

Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the
European Society of Cardiology (ESC) and the
European Association for Cardio-Thoracic Surgery (EACTS)

Developed with the special contribution of the
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Disclaimer. The ESC Guidelines represent the views of the ESC and were arrived at after careful consideration of the available evidence at the time they were written. Health professionals are encouraged to take them fully into account when exercising their clinical judgement. The guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patients, in consultation with that patient, and where appropriate and necessary the patient's guardian or carer. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

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Abbreviations and acronyms

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACEF	age, creatinine, ejection fraction
ACS	acute coronary syndrome
AF	atrial fibrillation
AHA	American Heart Association
AHF	acute heart failure
AMI	acute myocardial infarction
aPTT	activated partial thromboplastin time
ASA	acetylsalicylic acid
BiVAD	biventricular assist device
BMI	body mass index
BMS	bare metal stent
BTT	bridge to transplantation
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CAS	carotid artery stenting
CEA	carotid endarterectomy
CHADS ₂	CHF, hypertension, age, diabetes, stroke
CHF	chronic heart failure
CI	confidence interval
CIN	contrast-induced nephropathy
CKD	chronic kidney disease
CPB	cardiopulmonary bypass
CRT	cardiac resynchronization therapy
CT	computed tomography
CTO	chronic total occlusion
CVA	cerebrovascular accident
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
DT	destination therapy
EACTS	European Association for Cardio-Thoracic Surgery
EBAC	European Board for Accreditation in Cardiology
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenator
EF	ejection fraction
EMS	emergency medical service
ESC	European Society of Cardiology
ESRD	end stage renal disease
FFR	fractional flow reserve
FMC	first medical contact
GFR	glomerular filtration rate
GIK	glucose insulin potassium
GP	general physician
GPIIb–IIIa	glycoprotein IIb–IIIa
HF	heart failure
HR	hazard ratio
IABP	intra-aortic balloon pump
ICD	implantable cardioverter defibrillator
ICU	intensive care unit
ITA	internal thoracic artery
i.v.	intravenous
IVUS	intravascular ultrasound
LA	left atrium

LAD	left anterior descending
LCx	left circumflex
LM	left main
LMWH	low molecular weight heparin
LV	left ventricle
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
MACCE	major adverse cardiac and cerebral event
MACE	major adverse cardiac event
MDCT	multidetector computed tomography
MI	myocardial infarction
MIDCAB	minimally invasive direct coronary artery bypass
MPS	myocardial perfusion stress
MR	mitral regurgitation
MRI	magnetic resonance imaging
MVD	multivessel disease
NCDR	National Cardiovascular Database Registry
NPV	negative predictive value
NSTE-ACS	non-ST-segment elevation acute coronary syndrome
NYHA	New York Heart Association
OCT	optical coherence tomography
OMT	optimal medical therapy
OR	odds ratio
PAD	peripheral arterial disease
PCI	percutaneous coronary intervention
PES	paclitaxel-eluting stent
PET	positron emission tomography
PPV	positive predictive value
RCA	right coronary artery
RCT	randomized clinical trial
s.c.	subcutaneous
SCD	sudden cardiac death
SES	sirolimus-eluting stent
SPECT	single photon emission computed tomography
STEMI	ST-segment elevation myocardial infarction
SVG	saphenous vein graft
SVR	surgical ventricular reconstruction
TIA	transient ischaemic attack
TVR	target vessel revascularization
UFH	unfractionated heparin
VD	vessel disease
VSD	ventricular septal defect
VT	ventricular tachycardia
ZES	zotarolimus-eluting stent

1. Preamble

Guidelines and Expert Consensus Documents summarize and evaluate all available evidence with the aim of assisting physicians in selecting the best management strategy for an individual patient suffering from a given condition, taking into account the impact on outcome and the risk–benefit ratio of diagnostic or therapeutic means. Guidelines are no substitutes for textbooks and their legal implications have been discussed previously. Guidelines and recommendations

should help physicians to make decisions in their daily practice. However, the ultimate judgement regarding the care of an individual patient must be made by his/her responsible physician(s).

The recommendations for formulating and issuing ESC Guidelines and Expert Consensus Documents can be found on the ESC website (<http://www.escardio.org/knowledge/guidelines/rules>).

Members of this Task Force were selected by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) to represent all physicians involved with the medical and surgical care of patients with coronary artery disease (CAD). A critical evaluation of diagnostic and therapeutic procedures is performed including assessment of the risk–benefit ratio. Estimates of expected health outcomes for society are included, where data exist. The level of evidence and the strength of recommendation of particular treatment options are weighed and graded according to predefined scales, as outlined in Tables 1 and 2.

The members of the Task Force have provided disclosure statements of all relationships that might be perceived as real or potential sources of conflicts of interest. These disclosure forms are kept on file at European Heart House, headquarters of the ESC. Any changes in conflict of interest that arose during the writing period were notified to the ESC. The Task Force report received its entire financial support from the ESC and EACTS, without any involvement of the pharmaceutical, device, or surgical industry.

ESC and EACTS Committees for Practice Guidelines are responsible for the endorsement process of these joint Guidelines. The finalized document has been approved by all the experts involved in the Task Force, and was submitted to outside specialists selected by both societies for review. The document is revised, and finally approved by ESC and EACTS

and subsequently published simultaneously in the European Heart Journal and the European Journal of Cardio-Thoracic Surgery.

After publication, dissemination of the Guidelines is of paramount importance. Pocket-sized versions and personal digital assistant-downloadable versions are useful at the point of care.

Some surveys have shown that the intended users are sometimes unaware of the existence of guidelines, or simply do not translate them into practice. Thus, implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

2. Introduction

Myocardial revascularization has been an established mainstay in the treatment of CAD for almost half a century. Coronary artery bypass grafting (CABG), used in clinical practice since the 1960s, is arguably the most intensively studied surgical procedure ever undertaken, while percutaneous coronary intervention (PCI), used for over three decades, has been subjected to more randomized clinical trials (RCTs) than any other interventional procedure. PCI was first introduced in 1977 by Andreas Gruentzig and by the mid-1980s was promoted as an alternative to CABG. While both interventions have witnessed significant technological advances, in particular the use of drug-eluting stents (DES) in PCI and of arterial grafts in CABG, their role in the treatment of patients presenting with stable CAD is being challenged by advances in medical treatment, referred to as optimal medical therapy (OMT), which include intensive lifestyle and pharmacological management. Furthermore, the differences between the two revascularization strategies should be recognized. In CABG, bypass grafts are placed to the mid-coronary vessel beyond the ‘culprit’ lesion(s), providing extra sources of nutrient blood flow to the myocardium and offering protection against the consequences of further proximal obstructive disease. In contrast, coronary stents aim to restore the normal conductance of the native coronary vasculature without offering protection against new disease proximal to the stent.

Even with this fundamental difference in the mechanisms of action between the two techniques, myocardial revascularization provides the best results when focusing on the relief of ischaemia. In patients presenting with unstable angina, non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS), and ST-segment elevation myocardial infarction (STEMI), myocardial ischaemia is obvious and life-threatening. Culprit coronary stenoses are easily identified by angiography in the vast majority of cases. By contrast, in patients with stable CAD and multivessel disease (MVD) in particular, identification of the culprit stenosis or stenoses requires anatomical orientation by angiography combined with functional evaluation, obtained either by non-invasive imaging before catheterization, or during the invasive procedure using pressure-derived fractional flow reserve (FFR) measurements.

Many conditions, stable or acute, can be treated in different ways, including PCI or surgical revascularization. The advances in technology imply that most coronary

Table 1
Classes of recommendations

Classes of recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Table 2
Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Table 3

Recommended risk stratification scores to be used in candidates for percutaneous coronary intervention or coronary artery bypass grafting

Score	Calculation	Number of variables used to calculate risk		Validated outcomes	Class ^a / Level ^b		Ref. ^c
		Clinical	Angiographic		PCI	CABG	
EuroSCORE	www.euroscore.org/calc.html	17	0	Short- and long-term mortality	IIb B	I B	[2,3,6]
SYNTAX score	www.syntaxscore.com	0	11 (per lesion)	Quantify coronary artery disease complexity	IIa B	III B	[4]
Mayo Clinic Risk Score	[7,8]	7	0	MACE and procedural death	IIb C	III C	–
NCDR CathPCI	[5]	8	0	In-hospital mortality	IIb B	–	[5]
Parsonnet score	[9]	16	0	30-day mortality	–	III B	[9]
STS score ^d	http://209.220.160.181/STSWebRiskCalc261/	40	2	Operative mortality, stroke, renal failure, prolonged ventilation, deep sternal infection, re-operation, morbidity, length of stay <6 or >14 days	–	I B	[10]
ACEF score	[Age/ejection fraction (%) + 1 (if creatinine >2 mg/dL) [11]	2	0	Mortality in elective CABG	–	IIb C	–

^a Class of recommendation.^b Level of evidence.^c References.^d The STS score is undergoing periodic adjustment which makes longitudinal comparisons difficult.

ACEF = age, creatinine, ejection fraction; CABG = coronary artery bypass grafting; MACE = major adverse cardiac event; NCDR = National Cardiovascular Database Registry; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons.

lesions are technically amenable to PCI; however, technical feasibility is only one element of the decision-making process, which should incorporate clinical presentation, severity of angina, extent of ischaemia, response to medical therapy, and extent of anatomical disease by angiography. Both revascularization methods carry procedure-related risks that are different to some extent in nature, rate, and time domain. Thus patients and physicians need to 'balance short-term convenience of the less invasive PCI procedure against the durability of the more invasive surgical approach' [1].

Formulation of the best possible revascularization approach, taking into consideration the social and cultural context also, will often require interaction between cardiologists and cardiac surgeons, referring physicians or other specialists as desirable. Patients need help in taking informed decisions about their treatment, and the most valuable advice will likely be provided to them by the Heart Team. Recognizing the importance of the interaction between (interventional) cardiologists and cardiac surgeons, the leadership of both the ESC and EACTS has given this Joint Task Force, their respective Guideline Committee, and the reviewers of this document the mission to draft balanced, patient-centred, evidence-driven practice guidelines on myocardial revascularization.

3. Scores and risk stratification, impact of comorbidity

Myocardial revascularization is appropriate when the expected benefits, in terms of survival or health outcomes (symptoms, functional status, and/or quality of life), exceed the expected negative consequences of the procedure. Therefore, risk assessment is an important aspect of contemporary clinical practice, being of value to clinicians and patients. Over the long term, it allows quality control and the assessment of health economics, while also serving

as a means for individual operators, institutions and regulatory bodies to assess and compare performance. Numerous different models have been developed for risk stratification, and those in current clinical use are summarized in Table 3. Comparative analyses of these models are limited because available studies have largely evaluated individual risk models in different patient populations with different outcome measures reported at various time points. These limitations restrict the ability to recommend one specific risk model; however:

- The EuroSCORE validated to predict surgical mortality was recently shown to be an independent predictor of major adverse cardiac events (MACEs) in studies with both percutaneous and surgical treatment arms [2,3]. Therefore, it can be used to determine the risk of revascularization irrespective of, and even before, the selection of treatment strategy. It has little role, however, in determining optimal treatment.
- The SYNTAX score has been shown to be an independent predictor of MACE in patients treated with PCI but not with CABG [4]. Therefore it has a role in aiding the selection of optimal treatment by identifying those patients at highest risk of adverse events following PCI.
- The National Cardiovascular Database Registry (NCDR CathPCI risk score) has been validated in PCI patients and should only be used in this context [5].
- The Society of Thoracic Surgeons (STS) score, and the age, creatinine, and ejection fraction (ACEF) score have been validated in surgical patients, and therefore should only be used to determine surgical risk.

It is important to acknowledge that no risk score can accurately predict events in an individual patient. Moreover, limitations exist with all databases used to build risk models, and differences in definitions and variable content can affect the performance of risk scores when they are applied across different populations. Ultimately risk stratification should be used as a guide, while clinical judgement and multidisciplinary dialogue (Heart Team) remain essential.

Table 4
Multidisciplinary decision pathways, patient informed consent, and timing of intervention

	ACS				Stable MVD	Stable with indication for <i>ad hoc</i> PCI ^a
	Shock	STEMI	NSTE-ACS ^b	Other ACS ^c		
Multidisciplinary decision making	Not mandatory.	Not mandatory.	Not required for culprit lesion but required for non-culprit vessel(s).	Required.	Required.	According to predefined protocols.
Informed consent	Oral witnessed informed consent or family consent if possible without delay.	Oral witnessed informed consent may be sufficient unless written consent is legally required.	Written informed consent ^d (if time permits).	Written informed consent ^d .	Written informed consent ^d .	Written informed consent ^d .
Time to revascularization	Emergency: no delay.	Emergency: no delay.	Urgency: within 24 h if possible and no later than 72 h.	Urgency: time constraints apply.	Elective: no time constraints.	Elective: no time constraints.
Procedure	Proceed with intervention based on best evidence/availability.	Proceed with intervention based on best evidence/availability.	Proceed with intervention based on best evidence/availability. Non-culprit lesions treated according to institutional protocol.	Proceed with intervention based on best evidence/availability. Non-culprit lesions treated according to institutional protocol.	Plan most appropriate intervention allowing enough time from diagnostic catheterization to intervention.	Proceed with intervention according to institutional protocol defined by local Heart Team.

^a Potential indications for *ad hoc* PCI are listed in Table 5.

^b See also Table 12.

^c Other ACS refers to unstable angina, with the exception of NSTE-ACS.

^d This may not apply to countries that legally do not ask for written informed consent. ESC and EACTS strongly advocate documentation of patient consent for all revascularization procedures.

ACS = acute coronary syndrome; MVD = multivessel disease; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

4. Process for decision making and patient information

4.1. Patient information

Patient information needs to be objective and unbiased, patient oriented, evidence based, up-to-date, reliable, understandable, accessible, relevant, and consistent with legal requirements. Informed consent requires transparency, especially if there is controversy about the indication for a particular treatment (PCI vs. CABG vs. OMT). Collaborative care requires the preconditions of communication, comprehension, and trust. It is essential to realize that health care decisions can no longer be based solely on research results and our appraisal of the patient's circumstances. Patients taking an active role throughout the decision making process have better outcomes. However, most patients undergoing CABG or PCI have limited understanding of their disease and sometimes unreasonable expectations with regard to the proposed intervention, its complications, or the need for late reintervention, especially after PCI.

Informing patients about treatment choices allows them to reflect on the advantages and disadvantages associated with either strategy. Patients can only weigh this information properly in the light of their personal values and must have the time to reflect on the trade-offs imposed by the estimates. The patient deserves to fully understand the risks, benefits, and uncertainties associated with the condition and its treatment. Avoiding incomprehensible jargon, and consistent use of terminology that the patient understands, are mandatory. Informed medical decision making should consider short-term procedure-related benefits and risks as well as expected long-term risks and benefits in terms of

survival, relief of angina, quality of life, and the potential need for late reintervention. It is equally important that any bias of stakeholders towards various treatment options for CAD is made known to the patient. Specialty bias and self-referral should not interfere with the decision process. With the exception of unstable patients or candidates for *ad hoc* PCI (Table 4), the patient should be offered enough time, up to several days as required, between diagnostic catheterization and intervention to reflect on the results of the diagnostic angiogram, to seek a second opinion as desirable, or to discuss the findings and consequences with his or her referring cardiologist and/or primary care physician. An example of a suitable and balanced patient information document is provided in the Appendix of the online document.

There is growing public demand for transparency regarding site and operator results. Anonymous treatment should be avoided. It is the patient's right to know who is about to treat him or her and to obtain information on the level of expertise of the operator and the volume load of the centre. In addition, the patient should be informed whether all treatment options are available at the site and whether surgery is offered on site or not. Non-emergent high-risk PCI procedures, including those performed for distal left main (LM) disease, complex bifurcation stenosis involving large side branches, single remaining coronary artery, and complex chronic total occlusion (CTO) recanalization, should be performed by adequately experienced operators at centres that have access to circulatory support and intensive care treatment, and have cardiovascular surgery on site.

For patients with stable CAD and multivessel or LM disease, all relevant data should be reviewed by a clinical/non-invasive cardiologist, a cardiac surgeon, and an interventional cardiologist (Heart Team) to determine

the likelihood of safe and effective revascularization with either PCI or CABG [4]. To ensure this review, myocardial revascularization should in general not be performed at the time of diagnostic angiography, thereby allowing the Heart Team sufficient time to assess all available information, reach a consensus, and clearly explain and discuss the findings with the patient. Standard evidence-based interdisciplinary institutional protocols may be used for common case scenarios, but complex cases should be discussed individually to find the best solution for each patient.

The above obviously pertains to patients in a stable condition who can make a decision without the constraints of an emergency situation. If potential adverse events are negligible compared with the expected treatment benefit or there is no viable alternative to emergency treatment, informed decision making may not be possible.

Patients considered for revascularization should also be clearly informed of the continuing need for OMT including antiplatelet agents, statins, β -blockers, and angiotensin-converting enzyme (ACE) inhibitors, as well as other secondary prevention strategies (Section 13).

4.2. Multidisciplinary decision making (Heart Team)

The process for medical decision making and patient information is guided by the 'four principles' approach to health-care ethics: autonomy, beneficence, non-maleficence, and justice. The informed consent process should therefore not be looked at solely as a necessary legal requirement but should be used as an opportunity to optimize objective decision making. Awareness that other factors such as sex, race, availability, technical skills, local results, referral patterns, and patient preference, which sometimes contradict evidentiary best practice, may have an impact on the decision making process, independently of clinical findings, is mandatory. The creation of a Heart Team serves the purpose of a balanced multidisciplinary decision process [4]. Additional input may be needed from general practitioners, anaesthesiologists, geriatricians, or intensivists. Hospital teams without a cardiac surgical unit or with interventional cardiologists working in an ambulatory setting should refer to standard evidence-based protocols designed in collaboration with an expert interventional cardiologist and a cardiac surgeon, or seek their opinion for complex cases. Consensus on the optimal revascularization treatment should be documented. Standard protocols compatible with the current Guidelines may be used to avoid the need for systematic case-by-case review of all diagnostic angiograms.

Ad hoc percutaneous coronary intervention

Ad hoc PCI is defined as a therapeutic interventional procedure performed immediately (with the patient still on the catheterization table) following the diagnostic procedure as opposed to a staged procedure performed during a different session. *Ad hoc* PCI is convenient for the patient, associated with fewer access site complications, and often

Table 5

Potential indications for *ad hoc* percutaneous coronary intervention vs. revascularization at an interval

Ad hoc PCI
Haemodynamically unstable patients (including cardiogenic shock).
Culprit lesion in STEMI and NSTEMI-ACS.
Stable low-risk patients with single or double vessel disease (proximal LAD excluded) and favourable morphology (RCA, non-ostial LCx, mid- or distal LAD).
Non-recurrent restenotic lesions.
Revascularization at an interval
Lesions with high-risk morphology.
Chronic heart failure.
Renal failure (creatinine clearance <60 mL/min), if total contrast volume required >4 mL/kg.
Stable patients with MVD including LAD involvement.
Stable patients with ostial or complex proximal LAD lesion.
Any clinical or angiographic evidence of higher periprocedural risk with <i>ad hoc</i> PCI.

LAD = left anterior descending; LCx = left circumflex; MVD = multivessel disease; NSTEMI-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction.

Table 6

Recommendations for decision making and patient information

	Class ^a	Level ^b
It is recommended that patients be adequately informed about the potential benefits and short- and long-term risks of a revascularization procedure. Enough time should be spared for informed decision making.	I	C
The appropriate revascularization strategy in patients with MVD should be discussed by the Heart Team.	I	C

^a Class of recommendation.

^b Level of evidence.

MVD = multivessel disease.

cost-effective. However, in a review of >38 000 patients undergoing *ad hoc* PCI, 30% of patients were in categories that were regarded as potential candidates for CABG. *Ad hoc* PCI is therefore reasonable for many patients, but not desirable for all, and should not automatically be applied as a default approach. Institutional protocols designed by the Heart Team should be used to define specific anatomical criteria and clinical subsets that can or cannot be treated *ad hoc*. Based on resources and settings, geographical differences can be expected. Table 5 lists potential indications for *ad hoc* PCI. All other pathologies in stable patients, including lesions of the LM or proximal left anterior descending (LAD) artery and MVD involving the LAD artery, should be discussed by a Heart Team before a deferred revascularization procedure (PCI or CABG). Table 6 lists the recommendations for decision making and patient information.

5. Strategies for pre-intervention diagnosis and imaging

Exercise testing and cardiac imaging are used to confirm the diagnosis of CAD, to document ischaemia in patients with stable symptoms, to risk stratify patients with stable angina and an acute coronary syndrome (ACS), and to

Table 7

Indications of different imaging tests for the diagnosis of obstructive coronary artery disease and for the assessment of prognosis in subjects without known coronary artery disease^a

	Asymptomatic (screening)	Symptomatic Pretest likelihood ^b of obstructive disease			Prognostic value of positive result ^a	Prognostic value of negative result ^a	References
		Low	Intermediate	High			
Anatomical test							
Invasive angiography	III A	III A	III B A	I A	I A	I A	[12]
MDCT angiography	III B ^c	III B	III B	III B	III B	III B	[17–20]
MRI angiography	III B	III B	III B	III B	III C	III C	[22]
Functional test							
Stress echo	III A	III A	I A	III A ^d	I A	I A	[12]
Nuclear imaging	III A	III A	I A	III A ^d	I A	I A	[12]
Stress MRI	III B	III C	III B	III B ^d	III B	III B	[12,23–25]
PET perfusion	III B	III C	III B	III B ^d	III B	III B	[26]

^a For the prognostic assessment of known coronary stenosis, functional imaging is similarly indicated.

^b The pretest likelihood of disease is calculated based on symptoms, sex, and risk factors.

^c This refers to MDCT angiography, not calcium scoring.

^d In patients with obstructive CAD documented by angiography, functional testing may be useful in guiding the revascularization strategy based on the extent, severity, and localisation of ischaemia.

CAD = coronary artery disease; MDCT = multidetector computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography.

help choose treatment options and evaluate their efficacy. In practice, diagnostic and prognostic assessments are conducted in tandem rather than separately, and many of the investigations used for diagnosis also offer prognostic information [12]. In elective cases, the pre-test likelihood of disease is calculated based on symptoms, sex, and risk factors. Patients with an intermediate likelihood of obstructive CAD will undergo exercise testing while patients with a high likelihood undergo direct invasive examination. Boundaries defining intermediate likelihood of CAD are usually set at 10–90% or 20–80%. Because of high availability and low costs, an exercise electrocardiogram (ECG) is the most commonly used test to confirm the anginal nature of the symptoms and to provide objective evidence of inducible ischaemia. Its accuracy is limited however, especially in women [12]. Many of the patients with an intermediate likelihood of CAD post-exercise ECG are reclassified into higher or lower likelihood groups after non-invasive functional imaging.

The target of revascularization therapy is myocardial ischaemia, not the epicardial coronary disease itself. Revascularization procedures performed in patients with documented ischaemia reduce total mortality [13] through reduction of ischaemic burden [14]. Discrepancies between the apparent anatomical severity of a lesion and its functional effects on myocardial blood supply are common, especially in stable CAD. Thus, functional assessment, non-invasive or invasive, is essential for intermediate stenoses. Revascularization of lesions without functional significance can be deferred [15].

Another indication for non-invasive imaging before revascularization is the detection of myocardial viability in patients with poor left ventricle (LV) function. Patients who have viable but dysfunctional myocardium are at higher risk if not revascularized, while the prognosis of patients without viable myocardium is not improved by revascularization [16,17].

The current evidence supporting the use of various tests for the detection of CAD is based on meta-analyses and multicentre studies (Table 7). Few RCTs have assessed health

outcomes for diagnostic testing and the available evidence has been derived largely from non-randomized studies. On many occasions the choice of the test is based on local expertise and availability of the test. Although several tests can be used, it is important to avoid unnecessary diagnostic steps.

When considering any test to detect CAD one must also take into account the risks associated with the test itself. The risks of exercise, pharmacological stressors, contrast agents, invasive procedures, and cumulative ionizing radiation must be weighed against the risk of disease or delayed diagnosis.

In summary, documentation of ischaemia using functional testing is strongly recommended before elective invasive procedures, preferably using non-invasive testing before invasive angiography.

5.1. Detection of coronary artery disease

There are two non-invasive angiographic techniques that can directly image coronary arteries: multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI).

Multidetector computed tomography coronary angiography

The studies and meta-analyses of MDCT to detect CAD have generally shown high negative predictive values (NPVs), suggesting that MDCT is excellent in excluding significant CAD [18,19], while positive predictive values (PPVs) were only moderate. In the two multicentre trials published, one was consistent with the results of prior meta-analyses [20] but the other showed only moderate NPV (83–89%) [21]. Only about half of the stenoses classified as significant by MDCT are associated with ischaemia [22] indicating that MDCT angiography cannot accurately predict the haemodynamic significance of coronary stenosis.

