

# 2018 ESC/EACTS Guidelines on myocardial revascularization

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

*Developed with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI)*

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## KEYWORDS

- acute coronary syndromes
- antithrombotic therapy
- bare-metal stents
- coronary artery bypass grafting
- coronary artery disease
- drug-eluting stents
- guidelines
- Heart Team
- myocardial infarction
- myocardial ischaemia
- myocardial revascularization
- medical therapy
- percutaneous coronary intervention
- recommendation
- revascularization
- risk stratification
- stents
- stable angina
- stable coronary artery disease
- ST-segment elevation myocardial infarction
- SYNTAX score

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Sousa-Uva M, Neumann F-J, Ahlsson A, Alfonso F, Banning AP, Benedetto U et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *European Heart Journal* 2018, doi:10.1093/eurheartj/ehy394. Reproduced by permission of Oxford University Press on behalf of the European Society of Cardiology.

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## Abbreviations and acronyms

<b>ABC</b>	Age, Biomarkers, Clinical History		
<b>ABSORB II</b>	A Bioresorbable Everolimus-Eluting Scaffold Versus a Metallic Everolimus-Eluting Stent II	<b>b.i.d.</b>	Bis in die (twice daily)
<b>AIDA</b>	Amsterdam Investigator-Initiated Absorb Strategy All-Comers	<b>BIMA</b>	Bilateral internal mammary artery
<b>ACCOAST</b>	Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction	<b>BMS</b>	Bare-metal stent
<b>ACS</b>	Acute coronary syndrome	<b>BRAVE</b>	Bavarian Reperfusion Alternatives Evaluation
<b>ACUITY</b>	Acute Catheterization and Urgent Intervention Triage strategy	<b>BRS</b>	Bioresorbable scaffolds
<b>ADAPT-DES</b>	Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents	<b>BVS</b>	Bioresorbable vascular scaffold
<b>AF</b>	Atrial fibrillation	<b>CABG</b>	Coronary artery bypass grafting
<b>ALPHEUS</b>	Assessment of Loading With the P2Y <sub>12</sub> -Inhibitor Ticagrelor or Clopidogrel to Halt Ischemic Events in Patients Undergoing Elective Coronary Stenting	<b>CAD</b>	Coronary artery disease
<b>AMI</b>	Acute myocardial infarction	<b>CARDia</b>	Coronary Artery Revascularization in Diabetes
<b>AMACING</b>	A Maastricht Contrast-Induced Nephropathy Guideline	<b>CCS</b>	Canadian Cardiovascular Society
<b>ANTARCTIC</b>	Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome	<b>CEA</b>	Carotid endarterectomy
<b>ARCTIC</b>	Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting	<b>CHA<sub>2</sub>DS<sub>2</sub>-VASC</b>	Cardiac Congestive heart failure, Hypertension, Age ≥75 [Doubled], Diabetes mellitus, prior Stroke or transient ischaemic attack or thromboembolism [Doubled] - Vascular disease, Age 65-74 and Sex category [Female]
<b>ART</b>	Arterial Revascularization Trial	<b>CHAMPION</b>	Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition
<b>AS</b>	Aortic stenosis	<b>CI</b>	Confidence interval
<b>ASE</b>	American Society of Echocardiography	<b>CIN</b>	Contrast-induced nephropathy
<b>ATLANTIC</b>	Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST-Elevation Myocardial Infarction to Open the Coronary Artery	<b>CKD</b>	Chronic kidney disease
<b>ATLAS-ACS 2-TIMI 51</b>	Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard therapy in subjects with Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction 51	<b>CMR</b>	Cardiac magnetic resonance
<b>ATOLL</b>	Acute STEMI Treated with primary PCI and intravenous enoxaparin Or UFH to Lower ischaemic and bleeding events at short- and Long-term follow-up	<b>COMPASS</b>	Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease
<b>AWESOME</b>	Angina With Extremely Serious Operative Mortality Evaluation	<b>COURAGE</b>	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
<b>BARC</b>	Bleeding Academic Research Consortium	<b>CPG</b>	ESC Committee for Practice Guidelines
<b>BARI-2D</b>	Bypass Angioplasty Revascularization Investigation 2 Diabetes	<b>CT</b>	Computed tomography
<b>BES</b>	Biolimus-eluting stent	<b>CT-FFR</b>	CT-derived fractional flow reserve
<b>BEST</b>	Randomised Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent	<b>CTO</b>	Chronic total occlusion
		<b>CTSN</b>	Cardiothoracic Surgical Trial Network
		<b>CULPRIT-SHOCK</b>	Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock
		<b>CVA</b>	Cerebrovascular accident
		<b>CvLPRIT</b>	Complete Versus Lesion-Only Primary PCI Trial
		<b>DANAMI 3-DEFER</b>	The Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: DEFERred stent implantation in connection with primary PCI
		<b>DANAMI-3-PRIMULTI</b>	The Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: PRIMary PCI in MULTIVessel Disease
		<b>DAPT</b>	Dual antiplatelet therapy
		<b>DCB</b>	Drug-coated balloon
		<b>DEFINE-FLAIR</b>	Define Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization
		<b>DES</b>	Drug-eluting stents
		<b>DUS</b>	Duplex ultrasound
		<b>EACTS</b>	European Association for Cardio-Thoracic Surgery
			Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease

<b>EAPCI</b>	European Association for Percutaneous Cardiovascular Interventions	<b>i.v.</b>	Intravenous
<b>EBC TWO</b>	European Bifurcation Coronary TWO	<b>IABP</b>	Intra-aortic balloon pump
<b>ECG</b>	Electrocardiogram	<b>IABP-SHOCK II</b>	Intraaortic Balloon Pump in Cardiogenic Shock II Trial
<b>ECLS</b>	Extracorporeal life support	<b>ICD</b>	Implantable cardioverter defibrillator
<b>ECMO</b>	Extracorporeal membrane oxygenation	<b>iwFR</b>	Instantaneous wave-free ratio
<b>EES</b>	Everolimus-eluting stent	<b>IMA</b>	Internal mammary artery
<b>EF</b>	Ejection fraction	<b>IMR</b>	Ischaemic mitral regurgitation
<b>EMS</b>	Emergency medical service	<b>INR</b>	International normalized ratio
<b>EROA</b>	Effective regurgitant orifice area	<b>IRA</b>	Infarct-related artery
<b>ENTRUST-AF-PCI</b>	Evaluation of the safety and efficacy of an edoxaban-based antithrombotic regimen in patients with atrial fibrillation following successful percutaneous coronary intervention	<b>ISAR-CABG</b>	Is Drug-Eluting-Stenting Associated with Improved Results in Coronary Artery Bypass Grafts
<b>ESC</b>	European Society of Cardiology	<b>ISAR-REACT</b>	Intracoronary Stenting and Antithrombotic Regimen Rapid Early Action for Coronary Treatment
<b>EUROCTO</b>	Randomized Multicentre Trial to Compare Revascularization With Optimal Medical Therapy for the Treatment of Chronic Total Occlusions	<b>ISCHEMIA</b>	International Study of Comparative Health Effectiveness With Medical and Invasive Approaches
<b>EuroSCORE</b>	European System for Cardiac Operative Risk Evaluation	<b>IVUS</b>	Intravascular ultrasound imaging
<b>EUROMAX</b>	European Ambulance Acute Coronary Syndrome Angiography	<b>LAA</b>	Left atrial appendage
<b>EXCEL</b>	Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization	<b>LAD</b>	Left anterior descending
<b>FAME</b>	Fractional Flow Reserve versus Angiography for Multivessel Evaluation	<b>LEAD</b>	Lower extremity artery disease
<b>FDG-PET</b>	Fluorodeoxyglucose positron emission tomography	<b>LGE-CMR</b>	Late gadolinium enhancement cardiac magnetic resonance
<b>FFR</b>	Fractional flow reserve	<b>LIMA</b>	Left internal mammary artery
<b>FITT-STEMI</b>	Feedback Intervention and Treatment Times in ST-Elevation Myocardial Infarction	<b>LM/LMS</b>	Left main/left main stem
<b>FMC</b>	First medical contact	<b>LMWH</b>	Low-molecular-weight heparin
<b>FREEDOM</b>	Future Revascularization Evaluation in Patients with Diabetes Mellitus	<b>LPR</b>	Low platelet reactivity
<b>GLOBAL LEADERS</b>	Long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing biolimus-eluting stent implantation	<b>LV</b>	Left ventricle/left ventricular
<b>GP IIb/IIIa</b>	Glycoprotein IIb/IIIa	<b>LVAD</b>	Left ventricular assist device,
<b>GRAVITAS</b>	Gauging Responsiveness with A VerifyNow assay-Impact on Thrombosis And Safety	<b>LVEF</b>	Left ventricular ejection fraction
<b>HAS-BLED</b>	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/ alcohol	<b>MACCE</b>	Major adverse cardiac and cerebrovascular events
<b>HEAT-PPCI</b>	How Effective are Antithrombotic Therapies in primary PCI	<b>MACE</b>	Major adverse cardiac events
<b>HF</b>	Heart failure	<b>MADIT II</b>	Multicenter Automatic Defibrillator Implantation Trial II
<b>HFrEF</b>	Heart failure with reduced ejection fraction	<b>MATRIX</b>	Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX
<b>HORIZONS</b>	Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction	<b>MCS</b>	Mechanical circulatory support
<b>HPR</b>	High platelet reactivity	<b>MI</b>	Myocardial infarction
<b>HR</b>	Hazard ratio	<b>MINOCA</b>	Myocardial infarction with non-obstructive coronary arteries
		<b>MLA</b>	Minimal luminal area
		<b>MR</b>	Mitral regurgitation
		<b>MSCT</b>	Multi-slice computed tomography
		<b>MT</b>	Medical therapy
		<b>MVD</b>	Multivessel coronary artery disease
		<b>MVO</b>	Microvascular obstruction
		<b>NAC</b>	N-acetylcysteine
		<b>NNT</b>	Number needed to treat
		<b>NOAC</b>	Non-vitamin K antagonist oral anticoagulant
		<b>NOBLE</b>	Nordic-Baltic-British Left Main Revascularization Study

