter angina relief with CABG than PCI was seen at 1, but not 3, years.[264]

There are several potential reasons why PCI has failed to reduce mortality in stable, as opposed to unstable, CAD. Subtotal occlusions of a vessel supplying non-infarcted myocardium, stenoses greater than 90% that by definition represent vulnerable plaques,[278] significant, complex lesions that are prone to develop total occlusions, [279] and stenoses with unequivocally reduced fractional flow reserve (<0.80),[280] may represent optimal targets for PCI. However, randomized studies of PCI vs medical therapy to support this view are missing, although observational studies on registries argue in favour of PCI.[281] Possible explanations for the failure of PCI to improve prognosis might be the limited number of patients with proven significant ischemia enrolled in these trials, and adoption of complex,

elaborate techniques that have not proved their usefulness but expose the patient to additional risk of iatrogenic MI (14-18%),[282, 283] that has prognostic significance regardless of its extent.[283-286] PCI may reduce spontaneous MI compared to medical therapy, but at the expense of procedural MI that results in no difference in MI in total.[284] Even diagnostic coronary angiography may result in silent cerebral emboli detected by MRI in up to 10% of patients.[287] Interestingly, women face a higher risk of adverse cardiac outcomes than men do following PCI.[288] The Society for Cardiovascular Angiography and Interventions has proposed a limit of 10-fold rise of CK-MB or 70-fold of cTn (I or T) in order to define MI following revascularization.[289] However, using a highly sensitive cardiac troponin T assay, a substantially lower threshold (10× upper reference limit) has emerged as the optimal prognostic cut-off value.[290] A 2021 EAPCI document has proposed the post-PCI cTn cut-off threshold (>5 x 99th percentile URL) to define prognostically relevant 'major' periprocedural myocardial injury.[291] Additionally, PCI is directed at the lesions that cause ischaemic symptoms and does not change the natural history of coronary atherosclerosis in which non-obstructive lesions might progress suddenly to high-grade stenoses or vessel occlusion. These sites might have been bypassed by a coronary graft.[292]

Diabetics with multivessel disease

In the BARI trial in patients with multivessel disease, five-year survival was significantly better after CABG than after PCI, particularly in diabetics.[293] The BARI 2D trial in diabetics also demonstrated that patients with more extensive coronary disease and greater myocardial jeopardy had less cardiac death or MI when treated with CABG and optimum medical therapy than medical therapy alone, but there was no difference between PCI and optimal medical therapy.[223]

In the FREEDOM trial, 1900 patients with diabetes were randomly assigned to undergo either CABG or PCI with DES.[294] After 5 years of follow-up, the 947 patients assigned to undergo CABG had significantly lower mortality (10.9% vs. 16.3%) and fewer MIs (6.0% vs. 13.9%) than the 953 patients assigned to undergo PCI. However, patients in the CABG group had significantly more strokes (5.2% vs. 2.4%), mostly because of strokes that occurred within 30 days after revascularization. Treatment effects between CABG and PCI were not different in patients receiving insulin who had a higher rate of major cardiac adverse events in both revascularization arms.[295] In patients with chronic kidney disease (but with eGFR > 15 mL/min/1.73m^2) enrolled in the FREEDOM trial, CABG was superior to PCI without an increased risk of stroke.[296] In the long-term report of the FREEDOM, CABG was superior to PCI-DES in reducing all-cause mortality at a median follow-up of 7.5 years.[297]

In pooled analyses of individual patient data, CABG had a 5-year mortality benefit over PCI in patients with multivessel disease and diabetes.[298] whereas rates of stroke were

lower after PCI than CABG during the first 30 days but comparable thereafter during the next 5 years.[299]

In a pooled analysis of 4 randomized clinical trial of patients with left main disease considered equally suitable for PCI or CABG and with largely low to intermediate SYNTAX scores, diabetes was associated with higher rates of death and cardiovascular events through 5 years. Compared with CABG, PCI resulted in no difference in the risk of death and a lower risk of early stroke regardless of diabetes status, and a higher risk of spontaneous MI and repeat coronary revascularization, with larger late absolute excess risks in patients with diabetes.[300]