In summary, MDCT is reliable for ruling out significant CAD in patients with stable and unstable anginal syndromes and in patients with low to moderate likelihood of CAD. However, MDCT angiography typically overestimates the

severity of atherosclerotic obstructions and decisions for patient management require further functional testing.

Magnetic resonance imaging coronary angiography

Data suggest that MRI coronary angiography has a lower success rate and is less accurate than MDCT for the detection of CAD [18].

5.2. Detection of ischaemia

The tests are based on either reduction of perfusion or induction of ischaemic wall motion abnormalities during exercise or pharmacological stress. The most well-established stress imaging techniques are echocardiography and perfusion scintigraphy. Both may be used in combination with either exercise stress or pharmacological stress. Newer stress imaging techniques also include stress MRI, positron emission tomography (PET) imaging, and combined approaches. The term hybrid imaging refers to imaging systems in which two modalities [MDCT and PET, MDCT and single photon emission computed tomography (SPECT)] are combined in the same scanner, allowing both studies to be performed in a single imaging session.

Stress imaging techniques have several advantages over conventional exercise ECG testing, including superior diagnostic performance [12], the ability to quantify and localize areas of ischaemia, and the ability to provide diagnostic information in the presence of resting ECG abnormalities or when the patient is unable to exercise. For these reasons, stress imaging techniques are preferred in patients with previous PCI or CABG. In patients with angiographically confirmed intermediate coronary lesions, evidence of ischaemia is predictive of future events.

Stress echocardiography

Stress echocardiography is an established diagnostic test and is more accurate than exercise ECG test in the detection of ischaemia [12].

The most frequently used method is a physical exercise test typically using a bicycle ergometer, but pharmacological stressors such as dobutamine and less frequently dipyridamole can also be used. The technique requires adequate training and experience since it is more user dependent than other imaging techniques. Pooled sensitivity and specificity of exercise echocardiography are reported as 80–85% and 84–86%, respectively [12].

Recent technical improvements involve the use of contrast agents to facilitate identification of regional wall motion abnormalities and to image myocardial perfusion. These agents improve the interpretability of the images, but the technique of perfusion imaging is not yet established.

Perfusion scintigraphy

SPECT perfusion is an established diagnostic test. It provides a more sensitive and specific prediction of the presence of CAD than exercise ECG [12]. The reported sensitivity and specificity of exercise scintigraphy when compared with invasive angiography range between 85–90% and 70–75%, respectively [12].

Newer SPECT techniques with ECG gating improve diagnostic accuracy in various patient populations, including

women, diabetics, and elderly patients [23]. Adding information from a simultaneously performed calcium score using MDCT may further increase the accuracy [24].

Cardiovascular magnetic resonance imaging

Cardiac MRI stress testing with pharmacological stressors can be used to detect wall motion abnormalities induced by dobutamine infusion or perfusion abnormalities induced by adenosine. Cardiac MRI has been applied only recently in clinical practice and therefore fewer data have been published compared with other established non-invasive imaging techniques [12].

A recent meta-analysis showed that stress-induced wall motion abnormalities from MRI had a sensitivity of 83% and a specificity of 86% in patient-based analysis, and perfusion imaging demonstrated 91% sensitivity and 81% specificity [25]. When evaluated prospectively at multiple sites, the diagnostic performance of stress perfusion MRI shows similarly high sensitivity but lower specificity.

Multidetector computed tomography perfusion

MDCT can be used for perfusion imaging, but data obtained in clinical settings are scarce.

Positron emission tomography

Studies with myocardial perfusion PET have reported excellent diagnostic capabilities in the detection of CAD. The comparisons of PET perfusion imaging have also favoured PET over SPECT [26].

Meta-analysis of data obtained with PET demonstrated 92% sensitivity and 85% specificity for CAD detection, superior to myocardial perfusion SPECT. Myocardial blood flow in absolute units (mL/g/min) measured by PET further improves diagnostic accuracy, especially in patients with MVD, and can be used to monitor the effects of various therapies.

5.3. Hybrid/combined imaging

The combination of anatomical and functional imaging has become appealing because the spatial correlation of structural and functional information of the fused images may facilitate a comprehensive interpretation of coronary lesions and their pathophysiological relevance. This combination can be obtained either with image coregistration or with devices that have two modalities combined (MDCT and SPECT, MDCT and PET).

Single-centre studies evaluating the feasibility and accuracy of combined imaging have demonstrated that MDCT and perfusion imaging provide independent prognostic information. No large or multicentre studies are currently available.

5.4. Invasive tests

In common practice, many patients with intermediate or high pretest CAD likelihood are catheterized without prior functional testing. When non-invasive stress imaging is contraindicated, non-diagnostic, or unavailable, the measurement of FFR or coronary flow reserve is helpful. Even experienced interventional cardiologists cannot predict accurately the significance of most intermediate stenoses

on the basis of visual assessment or quantitative coronary angiography [27,28]. Deferral of PCI [15,28] or CABG [27] in patients with FFR >0.80 is safe and clinical outcome is excellent. Thus, FFR is indicated for the assessment of the functional consequences of moderate coronary stenoses when functional information is lacking.

5.5. Prognostic value

Normal functional imaging results are linked with excellent prognosis while documented ischaemia is associated with increased risk for MACE. Prognostic information obtained from MDCT imaging is becoming available.

5.6. Detection of myocardial viability

The prognosis of patients with chronic ischaemic systolic LV dysfunction is poor, despite advances in various therapies. Non-invasive assessment of myocardial viability should guide patient management. Multiple imaging techniques including PET, SPECT, and dobutamine stress echocardiography have been extensively evaluated for assessment of viability and prediction of clinical outcome after myocardial revascularization. In general, nuclear imaging techniques have a high sensitivity, whereas techniques evaluating contractile reserve have somewhat lower sensitivity but higher specificity. MRI has a high diagnostic accuracy to assess transmural extent of myocardial scar tissue, but its ability to detect viability and predict recovery of wall motion is not superior to other imaging techniques [16]. The differences in performance of the various imaging techniques are small, and experience and availability commonly determine which technique is used. Current evidence is mostly based on observational studies or meta-analyses, with the exception of two RCTs, both relating to PET imaging [17]. Patients with a substantial amount of dysfunctional but viable myocardium are likely to benefit from myocardial revascularization and may show improvements in regional and global contractile function, symptoms, exercise capacity, and long-term prognosis [16].

6. Revascularization for stable coronary artery disease

Depending on its symptomatic, functional, and anatomical complexity, stable CAD can be treated by OMT only or combined with revascularization using PCI or CABG. The main indications for revascularization are persistence of symptoms despite OMT and/or prognosis. Over the last two decades significant advances in all three treatment modalities have reduced many previous trials to historic value.

6.1. Evidence basis for revascularization

The evidence basis for CABG and PCI is derived from RCTs and large propensity-matched observational registries; both have important strengths, but also limitations.

By eliminating bias, individual RCTs and their subsequent meta-analyses [29–31] constitute the highest hierarchical

form of evidence-based medicine. However, their extrapolation to routine clinical practice is complicated by the fact that their patient populations are often not representative of those encountered in normal clinical practice (e.g. most RCTs of PCI and CABG in ‘multivessel’ CAD enrolled <10% of potentially eligible patients, most of whom actually had single or double vessel CAD). Analysis on an intention-to-treat basis is problematic when many patients cross over from medical therapy to revascularization or from PCI to CABG. Limited duration of follow-up (usually <5 years) incompletely depicts the advantages of CABG, which initially accrue with time but which may also eventually be eroded by progressive vein graft failure.

In contrast, by capturing data on all interventions, large observational registries may more accurately reflect routine clinical practice. In the absence of randomization, however, their fundamental limitation is that they cannot account for all confounding factors, which may influence both the choice and the outcome of different interventions. Propensity matching for both cardiac and non-cardiac comorbidity can only partially mitigate this problem. Accepting this limitation, independent registries have consistently reported that an initial strategy of CABG rather than PCI in propensity-matched patients with MVD or LM CAD improved survival over a 3- to 5-year period by ~5%, accompanied by a four- to seven-fold reduction in the need for reintervention [32–37]. The differing populations in RCTs and registries may partly explain the apparent differences in the respective efficacies of the two procedures, at least in patients with the most severe CAD.

6.2. Impact of ischaemic burden on prognosis

The adverse impact of demonstrable ischaemia on clinical outcome [death, myocardial infarction (MI), ACS, occurrence of angina] has been well recognized for over two decades [13,38]. While symptomatic patients with no or little evidence of ischaemia have no prognostic benefit from revascularization, asymptomatic patients with a significant mass of ischaemic myocardium do [13,38]. Most recently, in a small nuclear substudy of the COURAGE trial (which reported no overall survival benefit of PCI over OMT), involving just over 300 patients, 100 patients with >10% ischaemic myocardium had a lower risk of death or MI with revascularization [14].

6.3. Optimal medical therapy vs. percutaneous coronary intervention

The efficacy of PCI (with or without stenting) vs. OMT has been addressed in several meta-analyses [29,30,39–42] and a large RCT [43]. Most meta-analyses reported no mortality benefit, increased non-fatal periprocedural MI, and reduced need for repeat revascularization with PCI. One meta-analysis [41] reported a survival benefit for PCI over OMT (respective mortalities of 7.4% vs. 8.7% at an average follow-up of 51 months), but this study included patients with recent MI and CABG patients in the revascularized group. Another meta-analysis reported reduced mortality for PCI vs. OMT, even after exclusion of MI patients [hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.68–0.99] [30].

The COURAGE RCT [43] randomized 2287 patients with known significant CAD and objective evidence of myocardial ischaemia to OMT alone or to OMT + PCI. At a median follow-up of 4.6 years, there was no significant difference in the composite of death, MI, stroke, or hospitalization for unstable angina. Freedom from angina was greater by 12% in the PCI group at 1 year but was eroded by 5 years, by which time 21% of the PCI group and 33% of the OMT group had received additional revascularization ($P < 0.001$). The authors concluded that an initial strategy of PCI in stable CAD did not reduce the risk of death, MI, or MACE when added to OMT. The severity of CAD in COURAGE was, at most, moderate, with the relative proportions of one-, two- and three-vessel CAD being 31%, 39%, and 30%, while only 31% of patients had proximal LAD disease. Furthermore, patients with LM disease were excluded and most patients had normal LV function.

6.4. Percutaneous coronary intervention with drug-eluting stents vs. bare metal stents

Brophy et al. [44], in an analysis of 29 trials involving 9918 patients, reported no difference between bare metal stent (BMS) and balloon angioplasty in terms of death, MI, or the need for CABG, but an ~5% absolute reduction in restenosis with stenting. Subsequent meta-analyses [45] of RCTs comparing DES with BMS reported similar rates of death, cardiac death, and non-fatal MI, but a significant reduction in the need for subsequent or repeat target vessel revascularization (TVR) with DES. In contrast, Kirtane et al. [46], in an unadjusted analysis of 182 901 patients in 34 observational studies of BMS and DES, reported a significant reduction in mortality (HR 0.78, 95% CI 0.71–0.86) and MI (HR 0.87, 95% CI 0.78–0.97) with DES. After multivariable adjustment, the benefits of DES were significantly attenuated and the possibility that at least some of the clinical benefit of DES might be due to concomitant dual antiplatelet therapy (DAPT) could not be excluded. In a network meta-analysis restricted to patients with non-acute CAD, sequential advances in PCI techniques were not associated with incremental mortality benefit in comparison with OMT [42].

6.5. Coronary artery bypass grafting vs. medical therapy

The superiority of CABG to medical therapy in the management of specific subsets of CAD was firmly established in a meta-analysis of seven RCTs [31], which is still the major foundation for contemporary CABG. It demonstrated a survival benefit of CABG in patients with LM or three-vessel CAD, particularly when the proximal LAD coronary artery was involved. Benefits were greater in those with severe symptoms, early positive exercise tests, and impaired LV function. The relevance of these findings to current practice is increasingly challenged as medical therapy used in the trials was substantially inferior to current OMT. However, a recent meta-analysis reported a reduction in the HR for death with CABG vs. OMT (HR 0.62, 95% CI 0.50–0.77) [30]. In addition, the benefits of CABG might actually be underestimated because:

- most patients in the trials had a relatively low severity of CAD;

- analysis was conducted on an intention-to-treat basis (even though 40% of the medical group crossed over to CABG);
- only 10% of CABG patients received an internal thoracic artery (ITA); however the most important prognostic component of CABG is the use of one [47,48] or preferably two [49] ITAs.

6.6. Percutaneous coronary intervention vs. coronary artery bypass grafting

Isolated proximal left anterior descending artery disease

There are two meta-analyses of >1900 [50] and >1200 [51] patients, both of which reported no significant difference in mortality, MI, or cerebrovascular accident (CVA), but a three-fold increase in recurrent angina and a five-fold increase in repeat TVR with PCI at up to 5 years of follow-up.

Multivessel disease (including SYNTAX trial)

There have been >15 RCTs of PCI vs. CABG in MVD [52] but only one of OMT vs. PCI vs. CABG (MASS II) [53]. Most patients in these RCTs actually had normal LV function with single or double vessel CAD and without proximal LAD disease. Meta-analyses of these RCTs reported that CABG resulted in up to a five-fold reduction in the need for reintervention, with either no or a modest survival benefit or a survival benefit only in patients >65 years old (HR 0.82) and those with diabetes (HR 0.7) [29]. The 5-year follow-up of the MASS II [53] study of 611 patients (underpowered) reported that the composite primary endpoint (total mortality, Q-wave MI, or refractory angina requiring revascularization) occurred in 36% of OMT, 33% of PCI and 21% of CABG patients ($P = 0.003$), with respective subsequent revascularization rates of 9%, 11% and 4% ($P = 0.02$).

The SYNTAX trial

In contrast to the highly selective patient populations of previous RCTs, SYNTAX is a 5-year 'all comers' trial of patients with the most severe CAD, including those with LM and/or three-vessel CAD, who were entered into either the trial or a parallel nested registry if ineligible for randomization [4]. By having two components, SYNTAX therefore captured real treatment decisions in a trial of 1800 patients randomized to PCI or CABG and in a registry of 1077 CABG patients (whose complexity of CAD was deemed to be ineligible for PCI) and 198 PCI patients (considered to be at excessive surgical risk). At 1 year, 12.4% of CABG and 17.8% of PCI patients reached the respective primary composite endpoint ($P < 0.002$) of death (3.5% vs. 4.4%; $P = 0.37$), MI (3.3% vs. 4.8%; $P = 0.11$), CVA (2.2% vs. 0.6%; $P = 0.003$), or repeat revascularization (5.9% vs. 13.5%; $P < 0.001$) [4]. Unpublished data at 2 years showed major adverse cardiac and cerebral event (MACCE) rates of 16.3% vs. 23.4% in favour of CABG ($P < 0.001$). Because PCI failed to reach the pre-specified criteria for non-inferiority, the authors concluded at both 1 [4] and 2 years that 'CABG remains the standard of care for patients with three-vessel or LM CAD although the difference in the composite primary endpoint was largely driven by repeat revascularization'. Whether the excess of CVA in the CABG group in the first year was purely periprocedural or also due to lower

use of secondary preventive medication (DAPT, statins, antihypertensive agents, and ACE inhibitors) is not known.

Failure to reach criteria for non-inferiority therefore means that all other findings are observational, sensitive to the play of chance, and hypothesis generating. Nevertheless, in 1095 patients with three-vessel CAD, the MACCE rates were 14.4% vs. 23.8% in favour of CABG ($P < 0.001$). Only in the tercile of patients with the lowest SYNTAX scores (<23) was there no significant difference in MACCE between the two groups. It is also noteworthy that the mortality and repeat revascularization rates were similar in the 1077 CABG registry patients, even though these patients had more complex CAD.

Taking together all 1665 patients with three-vessel CAD (1095 in the RCT and 570 in the registry), it appears that CABG offers significantly better outcomes at 1 and 2 years in patients with SYNTAX scores >22 (79% of all patients with three-vessel CAD). These results are consistent with previous registries [32–37] reporting a survival advantage and a marked reduction in the need for repeat intervention with CABG in comparison with PCI in patients with more severe CAD.

Left main stenosis

CABG is still conventionally regarded as the standard of care for significant LM disease in patients eligible for surgery, and the CASS registry reported a median survival advantage of 7 years in 912 patients treated with CABG rather than medically [54]. While ESC guidelines on PCI state that ‘Stenting for unprotected LM disease should only be considered in the absence of other revascularization options’ [55], emerging evidence, discussed below, suggests that PCI provides at least equivalent if not superior results to CABG for lower severity LM lesions at least at 2 years of follow-up and can justify some easing of PCI restrictions. However, the importance of confirming that these results remain durable with longer term follow-up (at least 5 years) is vital.

While LM stenosis is a potentially attractive target for PCI because of its large diameter and proximal position in the coronary circulation, two important pathophysiological features may mitigate against the success of PCI: (i) up to 80% of LM disease involves the bifurcation known to be at particularly high risk of restenosis; and (ii) up to 80% of LM patients also have multivessel CAD where CABG, as already discussed, may already offer a survival advantage.

The most ‘definitive’ current account of treatment of LM disease by CABG or PCI is from the hypothesis-generating subgroup analysis of the SYNTAX trial. In 705 randomized LM patients, the 1-year rate of death (4.4% vs. 4.2%; $P = 0.88$), CVA (2.7% vs. 0.3%; $P = 0.009$), MI (4.1% vs. 4.3%; $P = 0.97$), repeat revascularization (6.7% vs. 12.0%; $P = 0.02$) and MACCE (13.6% vs. 15.8%; $P = 0.44$) only favoured CABG for repeat revascularization, but at a higher risk of CVA.

By SYNTAX score terciles, MACCE rates were 13.0% vs. 7.7% ($P = 0.19$), 15.5% vs. 12.6% ($P = 0.54$), and 12.9% vs. 25.3% ($P = 0.08$) for CABG vs. PCI in the lower (0–22), intermediate (23–32), and high (≥ 33) terciles, respectively. Unpublished data at 2 years show respective mortalities of 7.9% and 2.7% ($P = 0.02$) and repeat revascularization rates of 11.4% and 14.3% ($P = 0.44$) in the two lower terciles, implying that PCI may be superior to CABG at 2 years. Of note, among the

1212 patients with LM stenosis included in the registry or in the RCTs, 65% had SYNTAX scores ≥ 33 .

Support for the potential of PCI at least in lower risk LM lesions comes from several other sources. In a meta-analysis of 10 studies, including two RCTs and the large MAIN-COMPARE registry, of 3773 patients with LM stenosis, Naik et al. [56] reported that there was no difference between PCI and CABG in mortality or in the composite endpoint of death, MI, and CVA up to 3 years, but up to a four-fold increase in repeat revascularization with PCI. These results were confirmed at 5 years in the MAIN-COMPARE registry [57].

6.7. Recommendations

The two issues to be addressed are:

- (i) the appropriateness of revascularization (Table 8);
- (ii) the relative merits of CABG and PCI in differing patterns of CAD (Table 9).

Current best evidence shows that revascularization can be readily justified:

- (i) on symptomatic grounds in patients with persistent limiting symptoms (angina or angina equivalent) despite OMT and/or
- (ii) on prognostic grounds in certain anatomical patterns of disease or a proven significant ischaemic territory (even in asymptomatic patients). Significant LM stenosis, and significant proximal LAD disease, especially in the presence of multivessel CAD, are strong indications for revascularization. In the most severe patterns of CAD, CABG appears to offer a survival advantage as well as a marked reduction in the need for repeat revascularization, albeit at a higher risk of CVA, especially in LM disease.

Table 8
Indications for revascularization in stable angina or silent ischaemia

	Subset of CAD by anatomy	Class ^a	Level ^b	Ref. ^c
For prognosis	Left main >50% ^d	I	A	[30,31,54]
	Any proximal LAD >50% ^d	I	A	[30–37]
	2VD or 3VD with impaired LV function ^d	I	B	[30–37]
	Proven large area of ischaemia (>10% LV)	I	B	[13,14,38]
	Single remaining patent vessel >50% stenosis ^d	I	C	–
	1VD without proximal LAD and without >10% ischaemia	III	A	[39,40,53]
For symptoms	Any stenosis >50% with limiting angina or angina equivalent, unresponsive to OMT	I	A	[30,31,39–43]
	Dyspnoea/CHF and >10% LV ischaemia/viability supplied by >50% stenotic artery	IIa	B	[14,38]
	No limiting symptoms with OMT	III	C	–

^a Class of recommendation.

^b Level of evidence.

^c References.

^d With documented ischaemia or FFR <0.80 for angiographic diameter stenoses 50–90%.

CAD = coronary artery disease; CHF = chronic heart failure; FFR = fractional flow reserve; LAD = left anterior descending; LV = left ventricle; OMT = optimal medical therapy; VD = vessel disease.

Table 9

Indications for coronary artery bypass grafting vs. percutaneous coronary intervention in stable patients with lesions suitable for both procedures and low predicted surgical mortality

Subset of CAD by anatomy	Favours CABG	Favours PCI	Ref. ^a
1VD or 2VD – non-proximal LAD	IIb C	I C	–
1VD or 2VD – proximal LAD	I A	IIa B	[30,31,50,51]
3VD simple lesions, full functional revascularization achievable with PCI, SYNTAX score ≤22	I A	IIa B	[4,30–37,53]
3VD complex lesions, incomplete revascularization achievable with PCI, SYNTAX score >22	I A	III A	[4,30–37,53]
Left main (isolated or 1VD, ostium/shaft)	I A	IIa B	[4,54]
Left main (isolated or 1VD, distal bifurcation)	I A	IIb B	[4,54]
Left main + 2VD or 3VD, SYNTAX score ≤32	I A	IIb B	[4,54]
Left main + 2VD or 3VD, SYNTAX score ≥33	I A	III B	[4,54]

^a References.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; LAD = left anterior descending; PCI = percutaneous coronary intervention; VD = vessel disease.

Recognizing that visual attempts to estimate the severity of stenoses on angiography may either under- or over-estimate the severity of lesions, the increasing use of FFR measurements to identify functionally more important lesions is a significant development (Section 5.4).

It is not feasible to provide specific recommendations for the preferred method of revascularization for every possible clinical scenario. Indeed it has been estimated that there are >4000 possible clinical and anatomical permutations. Nevertheless, in comparing outcomes between PCI and CABG, Tables 8 and 9 should form the basis of recommendations by the Heart Team in informing patients and guiding the approach to informed consent. However, these recommendations must be interpreted according to individual patient preferences and clinical characteristics. For example, even if a patient has a typical prognostic indication for CABG, this should be modified according to individual clinical circumstances such as very advanced age or significant concomitant comorbidity.

7. Revascularization in non-ST-segment elevation acute coronary syndromes

NSTE-ACS is the most frequent manifestation of ACS and represents the largest group of patients undergoing PCI. Despite advances in medical and interventional treatments, the mortality and morbidity remain high and equivalent to that of patients with STEMI after the initial month. However, patients with NSTE-ACS constitute a very heterogeneous group of patients with a highly variable prognosis. Therefore, early risk stratification is essential for selection of medical as well as interventional treatment strategies. The ultimate goals of coronary angiography and revascularization are mainly two-fold: symptom relief, and improvement of prognosis in the short and long term. Overall quality of life, duration of hospital stay, and potential risks associated

with invasive and pharmacological treatments should also be considered when deciding on treatment strategy.

7.1. Intended early invasive or conservative strategies

RCTs have shown that an early invasive strategy reduces ischaemic endpoints mainly by reducing severe recurrent ischaemia and the clinical need for rehospitalization and revascularization. These trials have also shown a clear reduction in mortality and MI in the medium term, while the reduction in mortality in the long term has been moderate and MI rates during the initial hospital stay have increased (early hazard) [58]. The most recent meta-analysis confirms that an early invasive strategy reduces cardiovascular death and MI at up to 5 years of follow-up [59].

7.2. Risk stratification

Considering the large number of patients and the heterogeneity of NSTE-ACS, early risk stratification is important to identify patients at high immediate and long-term risk of death and cardiovascular events, in whom an early invasive strategy with its adjunctive medical therapy may reduce that risk. It is equally important, however, to identify patients at low risk in whom potentially hazardous and costly invasive and medical treatments provide little benefit or in fact may cause harm.

Risk should be evaluated considering different clinical characteristics, ECG changes, and biochemical markers. Risk score models have therefore been developed. The ESC Guidelines for NSTE-ACS recommend the GRACE risk score (<http://www.outcomes-umassmed.org/grace>) as the preferred classification to apply on admission and at discharge in daily clinical practice [60]. The GRACE risk score was originally constructed for prediction of hospital mortality but has been extended for prediction of long-term outcome across the spectrum of ACS and for prediction of benefit with invasive procedures [61].