<b>NSTE-ACS</b>	Non-ST-segment elevation acute coronary syndrome	<b>ROMA</b>	Randomization of Single vs. Multiple Arterial Grafts
<b>NSTEMI</b>	Non-ST-segment elevation myocardial infarction	<b>RR</b>	Relative risk
<b>NYHA</b>	New York Heart Association	<b>SASSICAIA</b>	Comparison of Loading Strategies With Antiplatelet Drugs in Patients Undergoing Elective Coronary Intervention
<b>OAC</b>	Oral anticoagulation	<b>SAVR</b>	Surgical aortic valve replacement
<b>OASIS-5</b>	Optimal Antiplatelet Strategy for Interventions-5	<b>s.c.</b>	Subcutaneous
<b>OCT</b>	Optical coherence tomography	<b>SCAD</b>	Stable coronary artery disease
<b>OR</b>	Odds ratio	<b>SCD-HEFT</b>	Sudden Cardiac Death in Heart Failure Trial
<b>ORBITA</b>	Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina	<b>SES</b>	Sirolimus-eluting stent
<b>PARR-2</b>	PET and Recovery following Revascularization	<b>SHOCK</b>	Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock
<b>PCI</b>	Percutaneous coronary intervention	<b>SIMA</b>	Single internal mammary artery
<b>Pd/Pa</b>	Distal coronary to aortic pressure	<b>SMART-DATE</b>	Smart Angioplasty Research Team-safety of 6-month duration of Dual Antiplatelet Therapy after percutaneous coronary intervention in patients with acute coronary syndromes
<b>PES</b>	Paclitaxel-eluting stent	<b>SPECT</b>	Single-photon emission computed tomography
<b>PET</b>	Positron emission tomography	<b>SR</b>	Sinus rhythm
<b>PF</b>	Platelet function	<b>STEEPLE</b>	Safety and Efficacy of Intravenous Enoxaparin in Elective Percutaneous Coronary Intervention Randomised Evaluation
<b>PIONEER</b>	Prevention of bleeding in patients with AF undergoing PCI	<b>STEMI</b>	ST-segment elevation myocardial infarction
<b>PLATFORM</b>	Prospective Longitudinal Trial of FFRct: Outcome and Resource Impacts,	<b>STICH</b>	Surgical Treatment for Ischemic Heart Failure
<b>PLATO</b>	Study of Platelet Inhibition and Patient Outcomes	<b>STICHES</b>	STICH Extension Study
<b>pLVAD</b>	Percutaneous left ventricular assist device	<b>STS</b>	Society of Thoracic Surgeons
<b>p.o.</b>	Per os (orally)	<b>SVG</b>	Saphenous vein graft
<b>POSEIDON</b>	Prevention of Contrast Renal Injury with Different Hydration Strategies	<b>SVR</b>	Surgical ventricular reconstruction
<b>PPI</b>	Proton pump inhibitor	<b>SWEDEHEART</b>	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
<b>PRAGUE-18</b>	Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction	<b>SYNTAX</b>	Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery
<b>PRAMI</b>	Preventive Angioplasty in Acute Myocardial Infarction	<b>TAP</b>	T and protrusion
<b>PRECISE-DAPT</b>	PREdicting bleeding Complications In patients undergoing Stent implantation and subsequent Dual Anti Platelet Therapy	<b>TAVI</b>	Transcatheter aortic valve implantation
<b>PRECOMBAT</b>	Premier of Randomised Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease	<b>TIA</b>	Transient ischaemic attack
<b>PRESERVE</b>	Prevention of Serious Adverse Events Following Angiography	<b>TIMI</b>	Thrombolysis in Myocardial Infarction
<b>q.d.</b>	Quaque die (once daily)	<b>TLR</b>	Target lesion revascularization
<b>RCT</b>	Randomized controlled trial	<b>TOTAL</b>	Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI
<b>RE-DUAL</b>	Randomised Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention	<b>TRIGGER-PCI</b>	Testing platelet Reactivity In patients undergoing elective stent placement on clopidogrel to Guide alternative therapy with prasugrel
<b>REMEDIAL II</b>	Renal Insufficiency After Contrast Media Administration II	<b>TRITON-TIMI 38</b>	TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction
<b>REPLACE-2</b>	The Randomised Evaluation in PCI Linking Angiomax to Reduced Clinical Events 2	<b>TROPICAL-ACS</b>	Testing responsiveness to platelet inhibition on chronic antiplatelet treatment for acute coronary syndromes
<b>RIVAL</b>	Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes	<b>TVR</b>	Target vessel revascularization

<b>TWILIGHT</b>	Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention
<b>UFH</b>	Unfractionated heparin
<b>VA</b>	Veno-arterial
<b>VACARDS</b>	Veterans Affairs Coronary Artery Revascularization in Diabetes Study
<b>VALIDATE</b>	Bivalirudin versus Heparin in ST-Segment and Non-ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy
<b>VKA</b>	Vitamin K antagonist

## 1 Preamble

Clinical practice guidelines summarize and evaluate all available evidence at the time of the writing process on a particular issue with the aim of assisting physicians in selecting the best management strategies for an individual patient with a given condition, taking into account the impact on outcome as well as the risk-benefit ratio of particular diagnostic or therapeutic means. Clinical practice guidelines are no substitutes for textbooks, but complement them, and cover the European Society of Cardiology (ESC) Core Curriculum topics. As such they should help physicians to make decisions in their daily practice. However, final decisions should be individualized by responsible physicians and the patient.

A great number of clinical practice guidelines have been issued in recent years both by the ESC as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC and joint society guidelines can be found on the ESC website (<https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines>). These Guidelines represent the official position of the ESC and the European Association for Cardio-Thoracic Surgery (EACTS) on this given topic and will be regularly updated.