Complex, multivessel disease, and high SYNTAX score

CABG is also preferable to PCI in patients with complex, multivessel disease, and high and intermediate SYNTAX scores. In the SYNTAX trial, 1800 patients with previously untreated left main or 3-vessel disease were randomly assigned to undergo CABG or PCI with first-generation paclitaxel-eluting stents.[301] At 10 years (SYNTAXES), 244 (27%) patients had died after PCI and 211 (24%) after CABG (p=0·092). Among patients with three-vessel disease, 151 (28%) of 546 had died after PCI versus 113 (21%) of 549 after CABG (hazard ratio 1·41 [95% CI 1·10–1·80]), and among patients with left main coronary artery disease, 93 (26%) of 357 had died after PCI versus 98 (28%) of 348 after CABG (0·90 [0·68–1·20], $P_{interaction}$=0·019). There was no treatment-by-subgroup interaction with diabetes. Thus, no significant difference existed in all-cause death between PCI using first-generation paclitaxel-eluting stents and CABG. However, CABG provided a significant survival benefit in patients with three-vessel disease, but not in patients with left main coronary artery disease.[301] The use of multiple arterial grafting is beneficial in this setting.[302] In a previous analysis, a higher rate of MI-related deaths had been detected in the PCI arm, mainly in patients with diabetes, 3-vessel disease, or high SYNTAX score.[303] In patients with high or intermediate scores, CABG was associated with a lower rate of mortality, MI and revascularization but no significant difference in stroke. In the BEST trial, 880 patients with multivessel CAD were randomized to CABG or second generation everolimus-eluting stents. No difference in mortality was detected, but at a follow-up of 4.6 years, there were significantly fewer spontaneous MIs and repeat-revascularization procedures in the CABG group than in the PCI group.[304] In the FAME-3 RCT, in patients with angiographically identified three-vessel coronary artery disease, CABG resulted in a lower incidence of the composite of death, myocardial infarction, stroke, or repeat revascularization at 1 year than FFR-guided PCI in which current-generation zotarolimus-eluting stents were used.[305] In 5651 patients with triple vessel CAD from the CREDO registry, CABG was associated with lower mortality but higher risk of stroke compared to PCI. Considering age groups, there was an excessive risk of mortality with PCI in patients ≥74 years of age, whereas no difference was seen in younger patients.[306] In another

observational registry of patients with 2 and 3-vessel disease, the risk of death was similar for PCI with everolimus-eluting stents compared to CABG. PCI was associated with a higher risk of MI (among patients with incomplete revascularization) and repeat revascularization but a lower risk (62%) of stroke.[307] However, in the most recent meta-analysis, no mortality benefit of CABG vs PCI was detected in patients with multivessel disease but without diabetes.[298]

These results suggest that CABG remains the preferred option for clinically suitable patients with complex disease (intermediate or high SYNTAX Scores).[308] PCI may be an acceptable alternative revascularization method to CABG when treating patients with less complex disease, and especially without diabetes, but its superiority over optimal medical therapy by means of mortality has not been shown.

Unprotected left main disease (≥50%)

Data on the optimal management of patients with left main disease are rather limited, particularly since in most studies that have addressed the issue a medical therapy arm was missing. Thus, comparisons exit only between CABG and PCI, and have mainly been considered in the context of the extent of disease in the other coronary arteries. The SYNTAX trial has demonstrated that in patients with left main coronary artery (LMCA) disease and low to intermediate SYNTAX scores, outcomes with PCI were equivalent to CABG.

Most recent (LE MANS, PRECOMBAT, EXCEL)[309 310, 311] although not all (NOBLE) [312] RCT have shown that PCI with drug-eluting stents may now also be used instead of CABG for unprotected left main coronary lesions, especially with associated low or intermediate anatomical complexity. The EXCEL trial of 1905 patients with left main disease and, 75% of them with low- or intermediate-risk SYNTAX scores (≤32) demonstrated non-inferiority at 3 years for the combined end point of all-cause death, stroke, or MI in patients treated with a contemporary thin-strut cobalt-chromium, everolimus-eluting stent versus CABG.[313] At 30 days, an increased initial hazard was found in patients treated with CABG, and PCI resulted in fewer cases of bleeding and transfusion, renal failure, infection, and major arrhythmias. However, major event rates were higher in the PCI group after 30 days, resulting in nearly identical 3-year composite primary end-point event rates in both groups. Notably, stent thrombosis rates were lower than symptomatic graft occlusion at all time periods. At 5 years, a primary outcome event had occurred in 22.0% of the patients in the PCI group and in 19.2% of the patients in the CABG group (P=0.13).[311] However, spontaneous MI occurred relatively infrequently within 5 years after revascularization but at a higher rate after PCI compared with CABG.[314] The NOBLE trial of 1201 patients treated with earlier generation, thicker-strut stents or CABG demonstrated superiority for CABG at 5 years, driven primarily by a higher rate of repeat revascularization and nonprocedural MI for PCI.[312] NOBLE did not routinely ascertain peri-procedural MI, which may occur more frequently with CABG than