A substantial benefit with an early invasive strategy has only been proved in patients at high risk. The recently published meta-analysis [59] including the FRISC II [62], the ICTUS [63], and the RITA III [64] trials showed a direct relationship between risk, evaluated by a set of risk indicators including age, diabetes, hypotension, ST depression, and body mass index (BMI), and benefit from an early invasive approach.

Troponin elevation and ST depression at baseline appear to be among the most powerful individual predictors of benefit from invasive treatment. The role of high sensitivity troponin measurements has yet to be defined.

7.3. Timing of angiography and intervention

The issue of the timing of invasive investigation has been a subject of discussion. A very early invasive strategy, as opposed to a delayed invasive strategy, has been tested in five prospective RCTs (Table 10).

A wealth of data supports a primary early invasive strategy over a conservative strategy. There is no evidence that any particular time of delay to intervention with

Table 10
Randomized clinical trials comparing different invasive treatment strategies

Trials	Early invasive / conservative						Early / late invasive				
	FRISC	TRUCS	TIMI 18	VINO	RITA-3	ICTUS	ELISA	ISAR-COOL	OPTIMA	TIMACS	ABOARD
Patients	2456	148	2220	131	1810	1199	220	410	142	3031	352
Enrolment period	1996–98	1997–98	1997–99	1998–2000	1997–2002	2001–03	2000–01	2000–02	2004–07	2003–08	2006–08
Time to angio (h) ^a	96/408	48/120	22/79	6.2/1464	48/1020	23/283	6/50	2.4/86	0.5/25	14/50	1.2/21
Mean age (year)	66	62	62	66	62	62	63	70	62	65	65
Women (%)	30	27	34	39	38	27	30	33	32	35	28
Diabetes (%)	12	29	28	25	13	14	14	29	20	27	27
Troponin ↑ at inclusion (%)	55	NA	54	100	75	67	68	67	46	77	74
Invasive (%) ^{a,b}	78/45	100/61	64/45	73/39	57/28	79/54	74/77	78/72	100/99	74/69	91/81
PCI/CABG (%) ^{a,b}	30/27	43/16	36/19	50/27	26/17	51/10	54/15	68/8	99/0	57/28	63/2
Primary outcome	D/MI 6 months	D/MI/H	D/MI/A 6 months	D/MI 6 months	D/MI 12 months	D/MI/A 12 months	Infarct size LDH	D/MI 1 month	D/MI/UR 30 days	D/MI/S 6 months	Troponin release
Endpoint met	+	–	+	+	+	–	+	+	–	–	–

^a At the time the primary endpoint was reported.

^b Early invasive/conservative and early/late invasive, respectively.

A = hospital readmission; D = death; H = duration of hospitalization; MI = myocardial infarction; S = stroke; UR = unplanned revascularization.

Table 11
Indicators predicting high thrombotic risk or high-risk for progression to myocardial infarction, which indicate emergent coronary angiography

Ongoing or recurrent ischaemia.
Dynamic spontaneous ST changes (>0.1 mV depression or transient elevation).
Deep ST depression in anterior leads V2–V4 indicating ongoing posterior transmural ischaemia.
Haemodynamic instability.
Major ventricular arrhythmia.

upstream pharmacological treatment, including intensive antithrombotic agents, would be superior to providing adequate medical treatment and performing angiography as early as possible [65]. Ischaemic events as well as bleeding complications tend to be lower and hospital stay can be shortened with an early as opposed to a later invasive strategy. In high-risk patients with a GRACE risk score >140, urgent angiography should be performed within 24 h if possible [66].

Patients at very high risk were excluded from all RCTs so that life-saving therapy was not withheld. Accordingly, patients with ongoing symptoms and marked ST depression in anterior leads (particularly in combination with troponin elevation) probably suffer from posterior transmural ischaemia and should undergo emergency coronary angiography (Table 11). Moreover, patients with a high thrombotic risk or high risk of progression to MI should be investigated with angiography without delay.

In lower risk subsets of NSTEMI-ACS patients, angiography and subsequent revascularization can be delayed without increased risk but should be performed during the same hospital stay, preferably within 72 h of admission.

7.4. Coronary angiography, percutaneous coronary intervention, and coronary artery bypass grafting

An invasive strategy always starts with angiography. After defining the anatomy and its associated risk features,

a decision about the type of intervention can be made. The angiography in combination with ECG changes often identifies the culprit lesion with irregular borders, eccentricity, ulcerations, and filling defect suggestive of intraluminal thrombi. For lesions with borderline clinical significance and in patients with MVD, FFR measurement provides important information for treatment decision making [28]. Angiography should be performed urgently for diagnostic purposes in patients at high risk and in whom the differential diagnosis of other acute clinical situations is unclear. Particularly in patients with ongoing symptoms or marked troponin elevation, but in the absence of diagnostic ECG changes, the identification of acute thrombotic occlusion (primarily of the circumflex artery) is important.

All trials that have evaluated early vs. late or invasive vs. medical management have included PCI and CABG at the discretion of the investigator. No prospective RCT has specifically addressed the selection of mode of intervention in patients with NSTEMI-ACS. In stabilized patients after an episode of ACS, however, there is no reason to interpret differently the results from RCTs comparing the two revascularization methods in stable CAD. The mode of revascularization should be based on the severity and distribution of the CAD.

If PCI is desirable it should be recommended to identify the culprit lesion with the help of angiographic determinants and with ECG guidance, and to intervene on this lesion first. In case of multiple angiographically significant non-culprit stenoses or lesions whose severity is difficult to assess, liberal use of FFR measurement is recommended in order to decide on the treatment strategy [28]. Multivessel stenting for suitable significant stenoses rather than stenting the culprit lesion only has not been evaluated appropriately in a randomized fashion. The optimal timing of revascularization is different for PCI and for CABG. While the benefit from PCI in patients with NSTEMI-ACS is related to its early performance, the benefit from CABG is greatest when patients can undergo surgery after several days of medical stabilization.

7.5. Patient subgroups

Although subgroups of patients such as women and the elderly may be at higher risk of bleeding, there are no data supporting the suggestion that they should be treated differently from other patients included in RCTs. A meta-analysis of eight RCTs showed that biomarker-positive women derived a benefit from an early invasive strategy comparable to that of men [67]. However, biomarker-negative women tended to have a higher event rate with an early invasive procedure. Thus, early invasive procedures should be avoided in low-risk, troponin-negative, female patients.

Age is one of the most important risk indicators, yet elderly patients experience a similar or greater benefit from early invasive procedures [59]. Among the oldest patients, one should prioritize relief of symptoms and avoidance of bleeding complications.

Table 12 lists the recommendations for revascularization in NSTEMI-ACS.

Table 12
Recommendations for revascularization in non-ST-segment elevation acute coronary syndrome

Specification	Class ^a	Level ^b	Ref. ^c
An invasive strategy is indicated in patients with: <ul style="list-style-type: none"> GRACE score >140 or at least one high-risk criterion. Recurrent symptoms. Inducible ischaemia at stress test. 	I	A	[64, 68–70]
An early invasive strategy (<24 h) is indicated in patients with GRACE score >140 or multiple other high-risk criteria.	I	A	[63, 64, 66, 70–72]
A late invasive strategy (within 72 h) is indicated in patients with GRACE score <140 or absence of multiple other high-risk criteria but with recurrent symptoms or stress-inducible ischaemia.	I	A	[59, 66, 68]
Patients at very high ischaemic risk (refractory angina, with associated heart failure, arrhythmias or haemodynamic instability) should be considered for emergent coronary angiography (<2 h).	Ila	C	–
An invasive strategy should not be performed in patients: <ul style="list-style-type: none"> At low overall risk. At a particular high-risk for invasive diagnosis or intervention. 	III	A	[59, 68]

^a Class of recommendation.

^b Level of evidence.

^c References.

8. Revascularization in ST-segment elevation myocardial infarction

8.1. Reperfusion strategies

8.1.1. Primary percutaneous coronary intervention

Primary PCI is defined as percutaneous intervention in the setting of STEMI without previous or concomitant fibrinolytic treatment. RCTs and meta-analyses comparing primary PCI with in-hospital fibrinolytic therapy in patients within 6–12 h after symptom onset treated in high-volume, experienced centres have shown more effective restoration of vessel patency, less re-occlusion, improved residual LV function, and better clinical outcome with primary PCI [73]. Cities and countries switching from fibrinolysis to primary PCI have observed a sharp decrease in mortality after STEMI [74, 75].

American College of Cardiology/American Heart Association (ACC/AHA) guidelines specify that primary PCI should be performed by operators who perform >75 elective procedures per year and at least 11 procedures for STEMI in institutions with an annual volume of >400 elective and >36 primary PCI procedures [76]. Such a policy decision is justified by the strong inverse volume-outcome relationship observed in high-risk and emergency PCI. Therefore, tolerance of low-volume thresholds for PCI centres for the purpose of providing primary PCI is not recommended.

It is essential to make every effort to minimize all time delays, especially within the first 2 h after onset of symptoms, by the implementation of a system of care network. As illustrated in Figure 1, the preferred pathway is immediate transportation of STEMI patients to a PCI-capable centre offering an uninterrupted primary PCI service by a team of high-volume operators. Patients admitted to hospitals without PCI facilities should be transferred to a PCI-capable centre and no fibrinolytics should be administered if the expected time delay between first medical contact (FMC) and balloon inflation is <2 h. If the expected delay is >2 h (or >90 min in patients <75 years old with large anterior STEMI and recent onset of symptoms), patients admitted to a non-PCI centre should immediately receive fibrinolysis and then be transferred to a PCI-capable centre where angiography and PCI should be performed in a time window of 3–24 h [77–80].

8.1.2. Fibrinolysis

Despite its frequent contraindications, limited effectiveness in inducing reperfusion, and greater bleeding risk, fibrinolytic therapy, preferably administered as a pre-hospital treatment [81], remains an important alternative to mechanical revascularization. In Europe, 5–85% of patients with STEMI undergo primary PCI, a wide range that reflects the variability or allocation of local resources and capabilities [82]. Even with an optimal network organization, transfer delays may be unacceptably long before primary PCI is performed, especially in patients living in mountain or rural areas or presenting to non-PCI centres. The incremental benefit of primary PCI, over timely fibrinolysis, is jeopardized when PCI-related delay exceeds 60–120 min, depending on age, duration of symptoms, and infarct location [83, 84].

Facilitated PCI, or pharmaco-mechanical reperfusion, is defined as elective use of reduced or normal-dose fibrinolysis combined with glycoprotein IIb–IIIa (GPIIb–IIIa) inhibitors or other antiplatelet agents. In patients undergoing PCI 90–120 min after FMC, facilitated PCI has shown no significant advantages over primary PCI. The use of tenecteplase and aspirin as facilitating therapy was shown to be detrimental compared with primary PCI, with increased ischaemic and bleeding events, and a trend towards excess mortality [85]. The combination of half-dose lytics with GPIIb–IIIa inhibitors showed a non-significant reduction in adverse events at the price of excess bleeding [86].

Pre-hospital full-dose fibrinolysis has been tested in the CAPTIM trial [81], using an emergency medical service (EMS) able to perform pre-hospital diagnosis and fibrinolysis, with equivalent outcome to primary PCI at 30 days and 5 years. Following pre-hospital fibrinolysis, the ambulance should

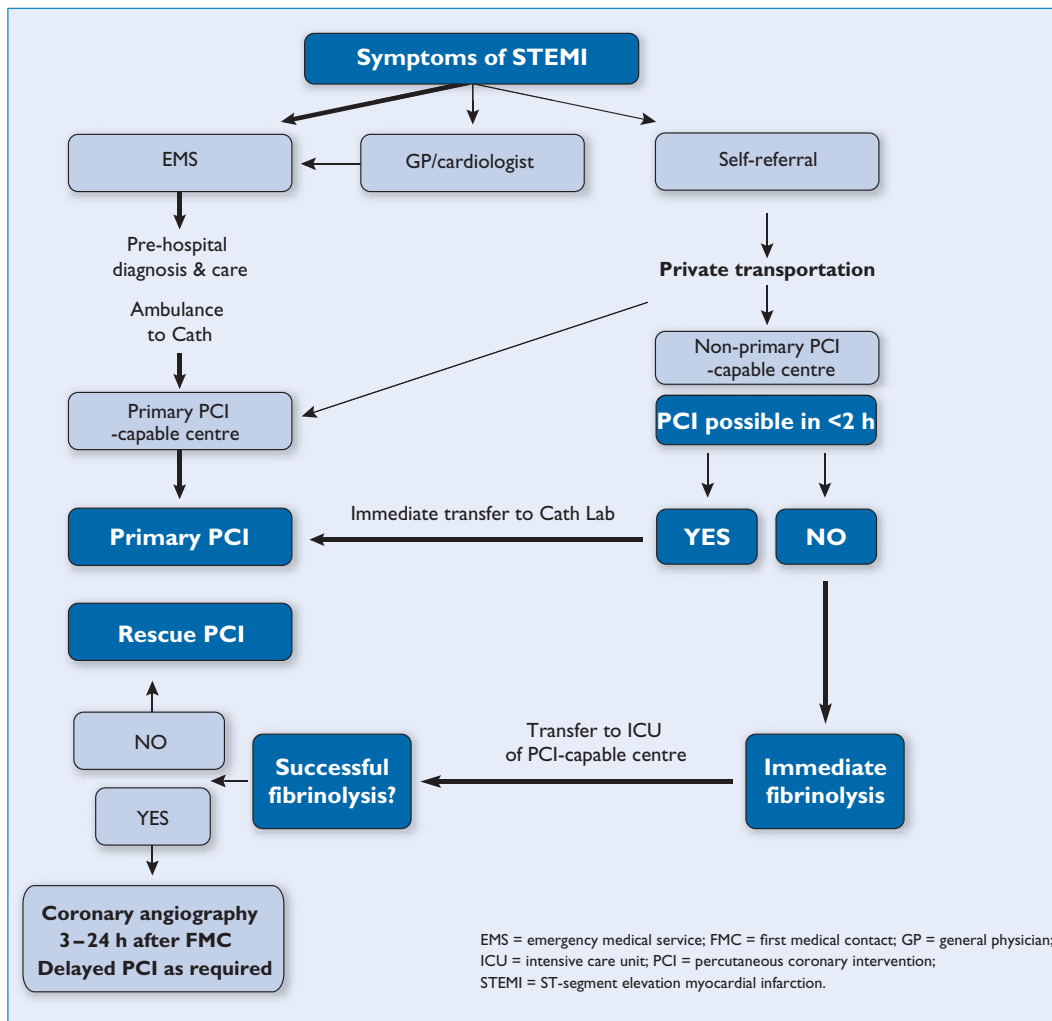


Fig. 1. Organization of ST-segment elevation myocardial infarction patient pathway describing pre- and in-hospital management and reperfusion strategies within 12 h of first medical contact.

transport the patient to a 24 h a day/7 days a week PCI facility.

8.1.3. Delayed percutaneous coronary intervention

In cases of persistent ST-segment elevation after fibrinolysis, defined as more than half of the maximal initial elevation in the worst ECG lead, and/or persistent ischaemic chest pain, rapid transfer to a PCI centre for rescue angioplasty should be considered [80,87]. Re-administration of a second dose of fibrinolysis was not shown to be beneficial.

In the case of successful fibrinolysis, patients are referred within 24 h for angiography and revascularization as required [77–79].

Patients presenting between 12 and 24 h and possibly up to 60 h from symptom onset, even if pain free and with stable haemodynamics, may still benefit from early coronary angiography and possibly PCI [88,89]. Patients without ongoing chest pain or inducible ischaemia, presenting between 3 and 28 days with persistent coronary artery occlusion, did not benefit from PCI [90,91]. Thus, in patients presenting days after the acute event with a fully developed Q-wave MI, only patients with recurrent angina and/or documented residual

ischaemia and proven viability in a large myocardial territory are candidates for mechanical revascularization.

8.1.4. Coronary artery bypass grafting

Emergent coronary artery bypass grafting

In cases of unfavourable anatomy for PCI or PCI failure, emergency CABG in evolving STEMI should only be considered when a very large myocardial area is in jeopardy and surgical revascularization can be completed before this area becomes necrotic (i.e. in the initial 3–4 h).

Urgent coronary artery bypass grafting

Current evidence points to an inverse relationship between surgical mortality and time elapsed since STEMI. When possible, in the absence of persistent pain or haemodynamic deterioration, a waiting period of 3–7 days appears to be the best compromise [92]. Patients with MVD receiving primary PCI or urgent post-fibrinolysis PCI on the culprit artery will need risk stratification and further mechanical revascularization with PCI or surgery. Older age, impaired LV function, and comorbidity are associated with a higher surgical risk.

8.2. Cardiogenic shock and mechanical complications

8.2.1. Cardiogenic shock

Cardiogenic shock is the leading cause of in-hospital death for MI patients. Optimal treatment demands early reperfusion as well as haemodynamic support to prevent end-organ failure and death. Definitions of cardiogenic shock, the diagnostic procedures as well as the medical, interventional, and surgical treatment are discussed in previous ESC Guidelines [93,94]. No time limit should be set between onset of symptoms and invasive diagnosis and revascularization in patients with cardiogenic shock, whether or not they previously received fibrinolytic treatment. In these patients, complete revascularization has been recommended, with PCI performed in all critically stenosed large epicardial coronary arteries [95].

8.2.2. Mechanical complications

Echocardiography should always be performed in acute heart failure (AHF) to assess LV function and to rule out life-threatening mechanical complications that may require surgery such as acute mitral regurgitation (MR) secondary to papillary muscle rupture, ventricular septal defect (VSD), free wall rupture, or cardiac tamponade. The natural history of these conditions is characterized by a rapid downhill course and medical treatment alone results in close to 100% mortality.

Free wall rupture requires prompt recognition and immediate pericardial drainage at the bedside. The incidence of post-MI VSD is 0.2%. With persistent haemodynamic deterioration despite the presence of an intra-aortic balloon pump (IABP), surgery should be performed as soon as possible [92]. Other than feasibility, there is limited evidence to support percutaneous attempts at defect closure either transiently using balloons or durably with implantation of closure devices. Acute MR due to papillary muscle rupture usually results in acute pulmonary oedema and should be treated by immediate surgery.

Whenever possible, pre-operative coronary angiography is recommended. Achieving complete revascularization in addition to correcting the mechanical defect improves the clinical outcome.

8.2.3. Circulatory assistance

The use of an IABP is recommended only in the presence of haemodynamic impairment [96,97]. The IABP should be inserted before angiography in patients with haemodynamic instability (particularly those in cardiogenic shock and with mechanical complications) [92]. The benefits of an IABP should be balanced against device-related complications, mostly vascular and more frequently observed in small stature patients and/or females, patients with peripheral arterial disease (PAD), and diabetics. An IABP should not be used in patients with aortic insufficiency or aortic dissection.

Mechanical circulatory assistance other than an IABP can be offered at tertiary centres with an institutional programme for mechanical assist therapy if the patient continues to deteriorate and cardiac function cannot maintain adequate circulation to prevent end-organ failure

(Figure 2). Extracorporeal membrane oxygenator (ECMO) implantation should be considered for temporary support in patients with AHF with potential for functional recovery following revascularization [98]. If the heart does not recover, the patient should undergo a thorough neurological assessment (especially in the setting of a pre-admittance out-of-hospital resuscitation or prolonged periods with low cardiac output). The patient may be considered for a surgical left ventricular assist device (LVAD) or biventricular assist device (BiVAD) therapy in the absence of permanent neurological deficits. In young patients with no contraindication for transplant, LVAD/BiVAD therapy as a bridge to transplant may be indicated [99]. In some patients, total implantable assist devices may be applied as a destination (or permanent) therapy.

Several mechanical assist devices that can be implanted percutaneously have been tested with disappointing results. The use of percutaneous centrifugal pumps (Tandem Heart) has not resulted in improved outcome after STEMI [97]. Despite early haemodynamic recovery, secondary complications have resulted in similar 30-day mortality rates. The use of a microaxial propeller pump (Impella) resulted in better haemodynamics but similar mortality after 30 days [100]. A meta-analysis summarizing the data from three RCTs (100 patients) showed no difference in 30-day mortality and a trend for more adverse events, such as bleeding and vascular complications in the group receiving percutaneous assist devices [101].

Table 13 lists the recommendations for reperfusion strategies in STEMI patients, Table 14 lists the recommendations for PCI in STEMI, and Table 15 lists the recommendations for the treatment of patients with AHF in the setting of acute MI (AMI).

Table 13
Recommendations for reperfusion strategies in ST-segment elevation myocardial infarction patients

	Class ^a	Level ^b	Ref. ^c
Implementation of a well-functioning network based on pre-hospital diagnosis, and fast transport to the closest available primary PCI-capable centre is recommended.	I	A	[74,75]
Primary PCI-capable centres should deliver 24 h per day/7 days per week on-call service, be able to start primary PCI as soon as possible and within 60 min from the initial call.	I	B	[76,82, 102–105]
In case of fibrinolysis, pre-hospital initiation by properly equipped EMS should be considered and full dose administered.	IIa	A	[81]
With the exception of cardiogenic shock, PCI (whether primary, rescue, or post-fibrinolysis) should be limited to the culprit stenosis	IIa	B	[96,106, 107]
In PCI-capable centres, unnecessary intermediate admissions to the emergency room or the intensive care unit should be avoided.	III	A	[94,108, 109]
The systematic use of balloon counterpulsation, in the absence of haemodynamic impairment, is not recommended.	III	B	[96,97]

^a Class of recommendation.

^b Level of evidence.

^c References.

EMS = emergency medical service; PCI = percutaneous coronary intervention.

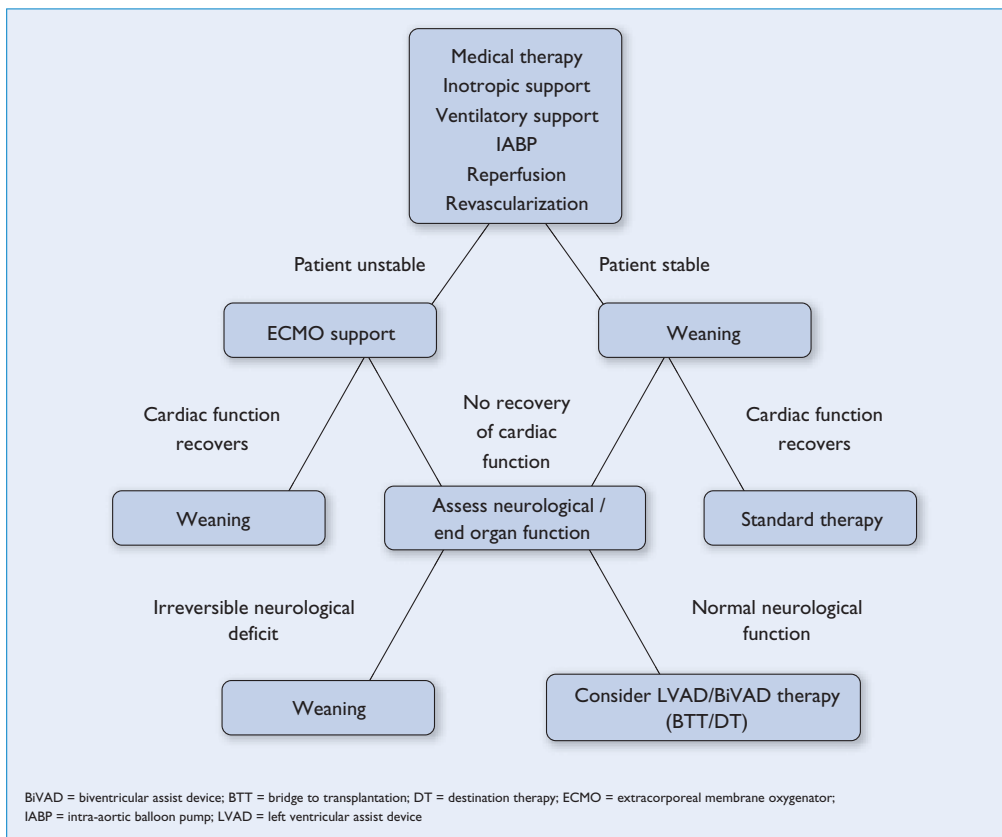


Fig. 2. Treatment algorithms for acute heart failure and cardiogenic shock. After failure of initial therapy including reperfusion and revascularization to stabilize haemodynamics, temporary mechanical support using an extracorporeal membrane oxygenator should be considered. If weaning from the extracorporeal membrane oxygenator fails or heart failure persists, left ventricular assist device/biventricular assist device therapy may be considered if neurological function is not permanently impaired.