Members of this Task Force were selected by the ESC and EACTS to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for diagnosis, management (including treatment) and/or prevention of a given condition according to the ESC Committee for Practice

Guidelines (CPG) and EACTS policy. A critical evaluation of diagnostic and therapeutic procedures was performed including assessment of the risk-benefit ratio. Estimates of expected health outcomes for larger populations were included, where data exist. The level of evidence and the strength of recommendation of particular treatment options were weighed and graded according to predefined scales, as outlined in **Tables 1 and 2**.

The experts of the writing and reviewing panels completed declarations of interest forms on what might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC and EACTS websites <http://www.escardio.org/guidelines> and <http://www.eacts.org>. Any changes in declarations of interest that arise during the writing period must be notified to the ESC and EACTS and updated. The Task Force received its entire financial support from the ESC and EACTS without any involvement from the healthcare industry.

The CPG-ESC and EACTS supervised and coordinated the preparation of these new Guidelines produced by the joint Task Force. These entities are also responsible for the endorsement process of these Guidelines. The ESC/EACTS Guidelines underwent extensive review by a wide panel of relevant external experts. After appropriate revisions it was approved by all the experts involved in the Task Force. The finalized document was approved by the ESC CPG and EACTS for joint publication in the European Heart Journal and the European Journal of Cardio-Thoracic Surgery.

The task of developing clinical practice guidelines covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. To implement the guidelines, condensed pocket guidelines, summary slides, booklets with essential messages, and an electronic version for digital applications (smartphones, etc.) are produced. These versions are abridged and, thus, if needed, one

**Table 2. Levels of evidence.**

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

**Table 1. Classes of recommendations.**

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
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.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

should always refer to the full text version, which is freely available on the ESC and EACTS websites. The National Societies of the ESC are encouraged to endorse, translate, and implement the ESC Guidelines. 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.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, and implementing them in clinical practice.

The guidelines do not, however, override the individual responsibility of healthcare 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.

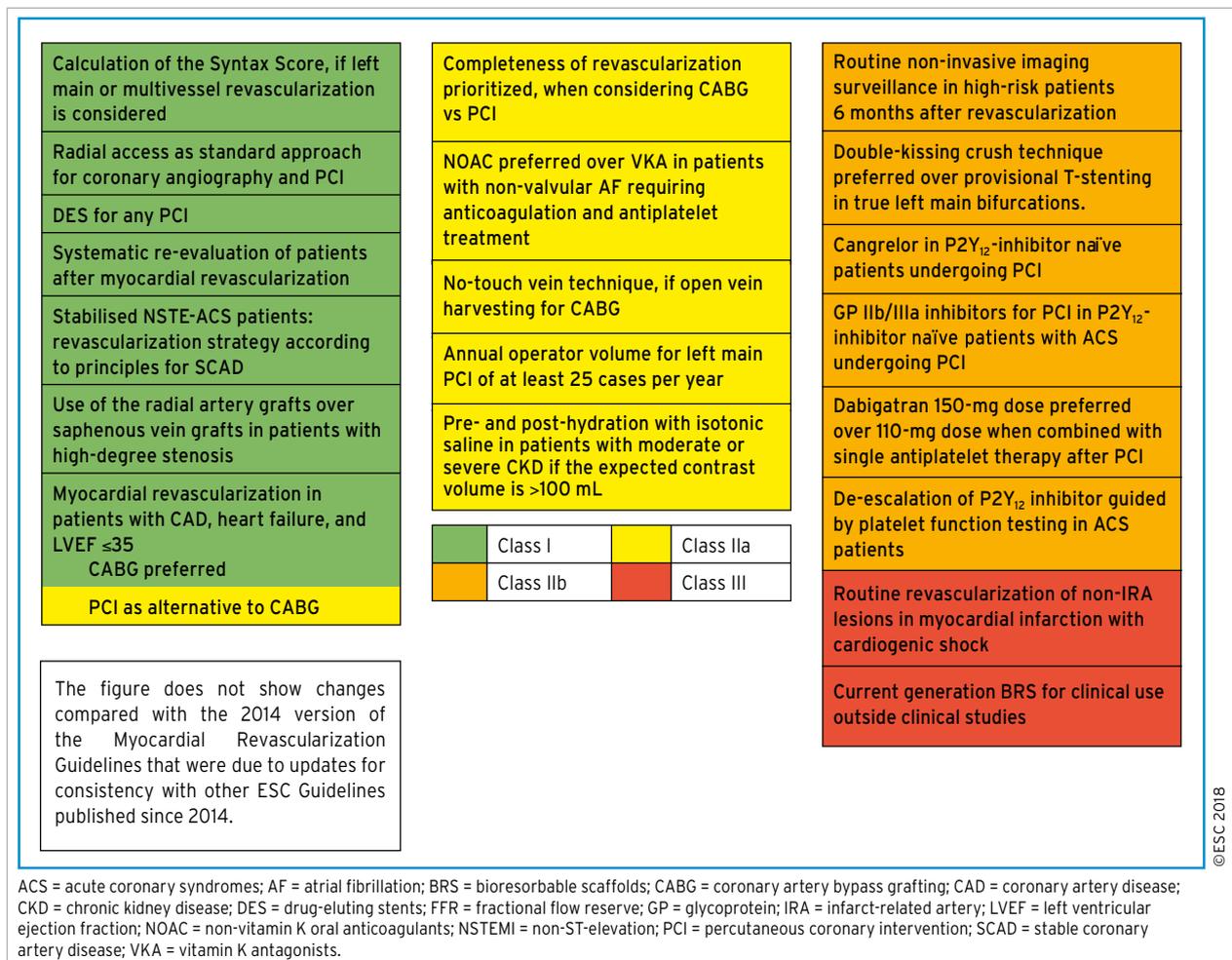
## 2 Introduction

These Guidelines represent the third time that the ESC and EACTS have brought together cardiologists and cardiac surgeons

in a joint Task Force to review the ever-increasing body of evidence, with the mission of drafting balanced, patient-centred practice Guidelines on myocardial revascularization. Summaries of the key changes in comparison with the previous Guidelines are provided in **Figures 1 and 2**.

There is considerable overlap of the current document with other Guidelines, specifically those on stable coronary artery disease, non-ST-elevation myocardial infarction, ST-elevation myocardial infarction, heart failure, valvular heart disease and the Focused Update on Dual Antiplatelet Therapy. Unless supported by new evidence, we followed the recommendations of these Guidelines where pertinent to our Guidelines, and refer the reader to the respective sections in those documents for detailed discussion. We reserve more in-depth discussion for topics that are specific to issues pertaining to myocardial revascularization that are not covered in other Guidelines. To keep the current document concise and reader-friendly, we also moved some of the detailed descriptions of study results to the **online Supplementary Data**.