PCI, and, surprisingly, an excess in stroke was reported after 30 days in the PCI arm versus the CABG arm. Stent thrombosis rates in NOBLE were 4-fold higher than in EXCEL and similar to the rate of symptomatic graft occlusion. In both trials, cardiovascular and all-cause mortality at follow-up of 3 or 5 years were not significantly different between PCI and CABG. In the most comprehensive meta-analyses, no mortality benefit for CABG over PCI was seen in patients with left main disease up to 5 years after the procedure, regardless of diabetes status and SYNTAX score.[298, 315, 316] In the most recent of these meta-analyses, including the SYNTAX, PRECOMBAT, NOBLE, and EXCEL RCTs, spontaneous myocardial infarction and repeat revascularisation were more common with PCI than with CABG, the risk of stroke was lower with PCI (meta-analysis of .[316] The 2022 ESC/EACTS review of the ESC guidelines of revascularization, therefore, gives a IIA (instead of I A) recommendation for left main disease and a low Syntax score (<22).[317]

When coronary intervention is chosen, the use of intracoronary imaging is important.[318] For provisional left main-crossover stenting, target minimum stent areas should be 10–12 mm² in the left main and 7–8 mm² in the LAD, with a minimum lumen area in the circumflex of >4 mm².[318]

LV dysfunction

There are no RCTs comparing CABG with PCI in multivessel patients with LV dysfunction. PCI with second generation everolimus-eluting stents might conceivably offer comparable long-term survival with CABG in patients with multivessel disease and reduced LV function, but no data from comparative trials exist. In a recent registry, PCI was associated with higher risk of MI (in those with incomplete revascularization) and repeat revascularization, and CABG was associated with higher risk of stroke.[319] In a propensity-matched study on patients with CAD, diabetes, and LV dysfunction, treated with PCI (n=869) or CABG(n-869), there was a significantly lower incidence of major adverse cardiac and cerebrovascular events and better long-term survival with CABG, without a higher risk for stroke.[320] In meta- analyses of published observational studies both CABG and PCI were superior to medical therapy alone, but CABG showed a survival benefit compared to PCI.[134, 267] Definitive randomized controlled trials comparing CABG and PCI in this setting are required.

Isolated proximal LAD

The presence of proximal LAD disease is of prognostic significance, and revascularization by CABG using a left internal mammary artery (LIMA) graft has been recommended in clinical practice guidelines. However, an observational treatment comparison using the New York state registry,[321] and a meta-analysis of 9 RCTs involving 1210 patients with isolated proximal LAD single vessel disease including diabetics, showed no difference in mortality or MI but fewer repeat revascularizations and more effective angina relief after CABG.[322] In

relatively recent trials, PCI with DES has been found noninferior to MIDCAB surgery,[323] although target lesion revascularization was more frequent in the PCI group.[324]

Chronic total occlusions

Data from New York's PCI registry reported that successful revascularization of chronic total occlusions is associated with improved survival compared with unsuccessful procedures,[325] and in a retrospective analysis of the UK Central Cardiac Audit Database, elective chronic total coronary occlusion angioplasty improved long-term survival compared with partial revascularization.[326] However, this has not been a universal finding,[327] and in all RCTs conducted so far, reopening of a total occlusion failed to demonstrate a mortality benefit (EXPLORE and DECISION-CTO trials).[328-330] In the DECISION-CTO, 834 patients with silent ischemia, stable angina or ACS, and de novo chronic total occlusion were randomized to either optimal medical therapy or PCI with or without stenting. At 3 years, the combined primary endpoint of all-cause death, MI, stroke, and repeat revascularization in the intention-to-treat population was similar for patients who received optimal medical therapy alone compared with the interventions.[328] In the EXPLORE trial on patients with STEMI and concurrent chronic total occlusion, there was no overall benefit for recanalization of the total occlusion in terms of LVEF or LVEDV.[329] In the EUROCTO trial on patients with stable angina pectoris related to a CTO, patients had less angina and a better quality of life following PCI, but at the cost of a numerical higher number of death or MI (not statistically significant).[330]