Table 14
Recommendations for percutaneous coronary intervention in ST-segment elevation myocardial infarction

Indication	Time from FMC	Class ^a	Level ^b	Ref. ^c
Primary PCI				
Is recommended in patients with chest pain/discomfort <12 h + persistent ST-segment elevation or previously undocumented left bundle branch block.	As soon as possible and at any rate <2 h from FMC ^d	I	A	[83,84,94]
Should be considered in patients with ongoing chest pain/discomfort >12 h + persistent ST-segment elevation or previously undocumented left bundle branch block.	As soon as possible	IIa	C	–
May be considered in patients with history of chest pain/discomfort >12 h and <24 h + persistent ST-segment elevation or previously undocumented left bundle branch block.	As soon as possible	IIb	B	[88,89]
PCI after fibrinolysis				
Routine urgent PCI is indicated after successful fibrinolysis (resolved chest pain/discomfort and ST-segment elevation).	Within 24 h ^e	I	A	[77–79]
Rescue PCI should be considered in patients with failed fibrinolysis.	As soon as possible	IIa	A	[80,87]
Elective PCI/CABG				
Is indicated after documentation of angina/positive provocative tests.	Evaluation prior to hospital discharge	I	B	[36,41–43]
Not recommended in patients with fully developed Q wave MI and no further symptoms/signs of ischaemia or evidence of viability in the infarct related territory.	Patient referred >24 h	III	B	[90,91]

^a Class of recommendation.

^b Level of evidence.

^c References.

^d <90 min if patient presents <2 h from symptoms onset and has large infarct and low bleeding risk.

^e In order to reduce delay for patients with no reperfusion, transfer to PCI centre of all post-fibrinolysis patients is recommended.

CABG = coronary artery bypass grafting; FMC = first medical contact; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 15
Recommendations for treatment of patients with acute heart failure in the setting of acute myocardial infarction

	Class ^a	Level ^b	Ref. ^c
Patients with NSTEMI-ACS or STEMI and unstable haemodynamics should immediately be transferred for invasive evaluation and target vessel revascularization.	I	A	[60,73,93,94]
Immediate reperfusion is indicated in AHF with ongoing ischaemia.	I	B	[60,93,94]
Echocardiography should be performed to assess LV function and exclude mechanical complications.	I	C	–
Emergency angiography and revascularization of all critically narrowed arteries by PCI/CABG as appropriate is indicated in patients in cardiogenic shock.	I	B	[95]
IABP insertion is recommended in patients with haemodynamic instability (particularly those in cardiogenic shock and with mechanical complications).	I	C	–
Surgery for mechanical complications of AMI should be performed as soon as possible with persistent haemodynamic deterioration despite IABP.	I	B	[92]
Emergent surgery after failure of PCI or of fibrinolysis is only indicated in patients with persistent haemodynamic instability or life-threatening ventricular arrhythmia due to extensive ischaemia (LM or severe 3-vessel disease).	I	C	–
If the patient continues to deteriorate without adequate cardiac output to prevent end-organ failure, temporary mechanical assistance (surgical implantation of LVAD/BiVAD) should be considered.	IIa	C	[98,99]
Routine use of percutaneous centrifugal pumps is not recommended.	III	B	[97,100,101]

^a Class of recommendation.

^b Level of evidence.

^c References.

AHF = acute heart failure; AMI = acute myocardial infarction; BiVAD = bi-ventricular assist device; CABG = coronary artery bypass grafting; IABP = intra-aortic balloon pump; LM = left main; LV = left ventricle; LVAD = left ventricular assist device; NSTEMI-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

9. Special conditions

9.1. Diabetes

Diabetic patients represent an increasing proportion of CAD patients, many of whom are treated with revascularization procedures [110]. They are at increased risk, including long-term mortality, compared with non-diabetic patients [29], whatever the mode of therapy used, and they may pose specific problems, such as higher restenosis and occlusion rates after PCI and CABG.

9.1.1. Indications for myocardial revascularization

The BARI 2D trial specifically addressed the question of myocardial revascularization in diabetic patients with mostly stable CAD [111]. The Heart Team reviewed the coronary angiograms and judged whether the most appropriate revascularization technique would be PCI or CABG. The patients were then randomized to either OMT only, or revascularization in addition to OMT. Of note, 4623 patients

were screened for participation in the trial, of which ~50% were included. Overall there was no difference after 5 years in the rates of death, MI, or stroke between OMT (12.2%) and revascularization (11.7%). In the PCI stratum, there was no outcome difference between PCI and OMT. In the surgical stratum, survival free of MACCE was significantly higher with CABG (77.6%) than with medical treatment only (69.5%, $P=0.01$); survival, however, was not significantly different (86.4% vs. 83.6%, $P=0.33$).

In NSTEMI-ACS patients, there is no interaction between the effect of myocardial revascularization and diabetic status [62,63,69]. In both the FRISC-2 and TACTICS-TIMI 18 trials [62,69], an early invasive strategy was associated with improved outcomes; in TACTICS-TIMI 18 [69], the magnitude of the benefit in diabetic patients was greater than in non-diabetics.

In STEMI patients, the PCAT-2 [112] collaborative analysis of 19 RCTs showed a similar benefit of primary PCI over fibrinolytic treatment in diabetic and non-diabetic patients. The odds ratio (OR) for mortality with primary PCI was 0.49 for diabetic patients (95% CI 0.31–0.79). Late PCI in patients with a completely occluded coronary artery after STEMI past the acute stage offered no benefit over medical therapy alone, both in diabetic and non-diabetic patients [90].

9.1.2. Type of intervention: coronary artery bypass grafting vs. percutaneous coronary intervention

All RCTs have shown higher rates of repeat revascularization procedures after PCI, compared with CABG, in diabetic patients [29]. A recent meta-analysis on individual data from 10 RCTs of elective myocardial revascularization [29] confirms a distinct survival advantage for CABG over PCI in diabetic patients. Five-year mortality was 20% with PCI, compared with 12.3% with CABG (OR 0.70, 95% CI 0.56–0.87), whereas no difference was found for non-diabetic patients; the interaction between diabetic status and type of revascularization was significant. The AWESOME trial [113] randomized high-risk patients (one-third with diabetes) to PCI or CABG. At 3 years, there was no significant difference in mortality between PCI-treated and CABG-treated diabetic patients. Finally, in diabetic patients from the SYNTAX trial [4], the MACCE rate at 1 year was twice as high with PCI using paclitaxel-eluting stent (PES), compared with CABG, a difference driven by repeat revascularization.

Though admittedly underpowered, the CARDia trial [114] is the only trial reported to date that was specifically designed to compare PCI using BMS (31%) or DES (69%) with CABG in diabetic patients. At 1 year, the combined incidence of death, MI, or stroke was 10.5% in the CABG arm and 13.0% in the PCI arm (HR 1.25, 95% CI 0.75–2.09). Repeat revascularization was 2.0% vs. 11.8%, respectively ($P<0.001$).

Besides RCTs, registry data, such as the New York registry [34], show a trend to improved outcomes in diabetic patients treated with CABG compared with DES (OR for death or MI at 18 months 0.84, 95% CI 0.69–1.01).

9.1.3. Specific aspects of percutaneous coronary intervention

A large collaborative network meta-analysis has compared DES with BMS in 3852 diabetic patients [115]. Mortality

appeared significantly ($P=0.02$) higher with DES compared with BMS when the duration of DAPT was <6 months (eight trials); in contrast, no difference in mortality and the combined endpoint death or MI was found when DAPT duration was ≥ 6 months (27 trials). Whatever the duration of DAPT, the need for repeat TVR was considerably less with DES than BMS [OR 0.29 for sirolimus-eluting stent (SES); 0.38 for PES], similar to the restenosis reduction observed in non-diabetic patients. There are no robust data to support the use of one DES over another in patients with diabetes.

9.1.4. Type of coronary artery bypass grafting intervention

Diabetic patients usually have extensive CAD and require multiple grafts. There is no direct randomized evidence regarding the use of only one vs. two ITA conduits in diabetic patients. Currently, only observational evidence suggests that using both arterial conduits improves outcomes, without compromising sternal stability [49]. A non-randomized comparison of bilateral ITA surgery with PCI in diabetic patients showed improved outcomes with the use of bilateral arterial grafts, though 5-year survival was not significantly different from that of PCI-treated patients [116]. Although diabetes is a risk factor for wound infection and mediastinitis, the impact of the use of bilateral ITA on these complications is debated.

9.1.5. Antithrombotic pharmacotherapy

There is no indication that antithrombotic pharmacotherapy should differ between diabetic vs. non-diabetic patients undergoing elective revascularization. In ACS trials, there is no indication that the antithrombotic regimen should differ between diabetic and non-diabetic patients [65,85,86]. Although an interaction between diabetic status and efficacy of GPIIb–IIIa inhibitors was noted in earlier trials without concomitant use of thienopyridines, this was not confirmed in the more recent Early-ACS trial [65]. In the current context of the use of high-dose oral antiplatelet agents, diabetic patients do not benefit from the routine addition of GPIIb–IIIa inhibitors.

9.1.6. Antidiabetic medications

There have been only a few specific trials of antidiabetic medications in patients undergoing myocardial revascularization.

Metformin

Because of the risk of lactic acidosis in patients receiving iodinated contrast media, it is generally stated that metformin should be interrupted before angiography or PCI, and reintroduced 48 h later, only after assessment of renal function. However, there is no convincing evidence for such a recommendation. Checking renal function after angiography in patients on metformin and stopping metformin when renal function deteriorates might be an acceptable alternative to suspension of metformin in all patients. In patients with renal failure, metformin should preferably be stopped before the procedure.

Sulfonylureas

Observational data have reported concern about the use of sulfonylureas in patients treated with primary PCI. This

has not been confirmed with the use of newer pancreatic-specific sulfonylureas.

Glitazones

Thiazolidinediones may be associated with lower restenosis rates after PCI with BMS; however, they are associated with an increased risk of heart failure.

Insulin

No trial has shown improved PCI outcome after STEMI with the administration of insulin or glucose insulin potassium (GIK) [117–119]. After CABG, the incidence of secondary endpoints, such as atrial fibrillation (AF), myocardial injury, wound infection, or hospital stay, was reduced after GIK infusion [120,121]. However, the NICE-SUGAR trial [122] assessed the impact of insulin therapy with tight blood glucose control in patients admitted to the intensive care unit for various clinical and surgical conditions. An increase in severe hypoglycaemic episodes was noted in the tighter blood glucose control arm of the trial, and 90-day mortality was increased.

Table 16 shows specific recommendations for revascularization in diabetic patients.

Table 16
Specific recommendations for diabetic patients

	Class ^a	Level ^b	Ref. ^c
In patients presenting with STEMI, primary PCI is preferred over fibrinolysis if it can be performed within recommended time limits.	I	A	[112]
In stable patients with extensive CAD, revascularization is indicated in order to improve MACCE-free survival.	I	A	[111]
Use of DES is recommended in order to reduce restenosis and repeat TVR.	I	A	[115]
In patients on metformin, renal function should be carefully monitored after coronary angiography/PCI.	I	C	–
CABG should be considered, rather than PCI, when the extent of the CAD justifies a surgical approach (especially MVD), and the patient's risk profile is acceptable.	Ila	B	[29,34,113,116]
In patients with known renal failure undergoing PCI, metformin may be stopped 48 h before the procedure.	Ilb	C	–
Systematic use of GIK in diabetic patients undergoing revascularization is not indicated.	III	B	[117,118,122]

^a Class of recommendation.

^b Level of evidence.

^c References.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; DES = drug-eluting stent; GIK = glucose insulin potassium; MACCE = major adverse cardiac and cerebral event; MVD = multivessel disease; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TVR = target vessel revascularization.

9.2. Myocardial revascularization in patients with chronic kidney disease

Cardiovascular disease is the main cause of mortality in patients with severe chronic kidney disease (CKD), particularly in combination with diabetes. Cardiovascular mortality is much higher among patients with CKD than in the general population, and CAD is the main cause of death among diabetic patients after kidney transplantation. Myocardial

revascularization procedures may therefore significantly improve survival of patients with CKD. However, the use of contrast media during diagnostic and interventional vascular procedures represents the most common cause of acute kidney injury in hospitalized patients. The detection of a minimum serum creatinine rise (5–10% from baseline), 12 h after angiography or PCI, may be a very simple and early indicator of contrast-induced nephropathy (CIN). CABG can also cause acute kidney injury or worsen CIN.

Definition of chronic kidney disease

Estimation of glomerular renal function in patients undergoing revascularization requires calculation of the glomerular filtration rate (GFR) and cannot be based on serum creatinine levels. Normal GFR values are ~100–130 mL/min/1.73 m² in young men, and 90–120 mL/min/1.73 m² in young women, depending on age, sex, and body size. CKD is classified into five different stages according to the progressive GFR reduction and evidence of renal damage. The cut-off GFR value of 60 mL/min/1.73 m² correlates significantly with MACE. In diabetic patients, the diagnosis of proteinuria, independently of GFR values, supports the diagnosis of CKD with similar prognostic implications due to diabetic macroangiopathy. Cystatin-c is an alternative marker of renal function and may be more reliable than serum creatinine in elderly patients (>75 years old).

Patients with mild or moderate chronic kidney disease

For patients with mild ($60 \leq \text{GFR} < 90 \text{ mL/min/1.73 m}^2$) or moderate ($30 \leq \text{GFR} < 60 \text{ mL/min/1.73 m}^2$) CKD, there is consistent evidence supporting CABG as a better treatment than PCI, particularly when diabetes is the cause of the CKD. An off-pump approach may be considered when surgical revascularization is needed. When there is an indication for PCI, there is only weak evidence suggesting that DES are superior to BMS in terms of reduced recurrence of

ischaemia. The potential benefit of DES should be weighed against the risk of side effects that derive from the need for prolonged DAPT, increased risk of late thrombosis, increased restenosis propensity of complex calcified lesions, and a medical condition often requiring multiple diagnostic and therapeutic procedures. Available data refer to the use of SESs and PESs, with no robust evidence favouring either one or any of the newer generation DES in this subset.

Patients with severe chronic kidney and end stage renal disease or in haemodialysis

In the subset of patients with severe CKD (GFR <30 mL/min/1.73 m²) and end stage renal disease (ESRD) or those in haemodialysis, differences in favour of surgery over PCI are less consistent. Surgery confers a better event-free survival in the long term, but in-hospital mortality and complication rates are higher, while the opposite is true for PCI. Selection of the most appropriate revascularization strategy must therefore account for the general condition of the patient and his or her life expectancy, the least invasive approach being more appropriate in the most fragile and compromised patient. DES has not been proved superior to BMS and should not be used indiscriminately. Indeed, it has well been established that CKD is an independent predictor of (very) late DES thrombosis with HR between 3.1 and 6.5.

Candidates for renal transplantation must be screened for myocardial ischaemia and those with significant CAD should not be denied the potential benefit of myocardial revascularization. PCI using BMS should be considered if subsequent renal transplantation is likely within 1 year.

Prevention of CIN

All patients with CKD undergoing diagnostic catheterization should receive preventive hydration with isotonic saline to be started at least 12 h before angiography and continued for at least 24 h afterwards, in order to reduce the risk of CIN (Table 17). OMT before exposure to contrast media should

Table 17
Recommendations for prevention of contrast-induced nephropathy

Intervention	Dose	Class ^a	Level ^b	Ref. ^c
All patients with CKD				
OMT (including statins, β -blockers, and ACE inhibitors or sartans) is recommended.	According to clinical indications.	I	A	[123]
Hydration with isotonic saline is recommended.	1 mL/kg/h 12 h before and continued for 24 h after the procedure (0.5 mL/kg/h if EF <35% or NYHA >2).	I	A	[127–130]
<i>N</i> -Acetylcysteine administration may be considered.	600–1200 mg 24 h before and continued for 24 h after the procedure.	IIb	A	[128,129]
Infusion of sodium bicarbonate 0.84% may be considered.	1 h before: bolus = body weight in kg \times 0.462 mEq i.v. infusion for 6 h after the procedure = body weight in kg \times 0.154 mEq per hour.	IIb	A	[127,128,130]
Patients with mild, moderate, or severe CKD				
Use of LOCM or IOCM is recommended.	<350 mL or <4 mL/kg	I ^d	A ^d	[124,131–133]
Patients with severe CKD				
Prophylactic haemofiltration 6 h before complex PCI should be considered.	Fluid replacement rate 1000 mL/h without weight loss and saline hydration, continued for 24 h after the procedure.	IIa	B	[134,135]
Elective haemodialysis is not recommended as a preventive measure.		III	B	[136]

^a Class of recommendation.

^b Level of evidence.

^c References.

^d Recommendation pertains to the type of contrast.

ACE = angiotensin-converting enzyme; CKD = chronic kidney disease; EF = ejection fraction; IOCM = iso-osmolar contrast media; i.v. = intravenous; LOCM = low osmolar contrast media; NYHA = New York Heart Association; OMT = optimal medical therapy; PCI = percutaneous coronary intervention.

include statins, ACE inhibitors or sartans, and β -blockers as recommended [123].

Although performing diagnostic and interventional procedures separately reduces the total volume exposure to contrast media, the risk of renal atheroembolic disease increases with multiple catheterizations. Therefore, in CKD patients with diffuse atherosclerosis, a single invasive approach (diagnostic angiography followed by *ad hoc* PCI) may be considered, but only if the contrast volume can be maintained below 4 mL/kg. The risk of CIN increases significantly when the ratio of contrast volume to GFR exceeds 3.7 [124].

For patients undergoing CABG, the effectiveness of the implementation of pharmacological preventive measures such as clonidine, fenoldopam, natriuretic peptides, N-acetylcysteine [125] or elective pre-operative haemodialysis remain unproved [126].

Table 18 lists the specific recommendations for patients with mild to moderate CKD.

Table 18

Specific recommendations for patients with mild to moderate chronic kidney disease

	Class ^a	Level ^b	Ref. ^c
CABG should be considered, rather than PCI, when the extent of the CAD justifies a surgical approach, the patient's risk profile is acceptable, and life expectancy is reasonable.	IIa	B	[32,137–139]
Off-pump CABG may be considered, rather than on-pump CABG.	IIb	B	[140]
For PCI, DES may be considered, rather than BMS.	IIb	C	–

^a Class of recommendation.

^b Level of evidence.

^c References.

BMS = bare metal stent; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DES = drug-eluting stent; PCI = percutaneous coronary intervention.

9.3. Myocardial revascularization in patients requiring valve surgery

Coronary angiography is recommended in all patients with valvular heart disease requiring valve surgery, apart from young patients (men <40 years and pre-menopausal women) with no risk factors for CAD, or when the risks of angiography outweigh the benefits, e.g. in cases of aortic dissection [141]. Overall, 40% of patients with valvular heart disease will have concomitant CAD. The indications for combining valve surgery with CABG in these patients are summarized in Table 19. Of note, in those patients undergoing aortic valve replacement who also have significant CAD, the combination of CABG and aortic valve surgery reduces the rates of perioperative MI, perioperative mortality, late mortality and morbidity when compared with patients not undergoing simultaneous CABG [142]. This combined operation, however, carries an increased risk of mortality of 1.6–1.8% over isolated aortic valve replacement.

Overall the prevalence of valvular heart disease is rising as the general population ages. Accordingly, the risk profile of patients undergoing surgery is increasing. The consequence of this change is that some patients requiring valve

Table 19
Recommendations for combined valve surgery and coronary artery bypass grafting

	Class ^a	Level ^b
Combined valve surgery and:		
CABG is recommended in patients with a primary indication for aortic/mitral valve surgery and coronary artery diameter stenosis $\geq 70\%$.	I	C
CABG should be considered in patients with a primary indication for aortic/mitral valve surgery and coronary artery diameter stenosis 50–70%.	IIa	C
Combined CABG and:		
Mitral valve surgery is indicated in patients with a primary indication for CABG and severe ^c ischaemic mitral regurgitation and EF >30%.	I	C
Mitral valve surgery should be considered in patients with a primary indication for CABG and moderate ischaemic mitral regurgitation provided valve repair is feasible, and performed by experienced operators.	IIa	C
Aortic valve surgery should be considered in patients with a primary indication for CABG and moderate aortic stenosis (mean gradient 30–50 mmHg or Doppler velocity 3–4 m/s or heavily calcified aortic valve even when Doppler velocity 2.5–3 m/s).	IIa	C

^a Class of recommendation.

^b Level of evidence.

^c Definition of severe mitral regurgitation is available in the ESC Guidelines on Valvular Heart Disease. *Eur Heart J* 2007;28:230–268 and www.escardio.org/guidelines.

CABG = coronary artery bypass grafting; EF = ejection fraction.

replacement and CABG may represent too high a risk for a single combined operation. Alternative treatments include using 'hybrid' procedures, which involve a combination of both scheduled surgery for valve replacement and planned PCI for myocardial revascularization. At present, however, the data on hybrid valve/PCI procedures are very limited, being confined to case reports and small case series [143]. Another option that may be considered in these high-risk surgical patients is transcatheter aortic valve implantation [144].

9.4. Associated carotid/peripheral arterial disease

9.4.1. Associated coronary and carotid artery disease

The incidence of significant carotid artery disease in patients scheduled for CABG depends on age, cardiovascular risk factors, and screening method. The aetiology of post-CABG stroke is multifactorial and the main causes are atherosclerosis of the ascending aorta, cerebrovascular disease, and macroembolism of cardiac origin. Carotid bifurcation stenosis is a marker of global atherosclerotic burden that, together with age, cardiovascular risk factors, previous stroke or transient ischaemic attack (TIA), rhythm and coagulation disturbances, increases the risk of neurological complications during CABG. Conversely, up to 40% of patients undergoing carotid endarterectomy (CEA) have significant CAD and may benefit from pre-operative cardiac risk assessment [123].

Risk factors for stroke associated with myocardial revascularization

The incidence of perioperative stroke after on-pump CABG varies from 1.5% to 5.2% in prospective studies

Table 20
Carotid artery screening before planned myocardial revascularization

	Class ^a	Level ^b
Duplex ultrasound scanning is recommended in patients with previous TIA/stroke or carotid bruit on auscultation.	I	C
Duplex ultrasound scanning should be considered in patients with LM disease, severe PAD, or ≥75 years.	IIa	C
MRI, CT, or digital subtraction angiography may be considered if carotid artery stenosis by ultrasound is >70% ^c and myocardial revascularization is contemplated.	IIb	C

^a Class of recommendation.

^b Level of evidence.

^c Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejcts.2010.08.019 and also at www.eacts.org.

CT = computed tomography; LM = left main; MRI = magnetic resonance imaging; PAD = peripheral arterial disease; TIA = transient ischaemic attack.

and from 0.8% to 3.2% in retrospective studies. The most common single cause of post-CABG stroke is embolization of atherothrombotic debris from the aortic arch, and patients with carotid stenosis also have a higher prevalence of aortic arch atherosclerosis. Although symptomatic carotid artery stenosis is associated with an increased stroke risk, 50% of strokes after CABG do not have significant carotid artery disease and 60% of territorial infarctions on computed tomography (CT) scan/autopsy cannot be attributed to carotid disease alone. Furthermore, only 45% of strokes after CABG are identified within the first day after surgery while 55% of strokes occur after uneventful recovery from anaesthesia and are attributed to AF, low cardiac output, or hypercoagulopathy resulting from tissue injury. Intraoperative risk factors for stroke are duration of cardiopulmonary bypass (CPB), manipulation of the ascending aorta, and arrhythmias. Off-pump CABG has been shown to decrease the risk of stroke, especially when the ascending aorta is diseased, and particularly if a no-touch aorta technique is used.

In patients with carotid artery disease undergoing PCI, although the risk of stroke is low (0.2%), ACS, heart failure (HF), and widespread atherosclerosis are independent risk factors. Recommendations for carotid artery screening before myocardial revascularization are listed in Table 20.

Carotid revascularization in patients scheduled for coronary artery bypass grafting or percutaneous coronary intervention

In patients with previous TIA or non-disabling stroke and a carotid artery stenosis (50–99% in men and 70–99% in women) the risk of stroke after CABG is high, and CEA by experienced teams may reduce the risk of stroke or death [145] (see figure in Appendix for methods of measuring carotid artery stenosis). There is no guidance on whether the procedures should be staged or synchronous. On the other hand, in asymptomatic unilateral carotid artery stenosis, isolated myocardial revascularization should be performed due to the small risk reduction in stroke and death rate obtained by carotid revascularization (1% per year) [145]. Carotid revascularization may be considered in asymptomatic men with bilateral severe carotid artery stenosis or contralateral occlusion if the risk of post-procedural 30-day mortality or

stroke rate can be reliably documented to be <3% and life expectancy is >5 years. In women with asymptomatic carotid disease or patients with a life expectancy of <5 years, the benefit of carotid revascularization is dubious [145]. In the absence of clear proof that staged or synchronous CEA or carotid artery stenting (CAS) is beneficial in patients undergoing CABG, all patients should be assessed on an individual basis, by a multidisciplinary team including a neurologist. This strategy is also valid for patients scheduled for PCI. For carotid revascularization in CABG patients see Table 21; for PCI patients see Table 22.