### 2.1 WHAT IS NEW IN THE 2018 GUIDELINES?



**Figure 1.** New recommendations.

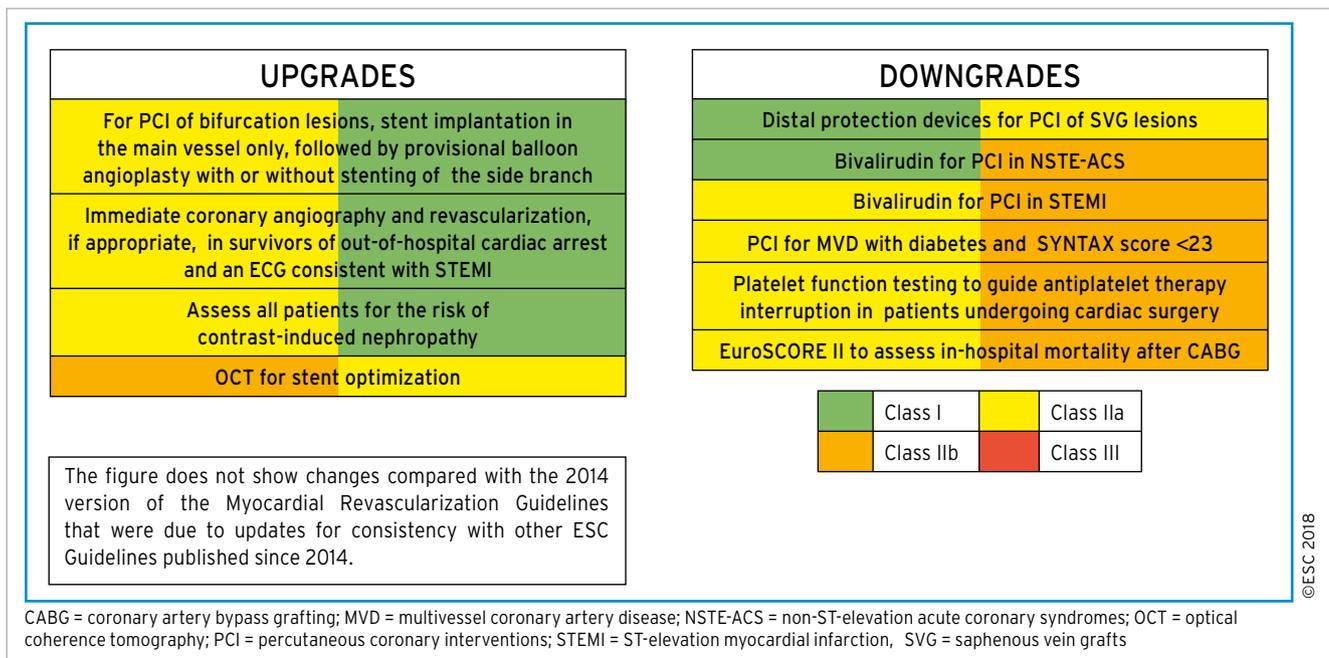


Figure 2. Changes in class of recommendation.

### 3 Diagnostic tools to guide myocardial revascularization

The use of diagnostic imaging and functional testing modalities to detect patients with coronary artery disease (CAD) is discussed in detail in the clinical practice Guidelines for patients with SCAD.<sup>1</sup> Further diagnostic assessment of patients with obstructive CAD is critical in order to identify patients and select specific lesions that are likely to benefit from myocardial revascularization, in addition to optimal medical therapy.

#### 3.1 NON-INVASIVE DIAGNOSTIC TOOLS

##### 3.1.1 ASSESSMENT OF MYOCARDIAL ISCHAEMIA

Non-invasive diagnostic assessment of patients with CAD being considered for myocardial revascularization comprises the assessment of ischaemia and the evaluation of viability in patients with regional wall motion abnormalities or reduced ejection fraction (EF).

Functional testing to assess ischaemia is critical for the assessment of stable patients with CAD. Documentation of ischaemia using functional testing before elective invasive procedures for CAD is the preferred approach. It may also have a role in the assessment of some patients presenting with acute coronary syndrome (ACS). Because of the low sensitivity of exercise electrocardiogram (ECG) testing in the assessment of patients with symptoms of angina, non-invasive imaging is recommended as the first-line test.<sup>1</sup> Detection of a large area of myocardial ischaemia by functional imaging is associated with impaired prognosis of patients and identifies patients who should undergo revascularization (see section 5).

In patients undergoing coronary computed tomography (CT), both CT-derived fractional flow reserve (CT-FFR) and CT

perfusion represent possible approaches to evaluate lesion-specific ischaemia. Although the evidence for both is limited at present, there are considerably more data from clinical investigations of CT-FFR. A number of trials have shown that correlation between CT-derived FFR and invasive FFR is high.<sup>2,3</sup> The non-randomized PLATFORM (Prospective Longitudinal Trial of FFRct: Outcome and Resource Impacts) study showed that in patients referred for invasive angiography due to chest pain (predominantly atypical angina) and intermediate pre-test probability of CAD, assessment with CT and CT-FFR reduced the number of patients with subsequently normal invasive coronary angiograms compared with standard care.<sup>4</sup> Currently, clinical trial data with CT-FFR are insufficient to make a recommendation for its use in clinical practice.

##### 3.1.2 ASSESSMENT OF MYOCARDIAL VIABILITY IN PATIENTS WITH HEART FAILURE AND CORONARY ARTERY DISEASE

In patients with regional wall motion abnormalities or ventricular dysfunction, heart failure (HF) can be caused by stunned or hibernating myocardium and may be reversed by revascularization. Assessment of myocardial viability may be done in order to select patients that are more likely to benefit from myocardial revascularization and can be achieved with several imaging modalities: myocardial contrast echocardiography, single-photon emission CT (SPECT), and late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) all assess cellular integrity; positron emission tomography (PET) assesses cellular metabolism; and dobutamine techniques assess contractile reserve.<sup>1,5</sup> Assessment of ischaemia provides incremental benefit over viability in mild to moderate CAD, but with extensive CAD viability assessment may be sufficient.<sup>6</sup> Patients with advanced HF and viable myocardium should

first undergo revascularization with coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) before being considered for mechanical circulatory support (MCS) or heart transplantation.<sup>7,8</sup>

The PARR-2 (PET and Recovery following Revascularization) trial included patients with severe left ventricular (LV) dysfunction being considered for revascularization or HF/transplantation workups, and randomized them to management assisted by fluoro-deoxyglucose PET (FDG-PET) or standard care.<sup>6</sup> The primary outcome of cardiac death, myocardial infarction (MI), or recurrent hospital stay for cardiac cause at 1 year was not improved in the group managed by FDG-PET [relative risk (RR) 0.82, 95% confidence interval (CI) 0.59-1.14, P=0.16], though the rate of compliance with the treatment recommended by FDG-PET was variable.

The viability substudy of the STICH (Surgical Treatment for Ischemic Heart Failure) trial found viable myocardium in 487/601 patients (81%) and none in 114 (19%).<sup>9</sup> There was a significant association between myocardial viability and outcome by univariate analysis, but not on multivariable analysis. The lack of correlation between myocardial viability and benefit from revascularization indicates that this strategy should not be the only test when selecting the optimal therapy.

#### Recommendations for non-invasive imaging in patients with coronary artery disease and heart failure with reduced ejection fraction

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Non-invasive stress imaging (CMR, stress echocardiography, SPECT, or PET) may be considered for the assessment of myocardial ischaemia and viability in patients with HF and CAD (considered suitable for coronary revascularization) before the decision on revascularization. <sup>9-11</sup>	IIb	B

CAD: coronary artery disease; CMR: cardiac magnetic resonance; HF: heart failure; PET: positron emission tomography; SPECT: single-photon emission computed tomography. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

### 3.2 INVASIVE DIAGNOSTIC TOOLS

#### 3.2.1 PRESSURE-DERIVED FRACTIONAL FLOW RESERVE

##### 3.2.1.1 Use of fractional flow reserve in patients with intermediate-grade coronary stenosis including left main stenosis

Coronary pressure-derived FFR is the current standard of care for the functional assessment of lesion severity in patients with intermediate-grade stenosis (typically around 40-90% stenosis) without evidence of ischaemia in non-invasive testing, or in those with multivessel disease.

Multiple studies have shown that PCI can be safely deferred if FFR is >0.75.<sup>12-15</sup> The DEFER trial enrolled 325 patients scheduled for PCI of an intermediate stenosis.<sup>15</sup> If FFR was ≥0.75, patients were randomly assigned to deferral (defer group; n=91) or performance (perform group; n=90) of PCI. The composite rate of cardiac death and acute MI (AMI) in the defer and perform groups was 3.3 vs. 7.9% (P=0.21).

However, most contemporary studies use an FFR cut-off of 0.80. A recent large-scale observational study supports the use of FFR >0.80 rather than 0.75 as a cut-off.<sup>16</sup> Indeed, the two largest studies in this field, DEFINE-FLAIR (Define Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization DES drug-eluting stent)<sup>17</sup> and iFR-SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies),<sup>18</sup> used the 0.80 cut-off for lesion selection by FFR, with favourable event rates at 1 year. Thus, 0.80 is the accepted FFR threshold for defining haemodynamically relevant lesions.