In the OAT, opening of an occluded artery beyond 24 hours after the MI in patients without residual ischemia also did not decrease the risk of death, reinfarction rate or development of LV failure.[331, 332]

Complete revascularization

The issue of complete revascularization is not settled in patients with stable coronary artery disease.[333] Although a comprehensive meta-analysis of RCT and observational studies indicated reduced mortality and MI with complete, as opposed to incomplete revascularization,[334] this is not unequivocally established either for CABG,[335, 336] or PCI.[337-339] In a retrospective study on asymptomatic patients (33% of them diabetic) who had been subjected to previous revascularization with CABG or PCI, the detection of inducible ischemia on myocardial perfusion scintigraphy did not indicate a survival benefit from repeat revascularization.[340] Leaving stenoses with nonsignificant FFR readings ungrafted during CABG has not been shown to be associated with excess hazard over a 3-year follow-up.[341] In the SYNTAX trial, a residual SYNTAX Score >8 was a powerful indicator of increased mortality at 5-years.[342]

Thus, complete anatomical revascularization (i.e. treatment of all coronary artery segments >1.5 mm in diameter and ≥50% diameter stenosis regardless of their functional

significance) is not supported by the available data, and incomplete anatomical but functionally adequate revascularization (i.e. treatment of coronary segments with ≥50% diameter stenosis and an FFR ≤0.8, or ≥70% diameter stenosis without FFR supplying viable myocardium) appears to offer comparable results.[333]

Summary of indications for revascularization

Apart from the and the remarkable effectiveness of modern medical therapy and the rate of complications of CABG and PCI, other potential explanations for the reported lack of benefit by revascularization in most cases of stable CAD include the confounding implications of coronary microvascular dysfunction,[343] and the possibility of co-existent non-ischaemic cardiomyopathy.[344]

However, revascularization is deemed appropriate in patients with high symptom burden, high-risk features, and high coronary disease burden.[210, 345] In a meta-analysis of RCTs on patients with stable ischemic heart disease, routine revascularization was not associated with improved survival but was associated with a lower risk of nonprocedural MI and unstable angina with greater freedom from angina at the expense of higher rates of procedural MI.[346] However, in a subsequent meta-analysis a consistent reduction of cardiac mortality in favour of elective coronary revascularisation plus medical therapy compared with medical therapy alone was detected in stable patients. The cardiac survival benefit after revascularisation improved with longer follow-up times and was associated with fewer spontaneous MIs.[211] PCI may also be indicated in the presence of vulnerable lesions detected at angiography.[94] The performance of revascularization also provides a strong impetus for aggressive risk factor modification with optimal medical therapy, which will benefit patients with both PCI and CABG.[347] This finding was demonstrated in the SYNTAX trial, in which optimal medical therapy at both discharge and 5 years, although achieved in only a minority of patients, was associated with a greater reduction in death, MI, or stroke than the differences between CABG and PCI.[348] Age should also be taken into account. There is a steeper rise of operative mortality after age 75 for coronary bypass and approaching octogenarian age for isolated valve surgery,[349] and nonagenarians have a considerably higher 30-day mortality compared to younger patients after PCI.[350] In the era of modern medical therapy the indications of revascularization are less well defined, and each case should be individualized. However, current recommendations by cardiology societies and experts can be summarized as:

No revascularization is indicated

1. Asymptomatic or mildly symptomatic patients without significant ischemia on noninvasive testing.

2. Non-significant disease (significant is defined as lesions with >70% stenosis and ischemia or >90% stenosis in two angiographic views or FFR<=0.8)
3. Occluded vessel 24h after MI and no significant residual ischemia.