Table 21
Carotid revascularization in patients scheduled for coronary artery bypass grafting

	Class ^a	Level ^b	Ref. ^c
CEA or CAS should be performed only by teams with demonstrated 30-day combined death-stroke rate: <3% in patients without previous neurological symptoms <6% in patients with previous neurological symptoms.	I	A	[145]
The indication for carotid revascularization should be individualized after discussion by a multidisciplinary team including a neurologist.	I	C	–
The timing of the procedures (synchronous or staged) should be dictated by local expertise and clinical presentation targeting the most symptomatic territory first.	I	C	–
In patients with previous TIA/non-disabling stroke, carotid revascularization:			
Is recommended in 70–99% carotid stenosis.	I	C	–
May be considered in 50–69% carotid stenosis in men with symptoms <6 months.	IIb	C	–
Is not recommended if carotid stenosis <50% in men and <70% in women.	III	C	–
In patients with no previous TIA/stroke, carotid revascularization:			
May be considered in men with bilateral 70–99% carotid stenosis or 70–99% carotid stenosis + contralateral occlusion.	IIb	C	–
Is not recommended in women or patients with a life expectancy <5 years.	III	C	–

^a Class of recommendation.

^b Level of evidence.

^c References.

CAS = carotid artery stenting; CEA = carotid endarterectomy; TIA = transient ischaemic attack.

Table 22
Carotid revascularization in patients scheduled for percutaneous coronary intervention

	Class ^a	Level ^b
The indication for carotid revascularization should be individualized after discussion by a multidisciplinary team including a neurologist.	I	C
CAS should not be combined with elective PCI during the same endovascular procedure except in the infrequent circumstance of concomitant acute severe carotid and coronary syndromes.	III	C

^a Class of recommendation.

^b Level of evidence.

CAS = carotid artery stenting; PCI = percutaneous coronary intervention.

Table 23
Recommendations for the method of carotid revascularization

	Class ^a	Level ^b	Ref. ^c
CEA remains the procedure of choice but selection of CEA versus CAS depends on multidisciplinary assessment.	I	B	[147, 149]
Aspirin is recommended immediately before and after carotid revascularization.	I	A	[150, 151]
Patients who undergo CAS should receive DAPT for at least 1 month after stenting.	I	C	–
CAS should be considered in patients with: <ul style="list-style-type: none"> • post-radiation or post-surgical stenosis • obesity, hostile neck, tracheostomy, laryngeal palsy • stenosis at different carotid levels or upper internal carotid artery stenosis • severe comorbidities contraindicating CEA. 	IIa	C	–
CAS is not recommended in patients with: <ul style="list-style-type: none"> • heavily calcified aortic arch or protruding atheroma • internal carotid artery lumen diameter <3 mm • contraindication to DAPT. 	III	C	–

^a Class of recommendation.

^b Level of evidence.

^c References.

CAS = carotid artery stenting; CEA = carotid endarterectomy; DAPT = dual antiplatelet therapy.

Choice of revascularization method in patients with associated carotid and coronary artery disease

See Table 23. Few patients scheduled for CABG require synchronous or staged carotid revascularization and, in this case, CEA remains the procedure of choice. Indeed the two most recent meta-analyses comparing CAS with CEA documented that CAS results in a significant increase in 30-day death or stroke compared with CEA (OR 1.60, 95% CI 1.26–2.02) [146]. This was confirmed by the International Carotid Stenting Study, which randomized 855 patients to CAS and 858 patients to CEA and showed that the incidence of stroke, death, or MI was 8.5% in the stenting group vs. 5.2% in the endarterectomy group (HR 1.69; $P=0.006$) [147]. In an MRI substudy, new post-procedural lesions occurred more frequently after CAS than after CEA (OR 5.2; $P<0.0001$) [148]. The recently published CREST trial [149], which included 50% of asymptomatic patients, showed that the 30-day risk of death, stroke, and MI was similar after CAS (5.2%) or CEA (2.3%). Perioperative MI rates were 2.3% after CEA and 1.1% after CAS ($P=0.03$), while perioperative stroke rates were 2.3 and 4.1%, respectively ($P=0.01$). Pooling these results with previous RCTs will help determine which patient subgroups might benefit more from CAS or CEA.

Both CEA and CAS should be performed only by experienced teams, adhering to accepted protocols and established indications. CAS is indicated when CEA has been contraindicated by a multidisciplinary team due to severe comorbidities or unfavourable anatomy. In patients with a mean EuroSCORE of 8.6, good results with CAS performed immediately before CABG (hybrid procedure) were reported by experienced operators. This strategy should be reserved for very high risk patients in need of urgent CABG and previous neurological symptoms. In patients scheduled for myocardial revascularization, without previous neurological

symptoms, who are poor surgical candidates owing to severe comorbidities, there is no evidence that revascularization, with either CEA or CAS, is superior to OMT. A systematic review of staged CAS and CABG, in which 87% of the patients were asymptomatic and 82% had unilateral lesions, showed a high combined death and stroke rate at 30 days (9%). This high procedural risk cannot be justified in neurologically asymptomatic patients with unilateral carotid disease.

9.4.2. Associated coronary and peripheral arterial disease

PAD is an important predictor of adverse outcome after myocardial revascularization, and portends a poor long-term prognosis [152]. Patients with clinical evidence of PAD are at significantly higher risk for procedural complications after either PCI or CABG. When comparing the outcomes of CABG vs. PCI in patients with PAD and MVD, CABG shows a trend for improved survival. Risk-adjusted registry data have shown that patients with MVD and PAD undergoing CABG have better survival at 3 years than similar patients undergoing PCI, in spite of higher in-hospital mortality. However, with no solid data available in this population, the two myocardial revascularization approaches are probably as complementary in patients with PAD as they are in other CAD patients.

Non-cardiac vascular surgery in patients with associated coronary artery disease

Patients scheduled for non-cardiac vascular surgery are at significant risk of cardiovascular morbidity and mortality due to a high incidence of underlying symptomatic or asymptomatic CAD. Pre-operative cardiac risk assessment in vascular surgery patients has been addressed in previously published ESC Guidelines [123]. Results of the largest RCT demonstrated that there is no reduction in post-operative MI, early or long-term mortality among patients randomized to prophylactic myocardial revascularization compared with patients allocated to OMT before major vascular surgery [153]. Included patients had preserved left ventricular ejection fraction (LVEF) and stable CAD. By contrast, the DECREASE-V pilot study [154] included only high-risk patients [almost half had ejection fraction (EF) <35% and 75% had three-vessel or LM disease], with extensive stress-induced ischaemia evidenced by dobutamine echocardiography or stress nuclear imaging. This study confirmed that prophylactic myocardial revascularization did not improve outcome [154]. Selected high-risk patients may still benefit from previous or concomitant myocardial revascularization with options varying from a one-stage surgical approach to combined PCI and peripheral endovascular repair or hybrid procedures [155].

RCTs selecting high-risk patients, cohort studies, and meta-analyses provide consistent evidence of a decrease in cardiac mortality and MI due to β -blockers and statins, in patients undergoing high-risk non-cardiac vascular surgery [123] or endovascular procedures [152].

Table 24 summarizes the management of associated coronary and PAD.

Table 24

Management of patients with associated coronary and peripheral arterial disease

	Class ^a	Level ^b	Ref. ^c
In patients with unstable CAD, vascular surgery is postponed and CAD treated first, except when vascular surgery cannot be delayed due to a life-threatening condition.	I	B	[123]
β-blockers and statins are indicated prior to and continued post-operatively in patients with known CAD who are scheduled for high-risk vascular surgery.	I	B	[123]
The choice between CABG and PCI should be individualized and assessed by a Heart Team considering patterns of CAD, PAD, comorbidity, and clinical presentation.	I	C	–
Prophylactic myocardial revascularization prior to high-risk vascular surgery may be considered in stable patients if they have persistent signs of extensive ischaemia or a high cardiac risk.	IIb	B	[155]

^a Class of recommendation.^b Level of evidence.^c References.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention.

Renal artery disease

Although the prevalence of atherosclerotic renal artery stenosis in CAD patients has been reported to be as high as 30%, its management in patients needing myocardial revascularization is uncertain. Stented angioplasty has been current practice in the majority of cases. Weak evidence suggests that similar kidney function but better blood pressure outcomes have been achieved by percutaneous renal artery intervention. However, a recent RCT comparing stenting with medical treatment vs. medical treatment alone, in patients with atherosclerotic renal artery stenosis and impaired renal function, showed that stent placement had no favourable effect on renal function and led to a small number of procedure-related complications [156]. Despite a high procedural success rate of renal artery stenting, an improvement in hypertension has been inconsistent and the degree of stenosis that justifies stenting is unknown. Given the relatively small advantages of angioplasty over antihypertensive drug therapy in the treatment of hypertension, only patients with therapy-resistant hypertension and progressive renal failure in the presence of functionally significant renal artery stenosis may benefit from revascularization. Functional assessment of renal artery stenosis severity using pressure gradient measurements may improve appropriate patient selection [157].

Table 25

Management of patients with renal artery stenosis

	Class ^a	Level ^b	Ref. ^c
Functional assessment of renal artery stenosis severity using pressure gradient measurements may be useful in selecting hypertensive patients who benefit from renal artery stenting.	IIb	B	[157]
Routine renal artery stenting to prevent deterioration of renal function is not recommended.	III	B	[156]

^a Class of recommendation.^b Level of evidence.^c References.

Table 25 summarizes the management of patients with renal artery stenosis.

9.5. Myocardial revascularization in chronic heart failure

CAD is the most common cause of HF. The prognosis for patients with chronic ischaemic LV systolic dysfunction remains poor despite advances in various therapeutic strategies. The established indications for revascularization in patients with ischaemic HF pertain to patients with angina and significant CAD [158]. The associated risk of mortality is increased and ranges from 5 to 30%. The management of patients with ischaemic HF without angina is a challenge because of the lack of RCTs in this population. In this context, the detection of myocardial viability should be included in the diagnostic work-up of HF patients with known CAD. Several prospective and retrospective studies and meta-analyses have consistently shown improved LV function and survival in patients with ischaemic but viable myocardium, who subsequently underwent revascularization [16]. Conversely, patients without viability will not benefit from revascularization, and the high risk of surgery should be avoided. Patients with a severely dilated LV have a low likelihood of showing improvement in LVEF even in the presence of substantial viability. The possibility of combining myocardial revascularization with surgical ventricular reconstruction (SVR) to reverse LV remodelling has been addressed in a few RCTs [159]. The aim of SVR is to exclude scar tissue from the LV wall, thereby restoring the LV physiological volume and shape.

The Surgical Treatment Ischaemic Heart failure (STICH) Hypothesis 2 substudy compared CABG alone with combined CABG and SVR in patients with LVEF ≤35% [159]. No difference in the occurrence of the primary outcome (death from any cause or hospitalization for cardiac causes) between the CABG and the combined procedure groups was observed. However, the combined procedure resulted in a 16 mL/m² (19%) reduction in end-systolic volume index, larger than in the CABG-only group, but smaller than in previously reported observational studies. The latter observation raises concerns about the extent of the SVR procedure that was applied in this RCT [160]. Choosing to add SVR to CABG should be based on a careful evaluation of patients, including symptoms (HF symptoms should be predominant over angina), measurements of LV volumes, assessment of the transmural extent of myocardial scar tissue, and should be performed only in centres with a high level of surgical expertise. In this context, MRI is the standard imaging technique to assess myocardial anatomy, regional and global function, viability, and, more importantly, infarct size and percentage of transmural extent determined by late gadolinium enhancement.

The choice between CABG and PCI should be based on a careful evaluation of the anatomy of coronary lesions, expected completeness of revascularization, comorbidities, and associated significant valvular disease [141]. Data on PCI results in patients with ischaemic HF but without angina

Table 26

Recommendations for patients with chronic heart failure and systolic left ventricular dysfunction (ejection fraction $\leq 35\%$), presenting predominantly with anginal symptoms

	Class ^a	Level ^b	Ref. ^c
CABG is recommended for: <ul style="list-style-type: none"> significant LM stenosis LM equivalent (proximal stenosis of both LAD and LCx) proximal LAD stenosis with 2- or 3-vessel disease. 	I	B	[158]
CABG with SVR may be considered in patients with LVESV index ≥ 60 mL/m ² and scarred LAD territory.	IIb	B	[159, 160]
PCI may be considered if anatomy is suitable, in the presence of viable myocardium.	IIb	C	–

^a Class of recommendation.

^b Level of evidence.

^c References.

CABG = coronary artery bypass grafting; LAD = left anterior descending; LCx = left circumflex; LM = left main; LVESV = left ventricular end-systolic volume; PCI = percutaneous coronary intervention; SVR = surgical ventricular reconstruction.

Table 27

Recommendations for patients with chronic heart failure and systolic left ventricular dysfunction (ejection fraction $\leq 35\%$), presenting predominantly with heart failure symptoms (no or mild angina: Canadian Cardiovascular Society 1–2)

	Class ^a	Level ^b	Ref. ^c
LV aneurysmectomy during CABG is indicated in patients with a large LV aneurysm.	I	C	–
CABG should be considered in the presence of viable myocardium, irrespective of LVESV.	IIa	B	[16]
CABG with SVR may be considered in patients with a scarred LAD territory.	IIb	B	[159, 160]
PCI may be considered if anatomy is suitable, in the presence of viable myocardium.	IIb	C	–
Revascularization in the absence of evidence of myocardial viability is not recommended.	III	B	[16]

^a Class of recommendation.

^b Level of evidence.

^c References.

CABG = coronary artery bypass grafting; LAD = left anterior descending; LV = left ventricle; LVESV = left ventricular end-systolic volume; PCI = percutaneous coronary intervention; SVR = surgical ventricular reconstruction.

are limited. There is weak evidence suggesting that CABG is superior to PCI [36].

Many CAD patients with depressed LV function remain at risk of sudden cardiac death (SCD) despite revascularization and potential indications for implantable cardioverter defibrillator (ICD) therapy should be carefully examined (Section 9.7.3) [93].

Tables 26 and 27 summarize the recommendations for patients with CHF and systolic LV dysfunction (EF $\leq 35\%$), presenting predominantly with anginal symptoms or with HF symptoms, respectively.

9.6. Crossed revascularization procedures

9.6.1. Revascularization for acute graft failure

Early graft failure after CABG (<1 month) may occur in 8–30% of cases. Perioperative angiography showed failure of 8% of saphenous vein grafts (SVGs) and 7% of left ITA

grafts [161]. In symptomatic patients, early graft failure can be identified as the cause of ischaemia in ~75% of cases, while pericarditis or prolonged spasm is diagnosed in the remainder. PCI in acute post-operative graft failure may be an alternative to re-operation with acceptable results and fewer complications [161]. The target for PCI is the body of the native vessel or of the ITA graft while freshly occluded SVG or the anastomosis itself should not be targeted due to the risk of embolization or perforation. Surgery should be favoured if the graft or native artery appears unsuitable for PCI, or if several important grafts are occluded. In asymptomatic patients, re-operation or PCI should only be considered if the artery is of good size, severely narrowed and supplies a large territory of myocardium. Redo CABG or PCI should be decided by the Heart Team.

9.6.2. Revascularization for late graft failure

Ischaemia after CABG may be due to new disease, progression beyond the bypass graft anastomosis, or disease in the graft itself (Table 28).

Repeat revascularization in patients with graft failure is indicated in the presence of severe symptoms despite anti-anginal medication, and in patients with mild or no symptoms depending on risk stratification by non-invasive testing [32, 164].

Redo coronary artery bypass grafting or percutaneous coronary intervention

PCI in patients with previous CABG has worse acute and long-term outcomes than in patients without prior CABG. Patients who undergo repeat CABG have a two- to four-fold higher mortality than for the first procedure [165, 166]. A large series of the Cleveland Clinic Foundation showed that the risk of re-operation was mainly driven by comorbidity and less by the re-operation itself [165].

There are limited data comparing the efficacy of PCI vs. redo CABG in patients with previous CABG. In a propensity analysis of long-term survival after redo CABG or PCI in patients with MVD and high-risk features, short-term outcome after either technique was very favourable, with nearly identical survival at 1 and 5 years [32]. In the AWESOME RCT and registry, overall in-hospital mortality was higher with CABG than with PCI [167, 168].

Because of the initial higher mortality of redo CABG and the comparable long-term mortality, PCI is the preferred revascularization strategy in patients with patent left ITA and amenable anatomy. CABG is preferred for patients with more diseased or occluded grafts, reduced systolic LV function, more total occlusion of native arteries, as well as absence of a patent arterial graft [32]. The ITA is the conduit of choice for revascularization during redo CABG [169].

Table 28

Graft patency after coronary artery bypass grafting (%)

Graft	Patency at 1 year	Patency at 4–5 years	Patency at 10–15 years	Ref. ^a
SVG	>90	65–80	25–50	[47, 162]
Radial artery	86–96	89	Not reported	[162, 163]
Left ITA	>91	88	88	[161, 162]
Right ITA	Not reported	96	65	[162]

^a References.

ITA = internal thoracic artery; SVG = saphenous vein graft.

Table 29
Crossed revascularization procedures

	Class ^a	Level ^b	Ref. ^c
Following CABG			
In early graft failure			
Coronary angiography is indicated for highly symptomatic patients, or in the event of post-operative instability, or with abnormal biomarkers/ECG suggestive of perioperative MI.	I	C	–
Decision of redo CABG or PCI should be made by the Heart Team.	I	C	–
PCI is a superior alternative to re-operation in patients with early ischaemia after CABG.	I	B	[161]
The preferred target for PCI is the native vessel or ITA graft, not the freshly occluded SVG.	I	C	–
For freshly occluded SVG, redo CABG is recommended rather than PCI if the native artery appears unsuitable for PCI or several important grafts are occluded.	I	C	–
In late graft failure following CABG			
PCI or redo CABG is indicated in patients with severe symptoms or extensive ischaemia despite OMT.	I	B	[32,164]
PCI is recommended as a first choice, rather than redo CABG.	I	B	[32,165–168]
PCI of the bypassed native artery is the preferred approach when stenosed grafts >3 years old.	I	B	[170]
ITA is the conduit of choice for redo CABG.	I	B	[169]
Redo CABG should be considered for patients with several diseased grafts, reduced LV function, several CTO, or absence of a patent ITA.	Ila	C	–
PCI should be considered in patients with patent left ITA and amenable anatomy.	Ila	C	–
Following PCI			
In early failure following PCI			
Repeat PCI is recommended for early symptomatic restenosis after PCI.	I	B	[173–175]
Immediate CABG is indicated if failed PCI is likely to cause a large MI.	I	C	–
In late failure following PCI			
Patients with intolerable angina or ischaemia will eventually require CABG if:			
(a) lesions are unsuitable for PCI.	I	C	–
(b) there is additional non-discrete disease progression in other vessels.	I	C	–
(c) restenoses are repetitive and interventional options are not favourable.	I	C	–

^a Class of recommendation.

^b Level of evidence.

^c References.

CABG = coronary artery bypass grafting; CTO = chronic total occlusion; ECG = electrocardiogram; ITA = internal thoracic artery; LV = left ventricle; MI = myocardial infarction; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; SVG = saphenous vein graft.

Lesion subsets

Embolic complications and restenosis are significantly more frequent with SVG PCI than after ITA or native vessel PCI [170]. TVR in SVG intervention is driven mainly by progression in the non-target areas. Immediate results improve with protection devices but the efficacy of DES is less than with native vessel PCI [171].

PCI of the bypassed native artery should be the preferred approach provided the native vessel is not chronically occluded. PCI of a CTO may be indicated when ischaemic symptoms are present and there is evidence of significant ischaemia and viable myocardium in the territory supplied. CTO interventions should be performed by specialized operators with >80% success rates. If PCI of the native vessel fails, angioplasty of the stenosed SVG remains an option. In chronically occluded SVG the success rates are considerably lower with even higher complication and restenosis rates than in non-occluded SVG [32].

9.6.3. Revascularization for acute failure after percutaneous coronary intervention

If repeat PCI fails to abort evolving significant MI, immediate CABG is indicated [172]. When severe haemodynamic instability is present, IABP should be inserted prior to emergency revascularization. Cardiopulmonary assistance may be considered if the patient does not stabilize prior to emergency CABG.

9.6.4. Elective revascularization for late failure after percutaneous coronary intervention

Late failure after PCI is mostly due to restenosis and occasionally to (very) late stent thrombosis. Significant restenosis is commonly treated by PCI (balloon, DES, or drug-eluting balloon). Patients with intolerable angina or ischaemia will eventually require CABG, especially with unsuitable morphology for PCI (e.g. very long restenosis), additional non-discrete disease progression in other vessels or repetitive restenosis without favourable options for PCI. Diabetes, number of diseased vessels, type of lesion, lesion topography, and incomplete PCI revascularization have been identified as risk factors for subsequent CABG after PCI. Arterial grafts should be used preferentially to treat restenotic vessels. According to several studies, the operative risk of CABG may be increased, as compared with CABG without prior PCI. Prior stenting may compel more distal bypass grafting with less favourable results. Registry data showed increased complications after CABG with multiple prior PCI procedures.

9.6.5. Hybrid procedures

Hybrid myocardial revascularization is a planned, intentional combination of CABG, with a catheter-based intervention to other coronary arteries during the same hospital stay. Procedures can be performed consecutively in a hybrid operating room, or sequentially on separate occasions in the conventional surgical and PCI environments.

Table 30
Crossed revascularization procedures

	Class ^a	Level ^b	Ref. ^c
Hybrid procedure, defined as consecutive or combined surgical and interventional revascularization may be considered in specific patient subsets at experienced centres.	IIb	B	[176,177]

^a Class of recommendation.

^b Level of evidence.

^c References.

Hybrid procedure consisting of ITA to LAD and PCI of other territories appears reasonable when PCI of the LAD is not an option or unlikely to portend good results (Table 30). Indications should be selected by the Heart Team and potential opportunities for using a hybrid approach are listed here.

- (1) Primary PCI for posterior or inferior STEMI and severe CAD in non-culprit vessel(s), better suited for CABG.
- (2) Emergent PCI prior to surgery in patients with combined valvular and coronary disease, if the patient cannot be transferred for surgery, or in the presence of acute ischaemia.
- (3) Patients who had previous CABG and now require valve surgery and who have at least one important patent graft (e.g. ITA to LAD) and one or two occluded grafts with a native vessel suitable for PCI.
- (4) Combination of revascularization with non-sternotomy valve intervention (e.g. PCI and minimally invasive mitral valve repair, or PCI and trans-apical aortic valve implantation).
- (5) In patients with conditions likely to prevent healing after sternotomy, surgery can be restricted to the LAD territory using minimally invasive direct coronary artery bypass (MIDCAB) left ITA grafting. Remaining lesions in other vessels are treated by PCI.

9.7. Arrhythmias in patients with ischaemic heart disease

9.7.1. Atrial fibrillation

Atrial fibrillation in patients scheduled for coronary artery bypass grafting

The presence of AF in patients scheduled for CABG is independently associated with increased late cardiac morbidity and mortality and poor long-term prognosis [178,179]. Therefore, concomitant ablative treatment of AF during surgery may be considered in those patients although no prospective RCT has addressed this issue. All available studies are limited by small sample size or short follow-up periods.

Several ablation techniques have been proposed including the Corridor procedure, the Radial maze procedure, and the Cox-maze I–III. Currently, most groups favour the creation of ablation lines using a variety of energy sources including radiofrequency energy, microwave, cryoablation, laser, and high-intensity focused ultrasound. The success rates depend upon transmural and contiguity of the ablation lines, completeness of the lesion pattern, and evaluation method (ECG or Holter monitoring). Best reported results, between 65% and 95% at 6 months, have used bipolar radiofrequency

current and more extensive left atrium (LA) and bi-atrial lesions [180]. Poor chances of success include large LA size and pre-operative permanent AF duration. Complete exclusion of the LA appendage may be considered during a surgical ablation procedure to reduce the risk of stroke.

Atrial fibrillation after coronary artery bypass grafting

AF occurs in 27–40% of cases early after cardiac surgery and is associated with infection, renal failure, neurological complications, prolonged hospital stay, and increased cost.

Risk factors for developing post-operative AF include advanced age, need for prolonged ventilation (≥ 24 h), CPB, chronic obstructive lung disease, and pre-operative arrhythmias. Because an exaggerated inflammatory response is a possible aetiological factor, treatment with corticosteroids either as a single intravenous (i.v.) injection [181] or as oral prophylaxis, has been applied. Methylprednisolone (1 g) before surgery and dexamethasone (4 mg every 6 h) for 24 h significantly reduced the incidence of new-onset AF in two RCTs but possibly at the cost of more post-operative complications [181,182].