Haemodynamic relevance, as defined by FFR ≤ 0.80, correlates poorly with diameter stenosis by visual assessment. In the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial, only 35% of the 50-70% stenoses were haemodynamically relevant and, of the 71-90% stenoses, 20% were not. Only an estimated diameter stenosis >90% predicted haemodynamic relevance with high accuracy (96% correct classification). A number of studies have shown that utilization of an FFR-based assessment strategy at the time of angiography results in reclassification of the revascularization strategy (PCI, bypass surgery, or medical therapy) in a high proportion of patients with intermediate-grade lesions (>40% of patients are reclassified).<sup>19-22</sup> In addition, separate and pooled analyses of the patients included in those studies have shown that the end results of 'FFR-based reclassification' in patients investigated at the time of diagnostic angiography is neutral overall for the number of patients indicated for revascularization.<sup>23</sup>

A patient-level and study-level meta-analysis of 9173 lesions demonstrated that with lesions with FFR <0.75, revascularization reduced the 1 year risk of major adverse cardiac events (MACE), including a reduction in the composite risk of death and MI.<sup>24</sup> Thus, the FFR threshold of 0.75 is used to define more severe ischaemia that is of prognostic relevance.

The presence of intermediate grade left main stem (LMS) disease is not infrequent and angiographic evaluation may be challenging. Assessment using pressure-derived FFR is more challenging in comparison with non-LMS stenosis due to the requirement for disengagement of the guiding catheter and an inability to administer intracoronary adenosine. Some observational data exist to support the use of FFR in order to decide if revascularization should be deferred or performed.<sup>25</sup> In the largest study, which included 230 patients with intermediate-grade LMS stenosis, only 23% showed an FFR <0.80. Treatment was deferred in patients with an FFR ≥0.80 and bypass surgery was done in patients with an FFR <0.80.<sup>26</sup> Clinical outcomes at 5 years were similar in both groups. However, it is important to consider the potential influence of any untreated downstream disease in the left anterior descending (LAD) or left circumflex arteries, which may be associated with an increased risk of a false negative FFR.<sup>27</sup>

The value of FFR to evaluate intermediate stenosis and guide selection of lesions for revascularization at the time of bypass surgery has been shown in an observational study.<sup>28</sup> Of the

627 patients with intermediate stenosis that were evaluated, 429 had bypass without FFR and 198 had bypass with FFR; in the latter group, the proportion of patients with three-vessel disease was reclassified from 94 to 86%. Outcomes were similar in both groups at 3 years [hazard ratio (HR) for death/MI/target vessel revascularization (TVR)=1.03, 95% CI 0.67-1.69], though the group with FFR guidance was associated with a lower number of graft anastomoses and a lower rate of on-pump surgery compared with angiography-guided CABG surgery.

### 3.2.1.2 Use of fractional flow reserve to identify lesions requiring revascularization in patients with multivessel coronary artery disease undergoing percutaneous coronary intervention

FFR may also be useful for the selection of lesions requiring revascularization in patients with multivessel CAD. The FAME trial showed that in patients with multivessel disease randomized to an FFR-guided PCI strategy (using a cut-off  $\leq 0.80$  to indicate requirement for PCI), outcomes at 12 months in terms of death, non-fatal MI, and repeat revascularization were superior compared with angiography-guided PCI and utilized fewer resources.<sup>29</sup> In addition, the 2 year composite risk of death or MI was significantly lower with the FFR-guided PCI strategy.<sup>30</sup> Long-term follow-up at 5 years showed broadly consistent findings, although differences between groups in relation to the primary endpoint were no longer significant.<sup>31</sup> This suggests that FFR-guided PCI should be the preferred management strategy in these patients.

### 3.2.1.3 Fractional flow reserve-guided management vs. medical therapy in patients with coronary artery disease

In patients with SCAD and at least one stenosis with FFR  $\leq 0.80$ , the FAME 2 trial showed that PCI using drug-eluting stent (DES) implantation improved the primary endpoint of death, non-fatal MI, or urgent revascularization within 2 years compared with medical treatment alone, which was driven by a lower need for urgent revascularization.<sup>32</sup> The advantage of FFR-guided PCI over medical therapy alone was maintained at 3 years.<sup>33</sup>

### 3.2.2 OTHER PRESSURE-DERIVED INDICES

FFR evaluation requires maximal and stable hyperaemia, which is usually obtained by the administration of intravenous (i.v.) adenosine. Recently, there has been renewed interest in resting indices derived from resting gradients alone [distal coronary to aortic pressure (Pd/Pa) or instantaneous wave-free ratio (iwFR)]. Two recent large-scale randomized trials showed broadly comparable results between FFR-guided and iwFR-guided revascularization strategies in patients with intermediate-grade stenosis.<sup>17,18</sup> Revascularization was indicated in both trials if FFR was  $\leq 0.80$  or if iwFR was  $\leq 0.89$ . In the DEFINE-FLAIR trial, the primary endpoint of MACE at 1 year occurred in 6.8% in patients randomized to iwFR-guided revascularization vs. 7.0% in patients randomized to FFR-guided revascularization ( $P < 0.001$  for non-inferiority; HR 0.95, 95% CI 0.68-1.33,  $P=0.78$ ).<sup>17</sup> In the iFR-SWEDEHEART trial, the primary endpoint of death from any cause, non-fatal MI, or unplanned revascularization was 6.7% in the iwFR group and 6.1% in the FFR group ( $P=0.007$  for non-inferiority; HR 1.12, 95% CI 0.79-1.58,  $P=0.53$ ).<sup>18</sup> In this trial, 17.5% of patients had

ACS at the time of presentation. There was no interaction with outcomes. Both trials are limited by having a follow-up duration of only 1 year.

The SYNTAX II study (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery), a single-arm, prospective study in patients with multivessel disease incorporating a management strategy including combined iwFR/FFR assessment of stenosis severity in addition to intravascular ultrasound (IVUS)-guided stent implantation and guideline-directed medical therapy, showed encouraging outcomes compared with a historical cohort enrolled in the SYNTAX trial.<sup>34</sup>

Randomized trials comparing iwFR-guided revascularization with angiography-guided revascularization or medical therapy are not available. iwFR has not been extensively validated for patients with LMS stenosis.

There is no adequate randomized controlled trial (RCT) data to support the use of whole-cardiac cycle Pd/Pa for the guidance of revascularization decisions.

### 3.2.3 USE OF FRACTIONAL FLOW RESERVE AND PRESSURE-DERIVED INDICES IN PATIENTS WITH SEVERE AORTIC STENOSIS

In patients with intermediate coronary stenosis and concomitant severe aortic stenosis, although some observational studies exist (see section 11), there are no adequate RCT data to support the use of FFR or iwFR for the guidance of revascularization decisions.

### 3.2.4 USE OF INTRAVASCULAR IMAGING FOR THE DIAGNOSTIC ASSESSMENT OF STENOSIS

IVUS is an ultrasound-based modality of intravascular imaging with an axial resolution of about 150  $\mu\text{m}$ . IVUS imaging allows real-time tomographic assessment of vessel size, lumen area, and plaque composition and volume. In comparison with optical coherence tomography (OCT), it has more limited spatial resolution, but better penetration depth and potential advantages in terms of vessel sizing. OCT is a light-based modality of intravascular imaging with higher axial resolution compared with IVUS (15 vs. 150  $\mu\text{m}$ ). The disadvantages of OCT imaging are that it requires complete blood clearance from the lumen for imaging and that it has more limited penetration, which can limit the assessment of complete plaque burden and may impair accurate vessel sizing.

Potential clinical uses of intravascular imaging for diagnostic assessment in patients being considered for myocardial revascularization are the evaluation of stenosis severity in lesions with intermediate-grade stenosis, evaluation of lesion morphology in lesions ambiguous with angiographic assessment, and the characterization of plaque composition. The majority of the existing data from clinical trials relate to the use of intravascular imaging guidance during PCI and are discussed in section 16. The use of intravascular imaging to evaluate patients with stent failure is discussed in section 13.