CABG is indicated to improve survival

(Patients without significant comorbidities)

1. Left main disease (>50%) and SYNTAX score>=22.
2. Three vessel disease (>70%) and SYNTAX score>=22.
3. Three vessel disease, LVEF 35-50%, and diabetes.
4. Ischemic heart failure, LVEF<=35%, and CAD amenable to CABG.
5. Two vessel disease with proximal LAD stenosis.

PCI is indicated to improve symptoms

(Patients with coronary anatomy suitable for PCI)

1. Left main disease (>50%) and SYNTAX score<22.
2. Three vessel disease (>70%) and SYNTAX score>=22-33 and advanced age or comorbidities.
3. One- or two vessel disease with or without proximal LAD stenosis.
4. Two or three vessel disease with or without left main disease, and SYNTAX score <=22

Left main disease refers to stenosis >50% whereas in the other coronaries >70%.
In all other settings, the decision depends on patient individual risks due to comorbidities and age.

Refractory angina

Refractory angina refers to long-lasting symptoms due to established reversible ischaemia, which cannot be controlled by escalating medical therapy, bypass grafting, or stenting. In the current era, proportion of patients with coronary artery disease who have daily or weekly angina ranges from 2% to 24%.[351, 352] Treatment is important to improve the quality of life, and novel strategies such as coronary sinus reducer, rextracorporeal shock wave therapy, low-intensity pulse ultrasound are also available.[351, 352] Treatment options are presented in Table 19.

Evaluation and Risk Assessment Before Non-cardiac Surgery

A detailed discussion on cardiovascular morbidity and mortality in patients undergoing noncardiac surgery is presented in the relevant section on Noncardiac Surgery.

The earliest optimal time for elective surgery after stenting is one month in stable patients and 3 months in patients with an ACS.[353] Myocardial infarction, stroke within 3 months before surgery and coronary stenting within 6 months before surgery are risk factors for cardiac events during noncardiac surgery.[354, 355] In a VA study among patients undergoing noncardiac surgery within 2 years of coronary stent placement, cardiac events were associated with emergency surgery, MI within the prior 6 months, and advanced cardiac disease (Cardiac Risk Index >2) but not stent type or timing of surgery beyond 6 months after stent implantation.[354] The risk is higher in the first 6 weeks after stenting (2.8%), and becomes 2.0% between 6 weeks and 6 months, and 0.9% after 6 months,[356] and may remain high up to 1 year following stenting regardless of the type of the stent.[357] It seems, however, that the risk is actually high only the first month after DES implantation.[358] In patients needing surgery early after stent implantation, consideration should be given to perioperative continuation of oral antiplatelet therapy (at least aspirin). Preoperative bridging with a glycoprotein IIb/IIIa inhibitor in patients undergoing surgery after coronary stenting does not abolish the risk of perioperative stent thrombosis and may carry increased risk for bleeding.[359] Tables 20-22, and Figures 26-29 present recommendations about interruption of antiplatelet therapy in patients who need non-cardiac surgery.

Transplantation is generally not recommended 4 weeks after balloon angioplasty, 3 months after BMS, and 12 months after DES. In case of urgent surgery, however, clopidogrel must be stopped for 5 days, or even continued in case of low bleeding risk. In patients without stents, the use of aspirin perioperatively in patients with and without preexisting vascular disease increases the risk of bleeding without any effect on the rate of a composite of death or nonfatal myocardial infarction (POISE-2 trial).[360]

Long-term Management

Recommendations for long-term management and follow-up are presented in Table 23 and Figures 30 and 31. Measures for secondary prevention are also implemented as described in the Therapy section. Echocardiography and tests for ischemia are indicated when new symptoms appear. Annual treadmill exercise testing in patients who have no change in clinical status, may also be performed in moderate- or high-risk patients. However, the value of routine testing or catheterization following stenting is questionable.[361] In patients entering a formal cardiac rehabilitation program after PCI treadmill exercise testing is reasonable, but routine periodic stress testing of asymptomatic patients after PCI without specific clinical

indications are not recommended. Recommendations on Sports are provided in Table 24 and Figure 32. Sexual activity should be individualized (Table 25). Recommendations for adult cancer survivors with coronary artery disease are presented in Table 26. Recommendations for pregnancy are provided in Table 27.

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