β -blockers, sotalol, and amiodarone reduce the risk of post-operative AF [183,184]. There is a wealth of safety and efficacy data, including two recent meta-analyses, supporting the routine use of β -blockers in post-operative cardiac surgical patients to reduce the incidence of post-operative AF (OR 0.36, 95% CI 0.28–0.47) [185,186]. Dosages vary widely between trials based on body size and LV function. As shown by several RCTs and meta-analyses [183,184,186], amiodarone is effective for the prophylaxis of AF. The largest RCT reported atrial tachyarrhythmias in 16.1% of amiodarone-treated patients compared with 29.5% of placebo-treated patients (HR 0.52, 95% CI 0.34–0.69), a 13.4% absolute risk reduction [184]. However, amiodarone trials excluded patients with low resting heart rate, second or third degree atrioventricular block, or New York Heart Association (NYHA) class III or IV.

Table 31
Prevention and treatment of atrial fibrillation with coronary artery bypass grafting

	Class ^a	Level ^b	Ref. ^c
β -blockers are recommended to decrease the incidence of AF after CABG.	I	A	[185,186,189,190]
Sotalol should be considered to decrease the incidence of AF after CABG.	IIa	A	[183,185,186]
Amiodarone should be considered to decrease the incidence of AF after CABG.	IIa	A	[183,184,186]
Statins should be considered to decrease the incidence of AF after CABG.	IIa	B	[187,188]
Corticosteroids may be considered to decrease the incidence of AF after CABG.	IIb	B	[181,182]
Restoring sinus rhythm in patients having CABG may be considered in order to increase survival.	IIb	B	[178,179]
Performing AF ablation during CABG may be considered an effective strategy.	IIb	C	–

^a Class of recommendation.

^b Level of evidence.

^c References.

AF = atrial fibrillation; CABG = coronary artery bypass grafting.

Two RCTs evaluating the effect of statin pre-treatment suggested effectiveness in preventing post-operative AF, possibly through anti-inflammatory effects (OR 0.57, 95% CI 0.42–0.77) [187,188].

Table 31 summarizes the recommendations concerning the prevention and treatment of atrial fibrillation in CABG patients.

Percutaneous coronary intervention and atrial fibrillation

In patients with paroxysmal AF it is worthwhile to rule out ischaemia as a potential cause. A high prevalence of obstructive CAD was observed among patients with AF undergoing systematic multislice CT, confirming the hypothesis that AF could be a marker of advanced coronary atherosclerosis. Issues related to antiplatelet therapy in patients under anticoagulants are discussed in Section 12.4.

9.7.2. Supraventricular arrhythmias other than atrial fibrillation or flutter

The relationship between supraventricular arrhythmia other than AF and/or atrial flutter and CAD is unclear. During supraventricular tachycardia episodes, ECG changes and clinical symptoms suggestive of cardiac ischaemia may be present. Screening for CAD should be restricted to patients with typical symptoms outside arrhythmia episodes, who have a high-risk profile or increasing frequency of arrhythmia episodes [191].

Because of the effectiveness of percutaneous catheter ablation techniques for the treatment of accessory pathways, such as in Wolff–Parkinson–White syndrome, surgery should be restricted to patients after failed catheter ablation, with complex congenital heart disease or scheduled for valve surgery. Anti-arrhythmic surgical procedures should be performed in experienced centres.

9.7.3. Ventricular arrhythmias

In the setting of transient cardiac ischaemia, within 24–48 h of ACS, during primary PCI for STEMI or late after MI, ventricular arrhythmias are a major cause of death. Large RCTs have shown a beneficial effect of ICD therapy in survivors of life-threatening arrhythmias and in patients at risk of sudden death (primary prevention).

Primary prevention

Patients with LVEF \leq 35% are at risk of sudden cardiac death and may benefit from ICD therapy. However, screening for and treating cardiac ischaemia is required prior to ICD implantation because LV function may recover after revascularization of viable myocardium [16]. ICD therapy should be postponed for at least 3 months after PCI or CABG to allow time for LV recovery. In patients with large scar areas, recovery of LVEF is less likely and ICD implantation may be considered appropriate shortly after revascularization.

Secondary prevention

Patients surviving out-of-hospital cardiac arrest are at high risk of recurrence. Prevention of potentially lethal recurrence starts with a systematic evaluation of the underlying pathology and the subsequent risk for recurrence,

to allow the implementation of an individualized treatment plan.

Ventricular arrhythmias are associated with acute or chronic CAD. Revascularization of hibernating myocardium may improve electrical stability and reduces the likelihood of ventricular arrhythmias. However, several studies demonstrated that a significant number of patients remained arrhythmia inducible after revascularization resulting in a 13% SCD rate. Patients are candidates for ICD therapy if revascularization cannot be achieved or in the case of prior MI with significant LV dysfunction.

In patients with monomorphic sustained ventricular tachycardia (VT), revascularization may help to lower the number of recurrences but is not considered to be sufficient and ICD implantation is the first line of SCD prevention. However, percutaneous endo- or epicardial catheter ablation procedures are becoming increasingly successful and may be considered in patients with haemodynamically stable VT.

9.7.4. Concomitant revascularization in heart failure patients who are candidates for resynchronization therapy

In patients scheduled for cardiac resynchronization therapy (CRT) or CRT combined with ICD therapy, having concomitant cardiac surgery (a revascularization procedure or LV reconstruction/valve repair), epicardial LV lead implantation may be considered. Potential advantages include avoidance of subsequent transvenous LV lead placement and convenient selection of the preferred lead location. When operating on already implanted patients, the ICD should be switched off. In patients having PCI, the ICD should be implanted first to avoid DAPT discontinuation.

10. Procedural aspects of coronary artery bypass grafting

10.1. Pre-operative management

Patients admitted for surgical revascularization are usually taking many medicines including β -blockers, ACE inhibitors, statins, and antiplatelet drugs. β -blockers should not be stopped to avoid acute ischaemia upon discontinuation.

10.2. Surgical procedures

Surgical procedures are complex interactions between human and material resources. The best performance is obtained through experience and routine, process control, case-mix, and volume load. The surgical procedure is performed within a hospital structure and by a team specialized in cardiac surgery. The surgical, anaesthesiological, and intensive care procedures are written down in protocols [192].

The initial development of CABG was made possible with the use of extracorporeal circulation and induced ventricular fibrillation. When aortic cross-clamping is used to perform the distal anastomoses, the myocardium can be protected against ensuing ischaemia by several methods.

CABG is performed using extracorporeal circulation (CPB) in 70% of all operations worldwide. This includes a median sternotomy, ITA(s) dissection, and, when appropriate,

simultaneous harvesting of the venous and or radial artery grafts. Endoscopic vein-graft harvesting cannot be recommended at present as it has been associated with vein-graft failure and adverse clinical outcomes. CPB requires profound anticoagulation using heparin for an activated clotting time >400 s.

Partial or total aortic cross-clamping allows the construction of proximal anastomoses. A single cross-clamp may be preferred with the aim of reducing atheroembolic events. Epiaortic ultrasonography, visualizing atherosclerotic plaques, can modify the surgical approach but was not shown to reduce the incidence of cerebral emboli [193].

10.2.1. Coronary vessel

CABG aims to revascularize coronary arteries, with a flow-reducing luminal stenosis, supplying a viable and sizeable area at risk. The most frequently grafted coronary arteries are the epicardial vessels, but intramural grafting is part of routine coronary surgery.

The patency of a constructed graft is influenced by characteristics of the anastomosed vessel, the outflow area, the graft material, its manipulation and construction. Important coronary characteristics are the internal lumen size, the severity of proximal stenosis, the quality of the wall at the site of anastomosis, and the distal vascular bed. Diffuse CAD is often seen in the presence of insulin-treated diabetes, long-standing and untreated hypertension, PAD, and CKD.

Different technical approaches have been applied to vessels with diffuse pathology such as very long anastomoses, patch reconstruction of the vessel roof with or without grafting to this roof, coronary endarterectomy, and multiple anastomoses on the same vessel, with no evidence of superiority of any one.

10.2.2. Bypass graft

The long-term benefit of CABG is maximized with the use of arterial grafts, specifically the ITA [194]. Available grafts include internal thoracic, radial, and gastro-epiploic arteries. All except the radial artery can remain connected to their anatomical inflow or be used as free graft, with the aorta or another graft as inflow.

The side-to-side anastomosis used in arterial and venous grafting eliminates an aortic anastomosis, decreases the amount of graft required, and increases total graft flow. The latter factor contributes to a higher patency rate. Partially or total ITA skeletonization increases its length and possibility of use. Rates of sternal wound infection and angiographic results are similar whether ITA is skeletonized or not. These techniques may allow a complete arterial revascularization.

Use of bilateral ITA is associated with higher post-operative sternal dehiscence and increased rate of mediastinitis in obese and possibly diabetic patients [195]. But event-free long-term survival, reduced risk of recurrent angina or MI, and reduced need for re-operation correlate well with the extensive use of arterial grafts [49,196,197].

Using radial artery grafts increases the number of arterial anastomoses beyond the use of both ITAs. At 5 years, patency rates of radial artery are possibly superior to saphenous

Table 32
Technical recommendations for coronary artery bypass grafting

	Class ^a	Level ^b	Ref. ^c
Procedures should be performed in a hospital structure and by a team specialized in cardiac surgery, using written protocols.	I	B	[192,196]
Arterial grafting to the LAD system is indicated.	I	A	[194]
Complete revascularization with arterial grafting to non-LAD coronary systems is indicated in patients with reasonable life expectancy.	I	A	[49,194,196,197,199]
Minimization of aortic manipulation is recommended.	I	C	–
Graft evaluation is recommended before leaving the operating theatre.	I	C	–

^a Class of recommendation.

^b Level of evidence.

^c References.

LAD = left anterior descending.

grafts but certainly inferior to ITA. This patency is strongly related to target vessel size and stenosis severity.

Graft flow measurement, related to graft type, vessel size, degree of stenosis, quality of anastomosis, and outflow area, is useful at the end of surgery. Flow <20 mL/min and pulsatility index >5 predict technically inadequate grafts, mandating graft revision before leaving the operating theatre [198].

Table 32 lists the evidence-based technical recommendations for CABG.

10.3. Early post-operative risk

Early clinical outcome at 3 months after CABG is characterized by a 1–2% mortality rate and a 1–2% morbidity rate for each of the following events: stroke, renal, pulmonary and cardiac failure, bleeding, and wound infection. The early risk interval in CABG extends for 3 months, is multifactorial, and depends on the interface between technical variability and patient comorbidity [197].

The survival outcome for all CABG operations performed in the UK in the 2004–08 period showed a 1.1% hospital mortality in 78 367 elective patients vs. 2.6% in 32 990 urgent patients [200]. In all patients without and 30 218 patients with LM stenosis, the respective mortalities were 1.5% and 2.5% (respective predicted elective mortalities 0.9% and 1.5%). In all patients without or 26 020 patients with diabetes, the respective mortalities were 1.6% and 2.6% (with respective predicted elective mortalities 1.0% and 1.6%).

Despite improved techniques and experience, part of the morbidity is caused by the extracorporeal circulation, prompting the off-pump approach. Complete off-pump procedures in the hands of trained surgical teams seem to be associated with a reduced risk of stroke, AF, respiratory and wound infections, less transfusion, and shorter hospital length of stay [201]. Highly experienced teams obtain similar 1-year outcomes, graft patency, and quality of life with off-pump vs. on-pump approaches. Thus, currently available data remain conflicting perhaps due to differences in patient selection and/or procedural techniques [202].

11. Procedural aspects of percutaneous coronary intervention

11.1. Impact of clinical presentation

Percutaneous coronary intervention for stable coronary artery disease

Proper patient information and preparation are mandatory for all PCI procedures, including elective and *ad hoc* interventions in patients with stable CAD (Section 4). Depending on the severity of the stenosis and in the absence of extensive calcification, many stable, non-occlusive lesions can be directly stented, without pre-dilatation. Severely fibrotic or calcified lesions, especially if they cannot be crossed by a balloon after successful wiring or be adequately dilated with non-compliant balloons despite high inflation pressure, may require pre-treatment with rotablation [55]. Acute ischaemia due to coronary dissection can be corrected with stents and emergency CABG is necessary in <0.1%.

Percutaneous coronary intervention for acute coronary artery disease

Various approaches have been evaluated to prevent distal embolization during PCI for unstable CAD. Although the concept of preventing embolization of thrombus or debris seems very rational, initial trials testing a variety of different concepts could not establish its clinical usefulness. A meta-analysis including 1467 STEMI patients enrolled in eight RCTs showed no difference in terms of blood flow normalization rate in the culprit epicardial vessel between patients allocated to distal protection devices or controls [203]. Therefore, the systematic use of distal protection devices cannot be recommended for PCI in lesions with a high thrombotic burden.

One limitation of distal placement of occlusive balloons or filters beyond thrombus-containing lesions is the obvious need to penetrate the thrombus at the risk of detaching small particles. Alternative devices that allow immediate suction are potentially more useful. There is evidence of benefit for direct catheter aspiration of thrombus in STEMI [204–206]. The TAPAS trial assigned 1071 patients to catheter-based thrombus aspiration (Export aspiration catheter) followed by primary PCI or conventional primary PCI [207]. Patients randomized to thrombus aspiration had a significantly higher rate of complete ST-segment resolution and improved myocardial blush grade. Although not powered to evaluate clinical outcome, cardiac mortality at 1 year was reduced (3.6% vs. 6.7%) [208]. Aspiration was performed in 84% of the patients, PCI was not performed in 6%, and no significant improvement in peak creatine kinase enzymes was noted. The results of the single-centre TAPAS RCT are confirmed by several smaller studies and meta-analyses. Therefore, the recommendation for systematic manual thrombus aspiration during primary PCI has been upgraded [94,204–208].

Treatment of 'no reflow'

No-reflow or slow-flow may occur as a consequence of downstream microvascular embolization of thrombotic or atheromatous (lipid-rich) debris and cause reperfusion injury. Reversing no-reflow is associated with a favourable

effect on LV remodelling even in the absence of significant improvement in regional contractile function. Intracoronary administration of vasodilators such as adenosine, verapamil, nicorandil, papaverine, and nitroprusside during and after primary PCI improves flow in the infarct-related coronary artery and myocardial perfusion and/or reduces infarct size, but large RCTs are lacking [55]. High-dose i.v. adenosine infusion was also associated with a reduction in infarct size, but clinical outcomes were not significantly improved [209].

11.2. Specific lesion subsets

Bifurcation stenosis

Coronary stenoses are frequently located at bifurcations and bifurcation lesions still represent a major challenge for PCI, in terms of both procedural technique and clinical outcome. Bifurcation lesions are best described according to the Medina classification. Despite many attempts with a variety of different stenting techniques (T-stenting, V-stenting, crush, and its modifications, culotte, etc.), the optimal strategy for every anatomical subset has not yet been established. Variables to be considered are plaque distribution, size and downstream territory of each vessel (main and side branch), and the bifurcation angle. Stent implantation in the main vessel only, followed by provisional angioplasty with or without stenting of the side branch, seems preferable compared with routine stenting of both vessels. FFR data from side branches suggest that angiography overestimates the functional severity of side branch stenosis. Final kissing balloon dilatation is recommended when two stents are eventually required. Several stents designed specifically for treatment of bifurcation lesions have undergone extensive evaluation with good angiographic and clinical results, especially with side branch size >2.5 mm. Comparative RCTs vs. provisional stenting are lacking.

The above comments apply to PCI of (unprotected) LM lesions, when indicated (Section 6). For bifurcation and LM lesions, DES are preferred with special attention to adequate sizing and deployment. For treatment of small vessels (<2.5 mm), DES with strong antiproliferative properties (late lumen loss ≤0.2 mm) are preferred to reduce restenosis rates [210].

Chronic total coronary occlusion

CTO is defined as TIMI 0 flow for >3 months. Following the negative results of two RCTs addressing the usefulness of opening occluded culprit coronary arteries in the early post-MI phase [90,91,211], there is some confusion regarding the indications for PCI in 'chronic' total occlusions. In asymptomatic patients within 3–28 days after MI, the OAT trial showed no survival advantage from PCI and less recurrent MI with the conservative approach [90,211]. The results of OAT do not necessarily pertain to CTOs. Observational studies suggest that a successfully revascularized CTO confers a significant 5- and 10-year survival advantage compared with failed revascularization. A New York State survey showed that incomplete revascularization by PCI leaving untreated CTOs led to higher 3-year mortality [199]. Thus, similar to non-chronically occluded vessels, revascularization of CTO may be considered in the presence of angina or ischaemia

Table 33
Recommendations for specific percutaneous coronary intervention devices and pharmacotherapy

	Class ^a	Level ^b	Ref. ^c
FFR-guided PCI is recommended for detection of ischaemia-related lesion(s) when objective evidence of vessel-related ischaemia is not available.	I	A	[15,28]
DES ^d are recommended for reduction of restenosis/re-occlusion, if no contraindication to extended DAPT.	I	A	[45,46,55,215]
Distal embolic protection is recommended during PCI of SVG disease to avoid distal embolization of debris and prevent MI.	I	B	[171,213]
Rotablation is recommended for preparation of heavily calcified or severely fibrotic lesions that cannot be crossed by a balloon or adequately dilated before planned stenting.	I	C	–
Manual catheter thrombus aspiration should be considered during PCI of the culprit lesion in STEMI.	IIa	A	[204–208]
For PCI of unstable lesions, i.v. abciximab should be considered for pharmacological treatment of no-reflow.	IIa	B	[55,209,212]
Drug-eluting balloons ^d should be considered for the treatment of in-stent restenosis after prior BMS.	IIa	B	[174,175]
Proximal embolic protection may be considered for preparation before PCI of SVG disease.	IIb	B	[214]
For PCI of unstable lesions, intracoronary or i.v. adenosine may be considered for pharmacological treatment of no-reflow.	IIb	B	[209]
Tornus catheter may be used for preparation of heavily calcified or severely fibrotic lesions that cannot be crossed by a balloon or adequately dilated before planned stenting.	IIb	C	–
Cutting or scoring balloons may be considered for dilatation of in-stent restenosis, to avoid slipping-induced vessel trauma of adjacent segments.	IIb	C	–
IVUS-guided stent implantation may be considered for unprotected left main PCI.	IIb	C	–
Mesh-based protection may be considered for PCI of highly thrombotic or SVG lesions.	IIb	C	–
For PCI of unstable lesions, intracoronary nitroprusside or other vasodilators may be considered for pharmacological treatment of no-reflow.	IIb	C	–

^a Class of recommendation.

^b Level of evidence.

^c References.

^d Recommendation is only valid for specific devices with proven efficacy/safety profile, according to the respective lesion characteristics of the studies.

DAPT = dual antiplatelet therapy; DES = drug-eluting stent; FFR = fractional flow reserve; IVUS = intravascular ultrasound; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; SVG = saphenous vein graft.

related to the corresponding territory. The potential long-term risk of radiation exposure should be considered. *Ad hoc* PCI is not recommended for CTOs. Success rates are strongly dependent on operator skills, experience with specific procedural techniques, and availability of dedicated equipment (specialized guidewires and catheters, such as the Tornus catheter or very low profile CTO balloons). Bilateral angiography and intravascular ultrasound (IVUS) imaging can be very helpful as well as special techniques such as guide anchoring, various retrograde approaches, and specific wiring manipulation techniques. Experience with proper management of coronary perforation and cardiac tamponade is required.

Saphenous vein graft disease

Patients undergoing PCI of SVG are particularly at risk of distal coronary embolization with increased risk of peri-procedural MI [170]. PCI of *de novo* SVG stenosis is considered a high-risk intervention because SVG atheroma is friable and more prone to distal embolization. A pooled analysis of five RCTs shows that GPIIb–IIIa inhibitors are less effective for SVG PCI than for PCI of native vessels [212]. Many different approaches have been evaluated to prevent distal embolization of particulate debris, including distal blocking/aspirating, proximal blocking, suction, filtering, or mesh-based devices [171]. Unlike occlusive devices, distal protection using filters offers the inherent advantage of maintaining antegrade perfusion and the opportunity for contrast injections. Combined data, mostly from comparative studies between devices and surrogate endpoints, support the use of distal embolic protection during SVG PCI [213,214]. Distal filters function better in SVG than in native coronary vessels where embolization may occur in

side branches that originate proximal to the protection filter. For SVG, the main limitation of filter devices is the absence of a proper landing zone, when a stenosis is located close to the distal graft anastomosis. Experience with mesh-covered stents is limited.

In-stent restenosis

Although plain balloon angioplasty is safe for the treatment of in-stent restenosis, it is associated with high recurrence rates [55]. During balloon dilatation of in-stent restenosis, balloons tend to prolapse into proximal and distal parts, potentially causing injury to adjacent coronary segments. Special balloons with blades or scoring wires reduce this risk by stabilizing the balloon during inflation. Laser, rotablation, atherectomy, and cutting balloons have proved to be ineffective for the treatment of in-stent restenosis. Intracoronary brachytherapy, with either β or γ radiation, was superior to balloon dilatation for the treatment of in-stent restenosis following BMS implantation, albeit with increased risk for late stent thrombosis [55]. Currently, intracoronary brachytherapy is of very limited use: restenosis rates have declined and in-stent restenoses after BMS are treated by DES or CABG [55]. Recent developments include the use of drug-eluting balloons (see below).

Table 33 lists the recommendations for specific PCI devices and pharmacotherapy.

11.3. Drug-eluting stents

Efficacy and safety of drug-eluting stents

Stainless steel stents were initially designed to treat major dissections, avoid acute vessel closure and prevent

Table 34

Recommended drug-eluting stents (in alphabetic order) that have achieved a primary clinical or surrogate angiographic endpoint

DES	Eluted drug	Trials and references
Clinical primary endpoint reached		
BioMatrix Flex	Biolimus A9	LEADERS [216]
Cypher	Sirolimus	SIRIUS [217]
Endeavor	Zotarolimus	ENDEAVOR-II, -III and -IV [218, 219]
Resolute	Zotarolimus	RESOLUTE-AC [220]
Taxus Liberté/ Element	Paclitaxel	TAXUS-IV and -V [221,222]/ PERSEUS-WH [223]
Xience V	Everolimus ^a	SPIRIT-III and -IV [224,225]
Angiographic primary endpoint reached		
Nevo	Sirolimus	NEVO RES I [226]
Nobori	Biolimus A9	NOBORI-I Phase-1 and -2 [227,228]
Yukon	Sirolimus	ISAR-Test [229]

Selection is based on adequately powered RCT with a primary clinical or angiographic endpoint. With the exception of LEADERS and RESOLUTE (all-comers trials), efficacy was investigated in selected *de novo* lesions of native coronary arteries.

^aPromus Element device elutes everolimus from a different stent platform.

DES = drug-eluting stent.

restenosis. Coronary stents are very effective in repairing dissections and covered stents can be life saving in cases of coronary perforation. However, due to a 20–30% rate of recurrence of angiographic stenosis within 6–9 months after implantation, restenosis within BMS has often been called the Achilles' heel of PCI. In native vessels, DES significantly reduce angiographic restenosis and ischaemia-driven TVR [45,215]. In RCTs, no significant differences were observed in the long-term rates of death or MI after DES or BMS use for either off-label or on-label indications [45,46]. In non-randomized large registry studies, DES use may reduce death and MI [46]. First-generation DES are safe and efficacious for both on-label and off-label use, when implanted in the native circulation, in spite of a slightly increased propensity for late and very late stent thrombosis [215]. Long-term results (≥ 5 years) are only available for SES, PES, and zotarolimus-eluting stent (ZES). There is, however, no class effect for DES: some DES were shown to be harmful and others are ineffective. Until today, >100 DES RCTs in >60 000 patients have been presented and at least 22 DES have been granted a CE mark. It should be recognized that the quality of the relevant RCTs is highly variable, especially regarding statistical powering and the selection of angiographic rather than primary clinical endpoints [55,215]. Accordingly, a small proportion only of the available DES can be recommended on the basis of pivotal trials (Table 34).

Are the differences between drug-eluting stents clinically relevant?

SES and PES have been extensively compared in numerous subsets, including diabetes [45,115,230]. While angiographic metrics are superior with SES, no robust clinically relevant differences up to 5-year follow-up were convincingly identified, except for further reduction in reintervention rates with SES vs. PES. The extent to which reduced TVR rates are driven in part by trial-mandated angiography in some studies remains debatable [231]. On the other hand, recent RCTs suggest that second-generation DES may

provide superior clinical outcomes to first-generation DES. In 3690 patients enrolled in the SPIRIT-IV trial, the primary endpoint of target lesion failure at 1 year was significantly lower in the Xience V group as compared with the Taxus-Express stent (4.2% vs. 6.8%) [225]. In 1800 patients enrolled in the all-comer single-centre COMPARE trial, the primary endpoint of ischaemia-driven TVR at 1 year was significantly lower for Xience V as compared with Taxus-Liberté DES (6% vs. 9%) [232]. Differences were driven in part by in-hospital MI and early stent thrombosis but neither trial was powered for these endpoints [233].