Regarding the assessment of intermediate-grade stenosis, a number of studies have evaluated the optimal cut-off of minimal lumen area for the identification of haemodynamically relevant lesions. One prospective registry showed overall moderate correlation of

minimal lumen area with FFR values, with cut-off values for detecting haemodynamically relevant stenosis (<2.4, <2.7, and <3.6 mm<sup>2</sup>) dependent on vessel size (reference vessel diameters <3.0, 3.0-3.5, and >3.5 mm, respectively).<sup>34a</sup> Generally, haemodynamic assessment with FFR should be preferred for this indication.

The presence of intermediate-grade LMS disease is not infrequent and angiographic assessment may be challenging. Assessment using IVUS evaluation of intermediate-grade LMS disease in patients being considered for bypass surgery or PCI is supported by data from a number of observational studies.<sup>35-38</sup> In a multicentre, prospective study, revascularization was mainly deferred if the minimal luminal area (MLA) was ≥6 mm<sup>2</sup> and performed in cases of an MLA <6 mm<sup>2</sup>.<sup>37</sup> After a 2 year follow-up, cardiac death-free survival was similar in both groups (98 and 95%, respectively). Another study suggested that deferral of intervention in 131 patients with an MLA ≥7.5 mm<sup>2</sup> showed favourable clinical outcomes.<sup>36</sup> In Asian patients with generally smaller heart sizes, studies have suggested that an IVUS MLA of 4.5-4.8 mm<sup>2</sup> may be the most appropriate.<sup>38</sup>

Recommendations on functional testing and intravascular imaging for lesion assessment		
Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
When evidence of ischaemia is not available, FFR or iwFR are recommended to assess the haemodynamic relevance of intermediate-grade stenosis. <sup>15,17,18,39</sup>	I	A
FFR-guided PCI should be considered in patients with multivessel disease undergoing PCI. <sup>29,31</sup>	Ila	B
IVUS should be considered to assess the severity of unprotected left main lesions. <sup>35-37</sup>	Ila	B

FFR: fractional flow reserve; iwFR: instantaneous wave-free ratio; IVUS: intravascular ultrasound; PCI: percutaneous coronary intervention.  
<sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

### 3.3 GAPS IN THE EVIDENCE

Further studies investigating the role of novel, combined, non-invasive anatomical and functional imaging are needed, such as randomized clinical trials with CT-FFR in patients with suspected and known CAD, as well as further clinical investigation of perfusion CT.

Randomized trials comparing iwFR-based management of patients with intermediate-grade stenosis compared with medical therapy are missing. Further study of whole-cardiac cycle Pd/Pa for the guidance of revascularization in the setting of randomized clinical trials is also required.

Further studies including randomized trials are needed to assess the value of functional vs. anatomical guidance for CABG.

## 4 Process for decision-making and patient information

### 4.1 PATIENT INFORMATION AND INFORMED CONSENT

Informed consent requires transparency, especially if there is debate over various treatment options. Active patient participation in the decision-making process should be encouraged. Patient information

needs to be unbiased, evidence-based, up-to-date, reliable, accessible, relevant, and consistent with legal requirements. Use of terminology that the patient understands is essential. Short-term procedure-related and long-term risks and benefits – such as survival, relief of angina, quality of life, the potential need for late reintervention, the need for prevention measures, and uncertainties associated with different treatment strategies – should be thoroughly discussed. Although current recommendations are mostly based on the ability of treatments to reduce adverse events including mortality, there is growing interest in patient-reported outcome measures.<sup>40,41</sup> Patients are not only interested to know how recommended treatment impacts on prognosis but also on their quality of life in the way they perceive it. A written evidence-based patient information document should be provided, potentially with decision aids.

Patients must have the time to reflect on the trade-offs imposed by the outcome estimates. In order to seek a second opinion or to discuss the findings and consequences with referring physicians, enough time should be allowed – up to several days, as required – between diagnostic catheterization and intervention. These recommendations pertain to patients in a stable condition, for whom various treatment options exist and who can make a decision without the constraints of an urgent or emergent situation (Table 3). The patient's right to decline the treatment option recommended by the Heart Team has to be respected. Patient refusal of a recommended treatment should be acknowledged in a written document after the patient has received the necessary information by the Heart Team members. In this case, the patient may be offered an alternative treatment option by the Heart Team.

The patient has the right to obtain information on the level of expertise of the operator, the workload of the centre, whether all treatment options – including surgery – are available on-site, and local results in the performance of percutaneous and surgical myocardial revascularization procedures. Patients considered for revascularization should also be clearly informed of the continuing need for medical therapy, as well as lifestyle modification and other secondary prevention strategies (see section 19).<sup>42</sup>

### 4.2 MULTIDISCIPLINARY DECISION-MAKING (HEART TEAM)

The Heart Team – comprising clinical or non-invasive cardiologists, cardiac surgeons, and interventional cardiologists, as well as anaesthetists and other specialists if deemed necessary – should provide a balanced, multidisciplinary decision-making process.<sup>43</sup> Additional input may be needed from other specialties involved in the care of the patient. The Heart Team should meet on a regular basis to analyse and interpret the available diagnostic evidence, determine the need for myocardial revascularization, and assess the relative short- and long-term safety and effectiveness of the percutaneous and surgical options. *Ad hoc* meetings of the Heart Team should facilitate and support efficient clinical workflows.

The need for an interdisciplinary approach is underlined by reports on (i) the underuse of revascularization procedures in 18-40% of patients with CAD<sup>44</sup> and (ii) inappropriate use of revascularization strategies with a lack of case discussions.<sup>45</sup>

The marked variability in PCI-to-CABG ratios between European countries (ranging from 2.4-7.6 in 2013, for example) has raised concerns regarding the appropriate selection of revascularization strategies.<sup>46</sup> Rates for the inappropriate use of PCI (10-15%)<sup>43,47,48</sup> and CABG (1-2%) are reported. Multidisciplinary decision-making in a Heart Team can minimize specialty bias and prevent self-referral from interfering with optimal patient care.<sup>49</sup>

Several reports from different centres have established that the treatment recommendations made in multidisciplinary Heart Team discussions are reproducible and implemented in the vast majority of cases (93-95%).<sup>50,51</sup>

Interdisciplinary institutional protocols should be developed for common case scenarios to avoid the need for systematic case-by-case review of all diagnostic angiograms. However, complex cases – defined by the protocols – should be discussed individually. In these cases, revascularization should not be performed at the time of diagnostic angiography, to allow sufficient time to assess all available information and clearly explain and discuss the findings with the patient. The rationale for a decision and consensus on the optimal revascularization treatment should be documented on the patient's chart. In institutions without an on-site cardiac surgery unit, collaboration with an external cardiac surgery unit is required to design protocols that define when Heart Team discussion is needed.

### 4.3 TIMING OF REVASCULARIZATION

Patients requiring myocardial revascularization may be at increased risk of adverse events during the waiting period.<sup>52</sup> A recent meta-analysis of observational studies calculated that a waiting period of 3 months for surgical myocardial revascularization may be associated with the risk of 1 death among 80 patients.<sup>53</sup> **Table 3** shows the preferred timing of revascularization depending on the clinical presentation and the extent and localization of CAD.<sup>54</sup> Sections 7 and 8 show additional and more specific information in this regard for patients with ACS.