Indications for drug-eluting stent

DES with proven efficacy should be considered by default in nearly all clinical conditions and lesion subsets, except if there are concerns or contraindications for prolonged DAPT (Table 35). Indications for DES in a few specific patient or lesion subsets remain a matter of debate. In selected STEMI patients [234,235], SES and PES were shown to be safe and effective (TYPHOON, HORIZONS-AMI, PASEO, and ZEST-AMI) with follow-up extending from 2 to 4 years. There is no solid evidence that one DES provides superior clinical outcome in patients with diabetes, due to the limited number of small-sized trials or the limitations of subgroup analyses [115]. Studies based on angiographic endpoints favour the use of DES with strong antiproliferative properties (late lumen loss ≤ 0.2 mm) [231].

The use of DES vs. BMS for treatment of *de novo* lesions in SVGs remains controversial [236].

Table 35 summarizes the relative clinical contraindications to the use of DES.

The optimal duration of DAPT after DES implantation is not known. Convincing data exist only for continuation up to 6 months [237]. Possibly, under some circumstances or with some DES, DAPT for 3 months could be sufficient but the evidence is not robust [219]. Recent evidence shows that (very) late stent thrombosis results from delayed hypersensitivity to components of the drug-polymer-device combination that causes necrotizing vasculitis and late malapposition [238]. Diabetics may require a longer duration of DAPT.

For situations listed in Table 35, a number of alternative approaches have been tested. The Genous bio-engineered BMS carries a layer of murine, monoclonal, antihuman CD34 antibody, aimed at capturing circulating endothelial CD34+ progenitor cells, possibly increasing the rate of healing. The single-centre pilot TRIAS RCT did not confirm initial promising results in patients at high risk of coronary restenosis [239].

Table 35

Relative clinical contraindications to the use of drug-eluting stents

<ul style="list-style-type: none"> Clinical history difficult to obtain, especially in the setting of acute severe clinical conditions (STEMI or cardiogenic shock).
<ul style="list-style-type: none"> Expected poor compliance with DAPT, including patients with multiple comorbidities and polypharmacy.
<ul style="list-style-type: none"> Non-elective surgery required in the short term that would require interruption of DAPT.
<ul style="list-style-type: none"> Increased risk of bleeding.
<ul style="list-style-type: none"> Known allergy to ASA or clopidogrel/prasugrel/ticagrelor.
<ul style="list-style-type: none"> Absolute indication for long-term anticoagulation.

ASA = acetylsalicylic acid; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; STEMI = ST-segment elevation myocardial infarction.

Drug-eluting balloons

The rationale of using drug-eluting balloons is based on the concept that with highly lipophilic drugs, even short contact times between the balloon and the vessel wall are sufficient for effective drug delivery. Using a paclitaxel-eluting balloon, three RCTs have targeted in-stent restenosis following BMS implantation: PACCOATH-I and -II [174,175] and PEPCAD-II [240]. As with DES, one cannot assume a class effect for all drug-eluting balloons. In the randomized PEPCAD III study, the combination of a drug-eluting balloon with cobalt chromium stent implantation was inferior to SES for *de novo* indications.

Future perspectives

Although some brands already provide a biodegradable polymer, current DES remain permanent implants that cannot be extracted like pacemakers or artificial heart valves. Furthermore, stents force the cardiac surgeons to anastomose bypass grafts more distally. Stents create disruptive artefacts on cardiac CT and magnetic resonance images. Therefore, fully biodegradable stents are in development [241].

11.4. Adjunctive invasive diagnostic tools

Intravascular ultrasound imaging and optical coherence tomography

Whereas angiography depicts only a two-dimensional lumen silhouette, IVUS allows tomographic assessment of lumen area, plaque size, and distribution. IVUS is a valuable adjunct to angiography, providing further insights into both diagnosis and therapy, including stent implantation. Interventional cardiologists have learnt much from IVUS, but it has been difficult to demonstrate that this knowledge acquired routinely translates into reduced MACE. Multiple studies have addressed the potential of IVUS to reduce restenosis and adverse events after BMS implantation, but conflicting results were obtained with the largest of these trials showing no difference between groups with or without IVUS guidance. For DES, it was recently shown that the threshold of stent expansion predictive of late events including restenosis and stent thrombosis is lower than for BMS (5.0–5.5 mm²). In a retrospective analysis of a multicentre registry comparing PCI with surgery for unprotected LM, IVUS-guided stent implantation was associated with a significant mortality reduction at 3 years [242]. No properly designed RCT has compared the clinical value of IVUS-guided stent implantation in the DES era.

The analysis of plaque composition based on radio-frequency backscatter, so-called 'virtual histology', characterizes plaques as fibrotic, fibrofatty with or without a necrotic core, or calcific. Although the PROSPECT trial [243] provided new insights regarding indications for stent implantation, the role of tissue characterization for everyday practice remains to be established.

Optical coherence tomography (OCT) is a light-based modality of intravascular imaging with higher spatial resolution than IVUS (15 vs. 100 μm). Its penetration is lower than IVUS but it provides detailed imaging of the endoluminal borders. At present, OCT is a valuable research tool.

Pressure-derived fractional flow reserve

Although non-invasive stress imaging should be the gold standard for evaluation of patients with known or suspected CAD, many patients come to the catheterization laboratory without prior functional testing. When a non-invasive imaging stress test is unavailable, FFR can be useful, especially in the presence of MVD. The concept that avoiding unnecessary stenting actually improves outcome was demonstrated in the DEFER [15] and FAME [28] trials. FFR is a valuable tool to determine whether or not an intermediate stenotic segment can cause downstream ischaemia in stable and unstable patients with MVD, in-stent restenosis, LM stenosis, and post-MI.

12. Antithrombotic pharmacotherapy

Treatment of CAD patients often requires the combination of anti-platelet and antithrombotic therapies to prevent thrombosis from activation of both platelets and the coagulation system. The choice, initiation, and duration of antithrombotic strategies for myocardial revascularization depend on the clinical setting (elective, acute, or urgent intervention). To maximize the effectiveness of therapy and reduce the hazard of bleeding, ischaemic and bleeding risks should be evaluated on an individual basis. A well-validated score for estimating bleeding risk is eagerly awaited.

12.1. Elective percutaneous coronary intervention

(a) Antiplatelet therapy

DAPT includes acetylsalicylic acid (ASA) 150–300 mg per os or 250 (–500) mg bolus i.v. followed by 75–100 mg per os daily for all patients plus clopidogrel 300 (600)-mg loading dose followed by 75 mg daily for all patients [55].

Since the vast majority of PCI procedures eventually conclude with stent implantation, every patient scheduled for PCI should be considered for pre-treatment with clopidogrel, regardless of whether stent implantation is intended or not. To ensure full antiplatelet activity, clopidogrel should be initiated at least 6 h prior to the procedure with a loading dose of 300 mg, ideally administered the day before a planned PCI. If this is not possible, a loading dose of 600 mg should be administered at least 2 h before PCI. Of note, this pre-loading strategy was not shown to improve outcome. A 600-mg clopidogrel loading dose may be preferable because of greater platelet inhibition than with the 300-mg standard dose, even if this is given >6 h before PCI. When diagnostic angiography is negative or no intervention is performed, clopidogrel can be stopped. When a 300-mg loading dose has been given and *ad hoc* PCI is performed, another 300-mg dose can be given. The use of a higher maintenance dose (150 mg) has been proposed in patients with high thrombotic risk (e.g. in diabetics, patients after recurrent MI, after early and late stent thrombosis, for complex lesions, or in life-threatening situations should occlusion occur). GPIIb–IIIa inhibitors should be used only in 'bail-out' situations (thrombus, slow flow, vessel closure, very complex lesions) [55]. Recent trials did not demonstrate additional benefit of GPIIb–IIIa inhibitors after a clopidogrel loading dose of 600 mg.

Table 36
Antithrombotic treatment options in myocardial revascularization

	Class ^a	Level ^b	Ref. ^c
Elective PCI			
Antiplatelet therapy			
ASA	I	B	[55]
Clopidogrel	I	A	[55]
Clopidogrel – pretreatment with 300 mg loading dose >6 h before PCI (or 600 mg >2 h before)	I	C	–
+ GPIIb–IIIa antagonists (bailout situation only)	IIa	C	–
Anticoagulation			
UFH	I	C	–
Enoxaparin	IIa	B	[244]
NSTE-ACS			
Antiplatelet therapy			
ASA	I	C	–
Clopidogrel (with 600 mg loading dose as soon as possible)	I	C	–
Clopidogrel (for 9–12 months after PCI)	I	B	[55]
Prasugrel ^d	IIa	B	[246,247]
Ticagrelor ^d	I	B	[248]
+ GPIIb–IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)			
Abciximab (with DAPT)	I	B	[249]
Tirofiban, Eptifibatide	IIa	B	[55]
Upstream GPIIb–IIIa antagonists	III	B	[65]
Anticoagulation			
Very high-risk of ischaemia ^e			
UFH (+GPIIb–IIIa antagonists) or	I	C	–
Bivalirudin (monotherapy)	I	B	[251]
Medium-to-high-risk of ischaemia ^e			
UFH	I	C	–
Bivalirudin	I	B	[251]
Fondaparinux	I	B	[250]
Enoxaparin	IIa	B	[55,60]
Low-risk of ischaemia ^e			
Fondaparinux	I	B	[250]
Enoxaparin	IIa	B	[55,60]
STEMI			
Antiplatelet therapy			
ASA	I	B	[55,94]
Clopidogrel ^f (with 600 mg loading dose as soon as possible)	I	C	–
Prasugrel ^d	I	B	[246,252]
Ticagrelor ^d	I	B	[248,253]
+ GPIIb–IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)			
Abciximab	IIa	A	[55,94]
Eptifibatide	IIa	B	[259,260]
Tirofiban	IIb	B	[55,94]
Upstream GPIIb–IIIa antagonists	III	B	[86]
Anticoagulation			
Bivalirudin (monotherapy)	I	B	[255]
UFH	I	C	–
Fondaparinux	III	B	[256]

^a Class of recommendation.

^b Level of evidence.

^c References.

^d Depending on approval and availability. Direct comparison between prasugrel and ticagrelor is not available. Long term follow-up is awaited for both drugs.

^e See Table 12 for definition of ischaemia risk.

^f Primarily if more efficient antiplatelet agents are contraindicated.

ASA = acetylsalicylic acid; DAPT = dual antiplatelet therapy; GPIIb–IIIa = glycoprotein IIb–IIIa; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UFH = unfractionated heparin.

(b) Anticoagulation

Unfractionated heparin (UFH) is currently the standard anti-thrombotic medication: 70–100 IU/kg i.v. bolus without GPIIb–IIIa inhibitors, and 50–70 IU/kg with GPIIb–IIIa inhibitors [55]. The STEEPLE trial has suggested a benefit of enoxaparin (0.5 or 0.75 mg/kg i.v. bolus) compared with UFH with reduced bleeding hazard but comparable efficacy [244]. This was at the cost of increased mortality in a lower-dose group, which was terminated early. An association between mortality and 0.5 mg/kg enoxaparin could not be demonstrated.

12.2. Non-ST-segment elevation acute coronary syndrome

High ischaemic risk is associated with ST-segment changes, elevated troponin, diabetes, and a GRACE score >140. A high bleeding risk is associated with female sex, age >75 years, bleeding history, GFR <30 mL/min, and use of femoral access (Section 7).

(a) Antiplatelet therapy

DAPT includes ASA 150–300 mg per os or 250 (–500) mg i.v. bolus, followed by 75–100 mg daily, and clopidogrel 600 mg loading dose, followed by 75 mg daily, or prasugrel 60 mg loading dose, followed by 10 mg daily, or ticagrelor 180 mg loading dose, followed by 90 mg twice daily, depending on drug availability. A higher clopidogrel maintenance dose for 1 or 2 weeks immediately following stent implantation has shown some benefit in terms of reduced MACE rates without significantly increased bleeding [245].

Prasugrel has been tested against the 300 mg loading dose of clopidogrel, both started in the catheterization laboratory after diagnostic angiography, in the TRITON TIMI 38 trial and proved beneficial with respect to a combined thromboembolic–ischaemic outcome [246]. Recurrent cardiovascular events were significantly reduced in prasugrel-treated patients. Severe bleeding complications increase with prasugrel use, specifically in patients with a history of stroke and TIA, in the elderly (≥ 75 years), and in underweight patients (<60 kg). Bleeding was also increased in prasugrel-treated patients referred for early CABG. Excluding patients with a higher bleeding risk, prasugrel offers significant benefit over clopidogrel with respect to cardiovascular events without increasing severe bleeding. In diabetic patients presenting with ACS, prasugrel confers a significant advantage over clopidogrel without increased bleeding [247]. Prasugrel should be used in patients who present with stent thrombosis whilst taking clopidogrel.

Ticagrelor, a non-thienopyridine ADP receptor blocker causing reversible inhibition of platelet function, has been compared with clopidogrel. The PLATO study confirmed a significant improvement of combined clinical endpoints including mortality in favour of ticagrelor [248]. The rate of severe non-CABG-related bleeding was similar to that of prasugrel in the TRITON-TIMI 38 trial, while CABG-related bleeding was lower than for clopidogrel, most probably a consequence of the faster inactivation of the agent after stopping intake.

GPIIb–IIIa inhibitors should be used in patients with high ischaemic risk undergoing PCI. The greatest benefit

of GPIIb–IIIa inhibitors vs. placebo was demonstrated in earlier RCTs when ADP receptor blockers were not routinely used [60]. The usefulness of upstream eptifibatide, with or without clopidogrel on board, was not confirmed in EARLY-ACS. The lack of benefit was associated with a higher bleeding risk [65]. The selective ‘downstream administration’ of abciximab in the catheterization laboratory, in combination with a 600 mg clopidogrel loading dose, has been shown to be effective in troponin-positive NSTEMI-ACS patients [249] and might therefore be preferred over upstream use.

(b) Anticoagulation

The golden rule is to avoid crossover especially between UFH and low molecular weight heparin (LMWH) [60] and to discontinue antithrombins after PCI except in specific individual situations (e.g. thrombotic complication).

Management prior to catheterization

Risk stratification in NSTEMI-ACS patients determines the use of specific agents and doses.

Patients at very high ischaemic risk (e.g. persistent angina, haemodynamic instability, refractory arrhythmias) should immediately be referred to the catheterization laboratory and receive UFH 60 IU/kg i.v. bolus, followed by infusion until PCI, combined with DAPT. In patients at high risk of bleeding, bivalirudin monotherapy with 0.75 mg/kg bolus followed by 1.75 mg/kg/h can be used.

In medium-to-high ischaemic risk patients (e.g. troponin positive, recurrent angina, dynamic ST changes) for whom an invasive strategy is planned within 24 (–48) h, options for anticoagulation are:

- In patients <75 years
 - UFH 60 IU/kg i.v. bolus, then infusion until PCI, controlled by activated partial thromboplastin time (aPTT)
 - or
 - Enoxaparin 1 mg/kg subcutaneous (s.c.) twice daily until PCI
 - or
 - Fondaparinux 2.5 mg daily s.c. until PCI
 - or
 - Bivalirudin 0.1 mg/kg i.v. bolus followed by infusion of 0.25 mg/kg/h until PCI
- In patients ≥ 75 years
 - UFH 60 IU/kg i.v. bolus, then infusion (aPTT controlled) until PCI
 - or
 - Enoxaparin 0.75 mg/kg twice daily until PCI
 - or
 - Fondaparinux 2.5 mg daily s.c.
 - or
 - Bivalirudin 0.1 mg/kg i.v. bolus followed by infusion of 0.25 mg/kg/h until PCI.

In low ischaemic risk patients (troponin negative, no ST-segment changes), a primarily conservative strategy is planned. Anticoagulation is maintained until PCI using fondaparinux 2.5 mg s.c. daily or enoxaparin 1 mg/kg s.c. twice daily (0.75 mg in patients ≥ 75 years) or UFH 60 IU/kg i.v. bolus followed by infusion (aPTT controlled).

Management during catheterization

The golden rule is to continue the initial therapy and avoid switching between antithrombins (with the exception of adding UFH to fondaparinux).

UFH. Continue infusion, activated clotting time measurement can be used: target range: 200–250 s with GPIIb–IIIa inhibitors; 250–350 s without GPIIb–IIIa inhibitors.

Enoxaparin. Less than 8 h since last s.c. application: no additional bolus; within 8–12 h of last s.c. application: add 0.30 mg/kg i.v. bolus; >12 h since last s.c. application: 0.75 mg/kg i.v. bolus.

Bivalirudin. Add an additional i.v. bolus of 0.5 mg/kg and increase the infusion rate to 1.75 mg/kg/h before PCI.

Fondaparinux. Add UFH 50–100 IU/kg when PCI is performed.

Fondaparinux, an indirect factor Xa inhibitor, has been tested against enoxaparin in the OASIS-5 trial [250]. While the combined ischaemic event rate was similar, severe bleeding complications were highly significantly reduced with fondaparinux. This favourable net clinical outcome with fondaparinux included reduced long-term mortality and stroke rates. Because of a higher rate of catheter thrombosis when fondaparinux alone was used, UFH should be added for patients referred for angiography and PCI.

Bivalirudin, a direct antithrombin, alone or in combination with GPIIb–IIIa inhibition, was compared with UFH/enoxaparin + GPIIb–IIIa inhibition. Bivalirudin monotherapy was superior to either regimen with respect to reduced bleeding, without increased ischaemic events [251].

12.3. ST-segment elevation myocardial infarction

(a) Antiplatelet therapy

DAPT consists of ASA 150–300 mg per os or 250 (–500) mg bolus i.v., followed by 75–100 mg daily, and prasugrel 60 mg loading dose, followed by 10 mg daily, or ticagrelor 180 mg loading dose, followed by 90 mg twice daily, depending on drug availability [94]. Clopidogrel 600 mg loading dose, followed by 75 mg daily, should be used primarily if the more effective ADP receptor blockers are contraindicated or unavailable.

Increasing the maintenance dose of clopidogrel for 1–2 weeks might be effective in STEMI patients, as shown in NSTEMI-ACS. Prasugrel is superior to clopidogrel (300 mg loading dose, 75 mg maintenance dose) in reducing combined ischaemic endpoints and stent thrombosis in STEMI patients without increasing the risk of severe bleeding [252].

A predefined subgroup analysis has demonstrated that STEMI or NSTEMI-ACS patients referred for PCI significantly benefit from ticagrelor, vs. clopidogrel, with similar bleeding rates [253].

Most studies of GPIIb–IIIa inhibitors in STEMI have evaluated abciximab (0.25 mg/kg i.v. bolus followed by infusion of 0.125 µg/kg/min up to a maximum of 10 µg/min for 12 h). Findings are mixed regarding the effectiveness of facilitation (early administration) with GPIIb–IIIa inhibitors before catheterization. While the only available RCT [86] showed no benefit, registries, meta-analyses, and *post hoc* analyses of APEX-AMI [254] show positive results. The controversial literature data, the negative outcome of the

only prospective RCT [86], and the beneficial effects of faster acting and more efficacious ADP receptor blockers in primary PCI do not support pre-hospital or pre-catheterization use of GPIIb–IIIa inhibitors.

(b) Anticoagulation

Options for anticoagulation include UFH 60 IU/kg i.v. bolus with GPIIb–IIIa inhibitor or UFH 100 IU/kg i.v. bolus without GPIIb–IIIa inhibitor, or bivalirudin 0.75 mg/kg bolus followed by 1.75 mg/kg/h. Antithrombins can be stopped after PCI for STEMI with few exceptions (LV aneurysm and/or thrombus, AF, prolonged bed rest, deferred sheath removal).

A recent study suggested bivalirudin monotherapy as an alternative to UFH plus a GPIIb–IIIa inhibitor [255]. Significantly lower severe bleeding rates led to a beneficial net clinical outcome indicating that bivalirudin may be preferred in STEMI patients at high risk of bleeding. One-year outcome of the HORIZONS RCT confirmed the beneficial action of bivalirudin monotherapy vs. UFH and a GPIIb–IIIa inhibitor. Uncertainty remains in the early phase of primary PCI, when thrombotic complications seem to be higher with bivalirudin monotherapy. However, this had no effect on long-term clinical outcome, probably because acute in-hospital stent thrombosis can be promptly addressed, unlike late out-of-hospital stent thrombosis.

Fondaparinux was inferior to UFH in the setting of primary PCI in patients with STEMI (OASIS-6 trial) [256].

12.4. Points of interest and special conditions

(a) Bleeding complications

Bleeding contributes to worse outcome and can be prevented by implementing the following measures:

- formally assess and document bleeding risk in every patient;
- avoid crossover between UFH and LMWH;
- adjust antithrombotic therapy doses based on weight and renal function (Table 37);
- use radial access in patients at high risk of bleeding;
- stop anticoagulation after PCI unless a specific indication exists;
- adopt selective downstream use of GPIIb–IIIa inhibitors, as required in the catheterization laboratory, in preference to unselective upstream use.

(b) Recommended duration of dual antiplatelet therapy

After percutaneous coronary intervention

- 1 month after BMS implantation in stable angina [55,60,94];
- 6–12 months after DES implantation in all patients [60,94];
- 1 year in all patients after ACS, irrespective of revascularization strategy.

Data suggest that certain patient populations (e.g. high risk for thromboembolic events, patients after SES or PES implantation), may benefit from prolonged DAPT beyond 1 year. The downside of this strategy is the increased rate of severe bleeding complications over time. Recent data suggest that DAPT for 6 months might be sufficient because late and very late stent thrombosis correlate poorly with discontinuation of DAPT.

Table 37
Recommendations of antithrombotic drug use in chronic kidney disease

Antiplatelet therapy	
ASA	No specific recommendations.
Clopidogrel	No information in patients with renal dysfunction.
Prasugrel ^a	No dosage adjustment is necessary for patients with renal impairment, including patients with end stage renal disease.
Ticagrelor ^a	No dose reduction required in patients with GFR <60 mL/min/1.73 m ² .
GPIIb–IIIa antagonists	
Abciximab	No specific recommendations for the use or dose adjustment in the case of renal failure.
Tirofiban	Dose adaptation required in patients with renal failure: 50% of the dose with GFR of <30 mL/min/1.73 m ² .
Eptifibatide	Dose adaptation in moderate renal impairment (GFR <60 mL/min/1.73 m ²). Contraindicated in severe renal dysfunction.
Anticoagulation	
UFH	Dose reduction necessary based on frequent aPTT measurements to control therapeutic range.
Enoxaparin (and other LMWHs)	In case of severe renal failure (GFR <30 mL/min/1.73 m ²) either to be avoided or 50% dose reduction and control of therapeutic levels by factor Xa-activity measurements. In patients with reduced GFR (range 30–60 mL/min/1.73 m ²) dose reduction to 75% of the recommended full dose.
Fondaparinux	Contraindicated in severe renal failure (<30 mL/min/1.73 m ²); drug of choice in patients with reduced renal function (GFR 30–60 mL/min/1.73 m ²) due to lower risk of bleeding complications compared with enoxaparin.
Bivalirudin	Consider reduction of infusion rate to 1.0 mg/kg/h in patients with severe renal dysfunction; consider use in patients with NSTEMI-ACS and reduced renal function (GFR 30–60 mL/min/1.73 m ²) undergoing angiography ± PCI due to lower bleeding risk compared with UFH + GPIIb–IIIa antagonists.

^a Depending on approval and availability.

aPTT = activated partial thromboplastin time; ASA = acetylsalicylic acid; GFR = glomerular filtration rate; GPIIb–IIIa = glycoprotein IIb–IIIa; LMWHs = low molecular weight heparins; NSTEMI-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

After coronary artery bypass grafting

Indications for DAPT and treatment duration depend primarily on the clinical indication (stable CAD, NSTEMI-ACS, STEMI), irrespective of the mode of revascularization. Secondary prevention demands lifelong antiplatelet therapy with 75–325 mg ASA daily (Section 13).

Antiplatelet agents also promote long-term graft patency, especially SVG. In cases of aspirin intolerance, clopidogrel should be used. There are no RCTs comparing the efficacy of clopidogrel or clopidogrel plus aspirin vs. aspirin alone on long-term graft patency.

(c) Triple antithrombotic therapy

Triple therapy consisting of ASA, clopidogrel (or prasugrel), and a vitamin K antagonist should only be given if a compelling indication exists, i.e. paroxysmal, persistent, or permanent AF with CHADS₂ score ≥2, mechanical valves, recent or recurrent history of deep venous thrombosis, or pulmonary embolism. Triple therapy should only be prescribed for the shortest necessary duration with frequent INR measurement (target INR 2–2.5) [257]. In patients with

a compelling indication for long-term anticoagulation, BMS implantation or stand-alone balloon angioplasty or CABG should be preferred over DES to restrict the duration of triple therapy to 1 month.

(d) Drug interactions and genetic testing: a clopidogrel-related topic

Statins interact with clopidogrel metabolism through CYP3A4, a drug interaction that has little if any clinical relevance.

Proton pump inhibitors are frequently administered in combination with DAPT to reduce the risk of gastrointestinal bleeding. European and US regulatory agencies have issued warnings regarding diminished clopidogrel action when combined with proton pump inhibitors (especially omeprazole and esomeprazole). *Post hoc* analyses of CREDO and TRITON-TIMI 38 RCTs [258] did not show increased thromboembolic events. Accordingly, proton pump inhibitors should not be withheld when indicated.

The presence of the CYP2C19 loss-of-function allele seems to be associated with an increased risk of atherothrombotic complications in clopidogrel-treated patients. This allele does not influence the action of prasugrel on platelet function.

(e) Renal dysfunction

The extent of CKD is strongly related to the risk of adverse in-hospital outcomes. As many antithrombotic drugs are metabolized or excreted by the kidneys, an accurate assessment of renal function is required for proper dose adjustment. In general, most antithrombotic agents are contraindicated or need dose reduction in CKD patients (Table 37). In patients referred for acute PCI, the first dose of an antithrombotic drug usually does not add to the risk of bleeding in cases of CKD. Repeated infusion or intake might lead to drug accumulation and increase bleeding risk. Accordingly, patients with CKD should receive the same first-line treatment as any other patient, in the absence of contraindications. Thereafter, dose adaptation is mandatory with respect to kidney function and specific antithrombotic agents may be preferred (Table 37).

(f) Surgery in patients on dual antiplatelet therapy

Management of patients on DAPT who are referred for surgical procedures depends on the level of emergency and the thrombotic and bleeding risk of the individual patient (Figure 3). Most surgical procedures can be performed on DAPT or at least on ASA alone with acceptable rate of bleeding. A multidisciplinary approach is required (cardiologist, anaesthesiologist, haematologist, and surgeon) to determine the patient's risk and to choose the best strategy.

In surgical procedures with high to very high bleeding risk, including CABG, it is recommended that clopidogrel be stopped 5 days before surgery and ASA continued. Prasugrel should be stopped 7 days before surgery based on its prolonged and more effective action than clopidogrel. In the PLATO trial, ticagrelor was discontinued 48–72 h before surgery. DAPT should be resumed as soon as possible including a loading dose for clopidogrel and prasugrel (if possible <24 h after operation).

In very high risk patients in whom cessation of antiplatelet therapy before surgery is judged to be too hazardous (e.g.

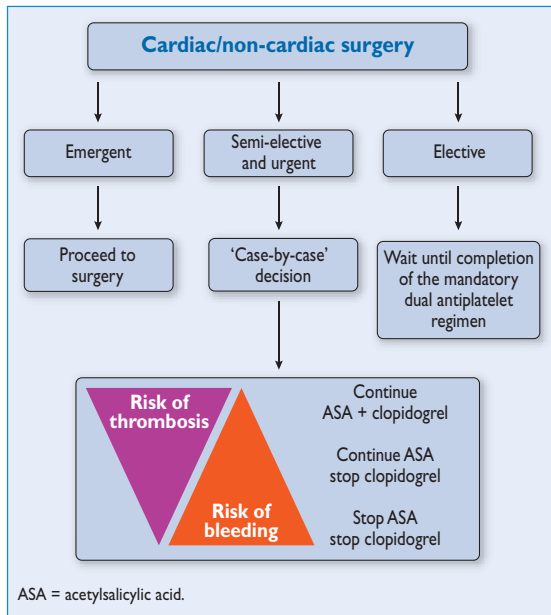


Fig. 3 – Algorithm for pre-operative management of patients considered for/undergoing surgery treated with dual antiplatelet therapy.

within the first weeks after stent implantation), it has been suggested that a patient be switched from clopidogrel 5 days before surgery to a reversible antiplatelet agent with a short half-life, e.g. the GPIIb–IIIa inhibitor tirofiban or eptifibatid, stopping the infusion 4h before surgery. The substitution of DAPT with LMWH or UFH is ineffective.

In surgical procedures with low to moderate bleeding risk, surgeons should be encouraged to operate on DAPT.

(g) Antiplatelet therapy monitoring

Residual platelet activity on DAPT can be measured in various ways, including point of care bedside tests. There is no consensus on the system to be used, on the definition of poor response, and on the course of action. Many studies have shown associations between unwanted effects and a lower response to DAPT; however, there is no evidence from RCTs that tailored antiplatelet therapy improves outcome. Monitoring of antiplatelet response by platelet function assays is currently used for clinical research, but not in daily clinical practice.

(h) Patients with ASA hypersensitivity

In patients with ASA hypersensitivity and in whom ASA therapy is mandatory, a rapid desensitization procedure may be performed.

(i) Heparin-induced thrombocytopenia

In patients with a history of heparin-induced thrombocytopenia, neither UFH nor LMWH should be used because of cross-reactivity. In this case, bivalirudin is the best option and other possible options are fondaparinux, argatroban, hirudin, lepirudin, and danaparoid.

13. Secondary prevention

13.1. Background and rationale

Myocardial revascularization must be accompanied by adequate secondary prevention strategies: OMT, risk factor

modification, and permanent lifestyle changes [12,60,94,158,261].

Cardiac rehabilitation and secondary prevention are an essential part of long-term management after revascularization because such measures reduce future morbidity and mortality, in a cost-effective way [60,94,158,262].

13.2. Modalities

Patients require counselling to adopt a healthy lifestyle and encourage adherence to their medication plan. The role of the interventional cardiologist and cardiac surgeon is to recommend cardiac rehabilitation and secondary prevention to all revascularized patients. Therapy should be initiated during hospitalization when patients are highly motivated. Adherence to lifestyle and risk factor modification requires individualized behavioural education and can be implemented during exercise-based cardiac rehabilitation. Education should be interactive with full participation of patient care-givers, providing an explanation for each intervention while early mobilization and physical conditioning programme should vary according to individual clinical status (Table 38) [261,263]. Adherence to the prescribed recommendations and the achievement of the planned goals should be evaluated during regular clinical evaluation (at 6-month intervals).

For functional evaluation and exercise training prescription, symptom-limited exercise testing can be safely performed 7–14 days after primary PCI for STEMI and as soon as 24h after elective PCI. Algorithms for prescription of functional evaluation at the onset of rehabilitation or exercise programmes after PCI and CABG are proposed in Figures 4 and 5: submaximal exercise evaluations and 6-min walk tests represent useful alternatives to symptom-limited stress testing, which should be considered as the first choice approach [262].

Echocardiography should be performed after CABG and can be considered after PCI to ascertain global LV function and regional wall motion. During physical training, exercise intensity should be set at 70–85% of the peak heart rate. In the case of symptomatic exercise-induced ischaemia, the level of exercise intensity can be set either at 70–85% of the ischaemic heart rate or just below the anginal threshold. In asymptomatic exercise-induced ischaemia, exercise to 70–85% of the heart rate at the onset of ischaemia (defined as ≥ 1 mm of ST depression) has been proposed.

Table 39 lists the pharmacological components of OMT. For practical purposes the mnemonic ‘ABCDE’ approach has been proposed: ‘A’ for antiplatelet therapy (Table 36), anticoagulation, angiotensin-converting enzyme inhibition, or angiotensin receptor blockade; ‘B’ for β -blockade and blood pressure control; ‘C’ for cholesterol treatment and cigarette smoking cessation; ‘D’ for diabetes management and diet; and ‘E’ for exercise.

13.3. Settings

Cardiac rehabilitation and secondary prevention programmes are implemented in or out of hospital, according to the clinical status and the local facilities. A structured in-hospital (residential) cardiac rehabilitation programme,

Table 38
Long-term lifestyle and risk factor management after myocardial revascularization

	Class ^a	Level ^b	Ref. ^c
Long-term management is based on risk stratification that should include:			
• full clinical and physical evaluation	I	C	–
• ECG	I	B	[12]
• laboratory testing	I	B	[12]
• HbA1c	I	A	[264]
• physical activity level by history and exercise testing	I	B	[12,265]
• echocardiogram prior to and after CABG.	I	C	–
Echocardiography should be considered pre- or post-PCI.	IIa	C	–
• Counselling on physical activity and exercise training should include a minimum of 30–60 min/day of moderately intense aerobic activity.	I	A	[12,94]
• Medically supervised programmes are advisable for high-risk patients (e.g. recent revascularization, heart failure).	I	B	[12]
Resistance training 2 days/week may be considered	IIb	C	–
• Diet and weight control management should aim at BMI <25 kg/m ² and waist circumferences <94 cm in men and <80 cm in women.	I	B	[263]
• It is recommended to assess BMI and/or waist circumferences on each visit and consistently encourage weight maintenance/reduction.	I	B	[12,266]
• The initial goal of weight-loss therapy is the reduction of body weight by ~10% from baseline.	I	B	[12]
• Healthy food choices are recommended.	I	B	[94]
• Dietary therapy and lifestyle changes are recommended.	I	B	[12]
• It is recommended to reach LDL-cholesterol <100 mg/dL (2.5 mmol/L).	I	A	[94]
• In high-risk patients, it is recommended to reach LDL-cholesterol <70 mg/dL (2.0 mmol/L).	I	B	[110]
Increased consumption of omega-3 fatty acids in the form of fish oil may be considered.	IIb	B	[261]
• It is recommended to implement lifestyle changes and pharmacotherapy in order to achieve blood pressure <130/80 mmHg.	I	A	[12,261]
• β-Blockers and/or ACE inhibitors are indicated as first-line therapy.	I	A	[12]
It is recommended to assess, at each visit, smoking status, to insist on smoking cessation, and to advise avoiding passive smoking.	I	B	[12,94]
In patients with diabetes, the following is recommended:			
• Lifestyle changes and pharmacotherapy to achieve HbA1c <6.5%.	I	B	[12,94]
• Vigorous modification of other risk factors.	I	B	[12]
• Coordination of diabetic care with a specialized physician.	I	C	–
Screening for psychological distress is indicated.	I	C	–
Annual influenza vaccination is indicated.	I	B	[12,94]

^a Class of recommendation.

^b Level of evidence.

^c References.

ACE = angiotensin-converting enzyme; BMI = body mass index; CABG = coronary artery bypass grafting; ECG = electrocardiogram; HbA1c = glycated haemoglobin; LDL = low density lipoprotein; PCI = percutaneous coronary intervention.

either in a hospital or in a dedicated centre, is ideal for high-risk patients, who may have persistent clinical, haemodynamic, or arrhythmic instability, or severe complications or comorbidities.

After uncomplicated PCI or CABG procedures, physical activity counselling can start the following day, and such patients can walk on the flat and up the stairs within a few days. After a revascularization procedure in patients with significant myocardial damage, physical rehabilitation should start after clinical stabilization.

The following general criteria should be considered in planning an exercise testing modality for exercise prescription: safety, i.e. stability of clinical, haemodynamic, and rhythmic parameters, ischaemic and angina threshold (in the case of incomplete revascularization), degree of LV impairment; associated factors (i.e. sedentary habits, orthopaedic limitations, occupational and recreational needs).

14. Strategies for follow-up

Although the need to detect restenosis has diminished in the DES era, a sizeable proportion of patients are still treated

with BMS or balloon angioplasty with high recurrence rates. Likewise, the durability of CABG results has increased with the use of arterial grafts and ischaemia stems mainly from SVG attrition and/or progression of CAD in native vessels.

Follow-up strategies should focus not only on the detection of restenosis or graft occlusion, but also on the assessment of patients' functional status and symptoms, as well as on secondary prevention. A baseline assessment of physical capacity is needed when entering a rehabilitation programme after revascularization [265].

Physical examination, resting ECG, and routine laboratory testing should be performed within 7 days after PCI. Special attention should be given to puncture site healing, haemodynamics, and possible anaemia or CIN. For ACS patients, plasma lipids should be re-evaluated 4–6 weeks after an acute event and/or initiation of lipid-lowering therapy to evaluate whether target levels have been achieved and to screen for liver dysfunction; the second plasma lipid control should be scheduled at 3 months [263]. For patients with stable CAD, there is a need to evaluate muscle symptoms and enzymes initially after statin introduction, then to evaluate muscle symptoms

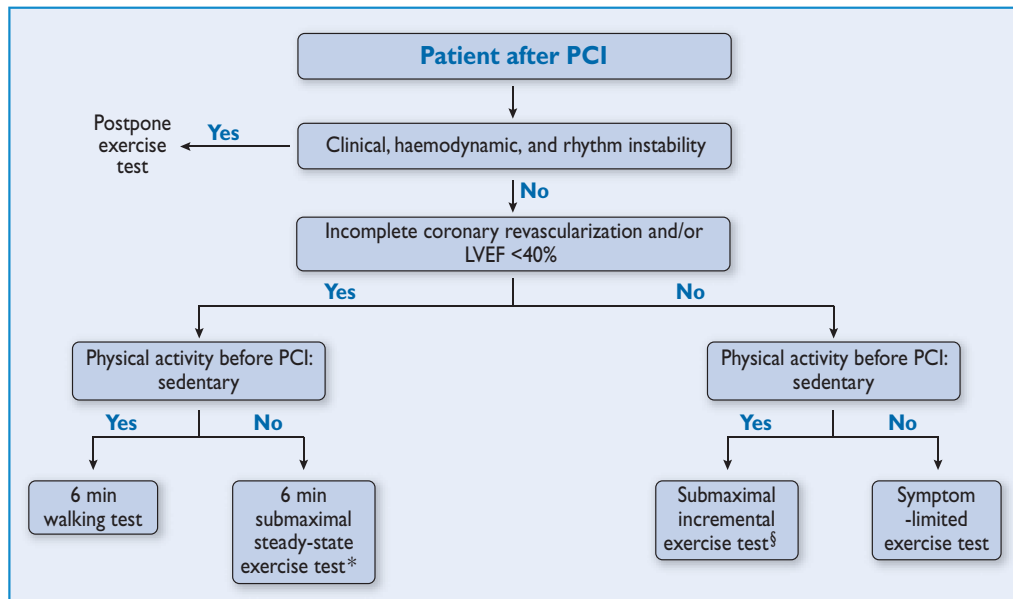


Fig. 4. Algorithm for prescription of functional evaluation at the onset of rehabilitation or exercise programme after percutaneous coronary intervention. The following general criteria should be considered in planning an exercise testing modality for exercise prescription: safety, i.e. stability of clinical, haemodynamic and rhythmic parameters, ischaemic and angina threshold (in the case of incomplete revascularization), degree of left ventricular ejection fraction impairment, associated factors (i.e. sedentary habits, orthopaedic limitations, occupational and recreational needs). *Upper limit for terminating submaximal 6-min single-stage (steady-state) exercise testing: rate of perceived exertion (Borg scale) 11–13/20 or maximal heart rate = heart rate at standing rest + 20–30 beats/min. §Upper limit for terminating submaximal incremental testing: maximal heart rate = 70% heart rate reserve or 85% of age-predicted maximal heart rate. LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

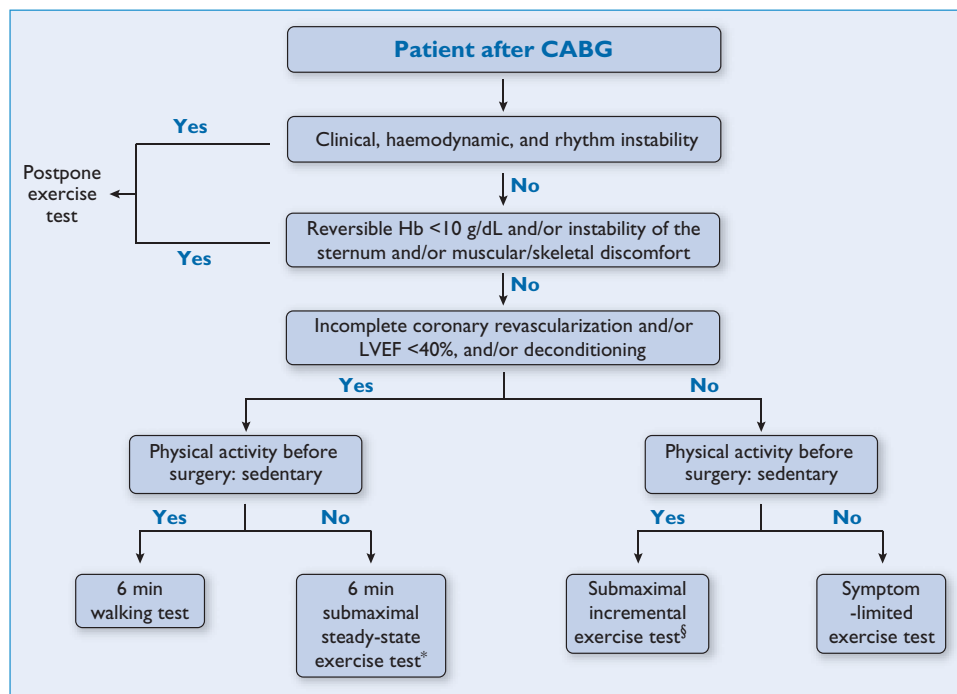


Fig. 5. Algorithm for prescription of functional evaluation at the onset of rehabilitation or exercise programme after coronary artery bypass grafting. The following general criteria should be considered in planning exercise testing modality for exercise prescription: safety; comorbidities, i.e. haemoglobin values, musculoskeletal discomfort, healing issues at the incision sites; associated factors, i.e. deconditioning due to prolonged hospitalization, sedentary habits, orthopaedic limitations, occupational and recreational needs (see also legend to Figure 4). CABG = coronary artery bypass grafting; Hb = haemoglobin; LVEF = left ventricular ejection fraction.

Table 39
Long-term medical therapy after myocardial revascularization

	Class ^a	Level ^b	Ref. ^c
• ACE inhibitors should be started and continued indefinitely in all patients with LVEF ≤40% and for those with hypertension, diabetes, or CKD, unless contraindicated.	I	A	[12]
• ACE inhibitors should be considered in all patients, unless contraindicated.	IIa	A	[94]
• Angiotensin receptor blockers are indicated in patients who are intolerant of ACE inhibitors and have HF or MI with LVEF ≤40%.	I	A	[12]
• Angiotensin receptor blockers should be considered in all ACE-inhibitor intolerant patients.	IIa	A	[94]
• It is indicated to start and continue β-blocker therapy in all patients after MI or ACS or LV dysfunction, unless contraindicated.	I	A	[12]
• High-dose lipid lowering drugs are indicated in all patients regardless of lipid levels, unless contraindicated.	I	A	[94,110,267]
• Fibrates and omega-3 fatty acids (1 g/day) should be considered in combination with statins and in patients intolerant of statins.	IIa	B	[12,261]
• Niacin may be considered to increase HDL cholesterol.	IIb	B	[268]

^a Class of recommendation.

^b Level of evidence.

^c References.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; CKD = chronic kidney disease; HDL = high density lipoprotein; HF = heart failure; LV = left ventricle; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

at each follow-up visit, and to evaluate enzymes if the patient presents muscle soreness, tenderness, or pain. Liver enzymes should be evaluated initially, 8–12 weeks after statin initiation, after dose increase, then annually or more frequently if indicated.

Stress testing

Previously published guidelines [269] and several authors warn against routine testing of asymptomatic patients. Others argue that all patients should undergo stress testing following revascularization, given the adverse outcome associated with silent ischaemia. Early stress testing in order to verify that culprit lesions have been successfully treated may be recommended after incomplete or suboptimal revascularization as well as in other specific patient subsets (Table 40). Stress ECG should preferably be combined with functional imaging, due to low sensitivity and specificity of stress ECG alone in this subset [269], its inability to localize ischaemia, and to assess improvement in regional wall motion of revascularized segments. Exercise is considered the most appropriate stressor, but in patients unable to exercise, pharmacologic stressors – dipyridamole, dobutamine, and adenosine – are recommended. The inability to perform an exercise stress test, by itself, indicates a worse prognosis. The choice between imaging modalities is based on similar criteria to those used before intervention (Section 5). With repeated testing, radiation burden should be considered as part of the test selection. Estimation of coronary flow using transthoracic Doppler echocardiography may be used

to assess coronary flow non-invasively, but larger studies are needed to confirm the accuracy of this technique.

Imaging stent or graft patency

CT angiography can detect occluded and stenosed grafts with very high diagnostic accuracy [18,19]. However, clinical assessment should not be restricted to graft patency but should include evaluation of the native coronary arteries. This will often be difficult because of advanced CAD and pronounced coronary calcification. Furthermore, it is acknowledged that anatomical imaging by CT angiography does not assess ischaemia, which remains essential for therapeutic decisions. CT angiography can detect in-stent restenosis, depending on stent type and diameter, yet the aforementioned limitations equally apply. Patients who have undergone unprotected LM PCI may be scheduled for routine control CT or invasive angiography within 3–12 months.

Recommendations for follow-up strategies in asymptomatic and symptomatic patients are summarized in Tables 40 and 41. These recommendations assume that patients comply with appropriate lifestyle changes and receive OMT [12,14,43,270].

Table 40
Strategies for follow-up and management in asymptomatic patients after myocardial revascularization

	Class ^a	Level ^b	Ref. ^c
Stress imaging (stress echo or MPS) should be used rather than stress ECG.	I	A	[12,269]
• With low-risk findings (+) at stress testing, the reinforcement of OMT and lifestyle changes should be considered.	IIa	C	–
• With high- to intermediate-risk findings (++) at stress testing, coronary angiography should be considered.			
Early imaging testing should be considered in specific patient subsets. ^d	IIa	C	–
Routine stress testing may be considered ≥2 years after PCI and >5 years after CABG.	IIb	C	–

^a Class of recommendation.

^b Level of evidence.

^c References.

^d Specific patient subsets indicated for early stress testing with imaging:

- predischarge, or early post-discharge imaging stress test in STEMI patients treated with primary PCI or emergency CABG;
- patients with safety critical professions (e.g. pilots, drivers, divers) and competitive athletes;
- users of 5-phosphodiesterase inhibitors;
- patients who would like to be engaged in recreational activities for which high oxygen consumption is required;
- patients resuscitated from sudden death;
- patients with incomplete or suboptimal revascularization, even if asymptomatic;
- patients with a complicated course during revascularization (peri-operative MI, extensive dissection during PCI, endarterectomy during CABG, etc.);
- patients with diabetes (especially those requiring insulin);
- patients with MVD and residual intermediate lesions, or with silent ischaemia.

(+) Low-risk findings at stress imaging are ischaemia at high workload, late onset ischaemia, single zone of low grade wall motion abnormality or small reversible perfusion defect, or no evidence of ischaemia.

(++) Intermediate- and high-risk findings at stress imaging are ischaemia at low workload, early onset ischaemia, multiple zones of high grade wall motion abnormality, or reversible perfusion defect.

CABG = coronary artery bypass grafting; ECG = electrocardiogram; MI = myocardial infarction; MPS = myocardial perfusion stress; MVD = multivessel disease; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Table 41

Strategies for follow-up and management in symptomatic patients after myocardial revascularization

	Class ^a	Level ^b	Ref. ^c
Stress imaging (stress echo or MPS) should be used rather than stress ECG.	I	A	[12,269]
It is recommended to reinforce OMT and life style changes in patients with low-risk findings (+) at stress testing.	I	B	[14,43, 270]
With intermediate- to high-risk findings (++) at stress testing, coronary angiography is recommended.	I	C	–
Emergent coronary angiography is recommended in patients with STEMI.	I	A	[94]
Early invasive strategy is indicated in high-risk NSTEMI-ACS patients.	I	A	[60]
Elective coronary angiography is indicated in low-risk NSTEMI-ACS patients.	I	C	–

^a Class of recommendation.^b Level of evidence.^c References.

(+) Low-risk findings at stress imaging are ischaemia at high workload, late onset ischaemia, single zone of low grade wall motion abnormality or small reversible perfusion defect, or no evidence of ischaemia.

(++) Intermediate- and high-risk findings at stress imaging are ischaemia at low workload, early onset ischaemia, multiple zones of high grade wall motion abnormality or reversible perfusion defect.

ECG = electrocardiogram; MPS = myocardial perfusion stress; NSTEMI-ACS = non-ST-segment elevation acute coronary syndrome; OMT = optimal medical therapy; STEMI = ST-segment elevation myocardial infarction.

Most of the statements in these clinical practice guidelines are supported by published evidence. Only a minority of the publications that support the written text were listed in the following abridged reference list of the guidelines. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejcts.2010.08.019 and also at www.eacts.org.

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