*Ad hoc* PCI is defined as a therapeutic intervention performed within the same procedure as the diagnostic coronary angiography. *Ad hoc* PCI is convenient, often cost-effective and safe, and is associated with fewer access site complications and lower radiation exposure.<sup>55,56</sup> However, in the USA, up to 30% of patients undergoing *ad hoc* PCI are potential candidates for CABG.<sup>56</sup> This number may be lower in Europe.<sup>45</sup> Although it is not advisable for *ad hoc* PCI to represent the default approach for complex SCAD, it may be justified if a full diagnostic work-up, including functional testing, is available and the patient is adequately informed on both percutaneous and surgical myocardial revascularization options (see section 4.1). Institutional protocols developed by the Heart Team in accordance with current Guidelines should define specific anatomical criteria and clinical subsets that may be – or

**Table 3. Multidisciplinary decision pathways, patient informed consent, and timing of revascularization.**

	ACS			SCAD without <i>ad hoc</i> PCI indication according to Heart Team protocol	SCAD with <i>ad hoc</i> PCI indication according to Heart Team protocol
	Shock	STEMI	NSTE-ACS		
Multidisciplinary decision-making	Not mandatory during the acute phase; mechanical circulatory support according to Heart Team protocol	Not mandatory during the acute phase	Not mandatory during the acute phase; after stabilization, recommended as in SCAD	Required	Not required
Informed consent	Witnessed verbal informed consent or family consent if possible without delay	Witnessed verbal informed consent may be sufficient unless written consent is legally required	Written informed consent <sup>a</sup> ; in emergency cases witnessed verbal informed consent may be sufficient	Written informed consent <sup>a</sup>	Written informed consent <sup>a</sup>
Time to revascularization	Emergency: no delay	Emergency: no delay	Urgency: within 2 h to within 72 h depending on the risk criteria	Within 2 weeks for high-risk patients <sup>b</sup> and within 6 weeks for all other patients	<i>Ad hoc</i>
Procedure	Proceed with intervention based on best evidence/availability. <i>Ad hoc</i> treatment of culprit lesion, staged treatment of non-culprit lesions according to institutional protocol or Heart Team decision.	Proceed with intervention based on best evidence/availability. Non-culprit lesions treated according to institutional protocol or Heart Team decision.	Proceed with intervention based on best evidence/availability. Non-culprit lesions treated according to institutional protocol or Heart Team decision.	Allow for enough time from diagnostic catheterization to decide on the appropriate intervention.	Proceed with intervention according to institutional protocol defined by Heart Team.

ACS: acute coronary syndromes; CCS: Canadian Cardiovascular Society; ESC: European Society of Cardiology; EACTS: European Association for Cardio-Thoracic Surgery; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; PCI: percutaneous coronary intervention; SCAD: stable coronary artery disease; STEMI: ST-segment elevation myocardial infarction. <sup>a</sup>This may not apply to countries that are not legally required to ask for written informed consent. The ESC and EACTS advocate the documentation of patient consent for all revascularization procedures. <sup>b</sup>Severe symptoms (CCS class 3), anatomy (left main disease or equivalent, three-vessel disease or proximal left anterior descending artery), or depressed ventricular function

**Recommendations for decision-making and patient information in the elective setting**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that patients undergoing coronary angiography are informed about benefits and risks, as well as potential therapeutic consequences, ahead of the procedure.	I	C
It is recommended that patients are adequately informed about short- and long-term benefits and risks of the revascularization procedure with information about local experience, and allowed enough time for informed decision-making.	I	C
It is recommended that institutional protocols are developed by the Heart Team to implement the appropriate revascularization strategy in accordance with current Guidelines.	I	C
In PCI centres without on-site surgery, it is recommended that institutional protocols are established with partner institutions providing cardiac surgery.	I	C

PCI: percutaneous coronary intervention. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

should not be – treated *ad hoc*. Stable patients with complex CAD, as reflected by a high SYNTAX score, should in general be discussed by the Heart Team and not be treated *ad hoc*.

## 5 Revascularization for stable coronary artery disease

### 5.1 RATIONALE FOR REVASCULARIZATION

The indications for revascularization in patients with SCAD who receive guideline-recommended medical treatment are the persistence of symptoms despite medical treatment and/or the improvement of prognosis.<sup>1</sup>

Several studies have shown that myocardial revascularization by PCI or CABG more effectively relieves angina, reduces the use of anti-anginal drugs, and improves exercise capacity and quality of life compared with a strategy of medical therapy alone during short- and long-term follow-up (**Supplementary Table 1**).<sup>32,33,57-62</sup> Recently, the ORBITA (Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina) trial randomly compared PCI with placebo (sham procedure) in patients with SCAD due to single-vessel CAD (diameter stenosis >70%) and preserved LV function in the presence of moderate symptoms of angina [Canadian Cardiovascular Society (CCS) class II in 59% of patients, duration 9 months] for the first time.<sup>63</sup> After 6 weeks of medication optimization (mean number of anti-anginal drugs: 3) and baseline cardiopulmonary exercise testing, 200 patients were randomized (105 PCI and 95 placebo). Following a 6-week post-randomization period, the primary endpoint of increment in exercise time was not significantly different, but estimates were imprecise (PCI minus placebo 16.6 sec, 95% CI –8.9 to 42.0, P=0.20). The dobutamine stress echocardiography peak stress wall motion score index improved with PCI (–0.09, 95% CI –0.15 to –0.04, P=0.001). ORBITA raises the issue of whether the symptom relief of PCI in the specific setting of stable single-vessel CAD may be related at least in part to a placebo effect. Limitations of the study, as acknowledged by the investigators and outlined elsewhere, include the short observation period (6 weeks), the inclusion of patients with mild symptoms pre-randomization (CCS class 0-I in 25% of patients), the group imbalance in ostial and proximal lesions (37 vs. 57%, P=0.005), loss to follow-up after randomization, and the insufficient power to detect a true difference.<sup>64</sup> This precludes definite conclusions at this stage. Nevertheless, the ORBITA study underlines the value of optimal medical therapy in the management of SCAD.

Three year follow-up of the FAME 2 study indicated yearly and sustained improvement of angina (10.2 vs. 28.5% at 1 month and 5.2 vs. 9.7% at 3 years) in favour of FFR-guided PCI, despite considerable crossover in the medical therapy arm.<sup>33</sup> Among patients with multivessel disease, the assessment of frequency of angina and quality of life measures in the SYNTAX, FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus), and EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trials consistently showed early and sustained improvement for both PCI and CABG during long-term follow-up.<sup>65-67</sup>

### 5.2 EVIDENCE BASIS FOR REVASCULARIZATION

The indications for revascularization in patients with stable angina or silent ischaemia are summarized in the recommendation table.

#### 5.2.1 REVASCULARIZATION WITH THE USE OF PERCUTANEOUS CORONARY INTERVENTION

Several meta-analyses comparing a strategy of PCI with initial medical therapy among patients with SCAD found no or only modest benefits in terms of survival or MI for an invasive strategy, taking into account the fact that up to 40% of patients crossed over after to revascularization during longer-term follow-up.<sup>91,98,99</sup> A network meta-analysis of 100 trials with 93 553 patients and 262 090 patient-years of follow-up comparing a strategy of initial medical therapy with revascularization reported improved survival using PCI with new-generation DES (everolimus: rate ratio 0.75, 95% CI 0.59-0.96; zotarolimus: rate ratio 0.65, 95% CI 0.42-1.00) compared with initial medical treatment.<sup>100</sup>

In the FAME 2 trial,<sup>32</sup> patients with SCAD and at least one functionally significant stenosis (invasive FFR ≤0.80) were randomly assigned to medical therapy or medical therapy plus FFR-guided PCI using new-generation DES. The 3 year report of the FAME 2 trial reported a lower incidence of the primary composite endpoints of death, MI, and urgent revascularization (10.1 vs. 22.0%; P<0.001), driven by a lower incidence of urgent revascularization in the PCI group (4.3 vs. 17.2%; P<0.001) and without significant differences in the rates of death and MI.<sup>33</sup> At 2 years of follow-up, the rate of death or MI was lower in the PCI than the medical therapy group (4.6 vs. 8.0%; HR 0.56, 95% CI 0.32-0.97, P=0.04) in a landmark analysis between 8 days and 2 years of follow-up, whereas event rates were higher during days 0-7 due to periprocedural MI (for overview of studies see **Supplementary Table 2**).<sup>97</sup>

**Indications for revascularization in patients with stable angina or silent ischaemia**

Extent of CAD (anatomical and/or functional)		Class <sup>a</sup>	Level <sup>b</sup>
For prognosis	Left main disease with stenosis >50%. <sup>c</sup> 68-71	I	A
	Proximal LAD stenosis >50%. <sup>c</sup> 62,68,70,72	I	A
	Two- or three-vessel disease with stenosis >50% with impaired LV function (LVEF ≤ 35%). <sup>c</sup> 61,62,68,70,73-83	I	A
	Large area of ischaemia detected by functional testing (>10% LV) or abnormal invasive FFR. <sup>d</sup> 24,59,84-90	I	B
	Single remaining patent coronary artery with stenosis >50%. <sup>c</sup>	I	C
For symptoms	Haemodynamically significant coronary stenosis in the presence of limiting angina or angina equivalent, with insufficient response to optimized medical therapy. <sup>e</sup> 24,63,91-97	I	A

CAD: coronary artery disease; FFR: fractional flow reserve; iwFR: instantaneous wave-free ratio; LAD: left anterior descending coronary artery; LV: left ventricular; LVEF: left ventricular ejection fraction. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence. <sup>c</sup>With documented ischaemia or a haemodynamically relevant lesion defined by FFR ≤0.80 or iwFR ≤0.89 (see section 3.2.1.1), or >90% stenosis in a major coronary vessel. <sup>d</sup>Based on FFR <0.75 indicating a prognostically relevant lesion (see section 3.2.1.1). <sup>e</sup>In consideration of patient compliance and wishes in relation to the intensity of anti-anginal therapy.

**5.2.2 REVASCULARIZATION WITH THE USE OF CORONARY ARTERY BYPASS GRAFTING**

The superiority of CABG over a strategy of initial medical therapy was established in a meta-analysis of seven RCTs<sup>68</sup> more than two decades ago, demonstrating a survival benefit of CABG in patients with SCAD and left main (LM) or three-vessel disease, particularly when the proximal LAD coronary artery was involved, and has been corroborated in more recent studies.<sup>100,101</sup> A network meta-analysis of 100 trials with 93 553 patients comparing a strategy of initial medical therapy with revascularization reported improved survival (RR 0.80, 95% CI 0.63-0.99) and a reduced risk of MI (RR 0.79, 95% CI 0.83-0.99) among patients undergoing CABG compared with initial medical treatment.<sup>100</sup>

In the STICH trial, 1212 patients with CAD and an LV ejection fraction (LVEF) ≤35% were randomized to initial medical therapy or CABG. The extended 10 year follow-up of the STICH trial

reported a significant reduction in all-cause (59 vs. 66%; HR 0.84, 95% CI 0.73-0.97; P=0.02) and cardiovascular mortality (41 vs. 49%; HR 0.79, 95% CI 0.66-0.93; P=0.006).<sup>81</sup> For an overview of studies, see **Supplementary Table 2**.

**5.3 PERCUTANEOUS CORONARY INTERVENTION VS. CORONARY ARTERY BYPASS GRAFTING**

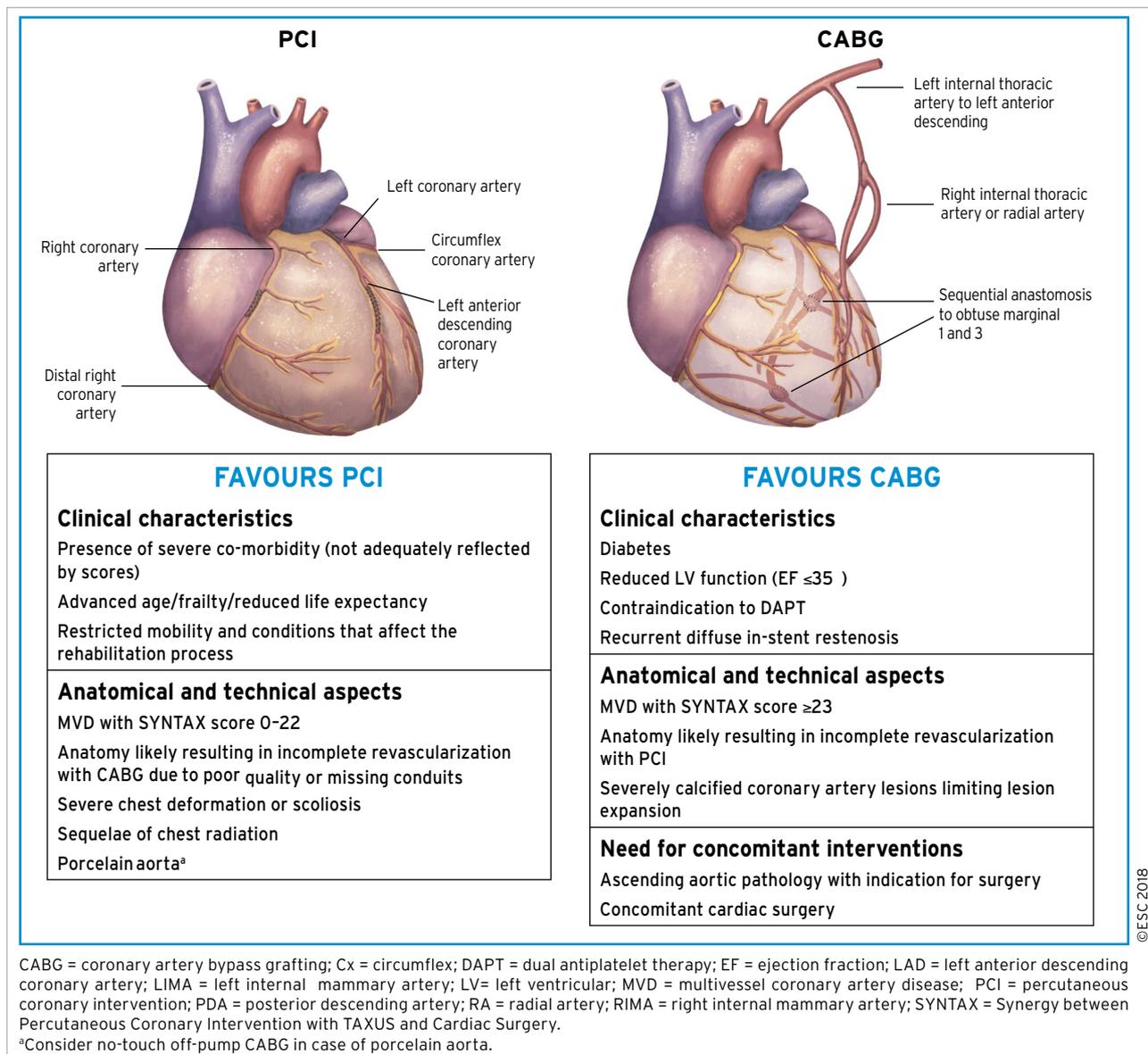
The recommendations for the type of revascularization (CABG or PCI) in patients with SCAD with suitable coronary anatomy for both procedures and low predicted surgical mortality are summarized below. The Heart Team should take into consideration the individual cardiac and extracardiac characteristics, in addition to patient preference, in the overall decision-making process (**Figure 3**). A summary of trials comparing the outcomes of patients treated with angioplasty vs. CABG and bare-metal stent (BMS) vs. CABG is shown in **Supplementary Table 3**, and of studies comparing DES and CABG in **Table 4**.

**Table 4. Randomized clinical trials comparing percutaneous coronary intervention with drug-eluting stents vs. surgical revascularization.**

Stent type and year of publication	Study	N	Baseline characteristics					Primary endpoint <sup>a</sup>			Secondary endpoints <sup>a</sup>				
			Age (y)	Women (%)	Diabetes (%)	MV disease (%)	EF (%)	Definition	Y	Results	Y	Death	MI	Revasc	Stroke
<b>DES</b>															
PES 2009	SYNTAX <sup>102</sup>	1800	65	22	25	MV 61 LM 39	–	Death, MI, stroke, or repeat revasc	1	17.8 vs. 12.4%	5	13.9 vs. 11.4%	9.7 vs. 3.8%*	25.9 vs. 13.7%*	2.4 vs. 3.7%
SES 2011	Boudriot <sup>103</sup>	201	68	25	36	LM 100	65	Death, MI, or repeat revasc	1	13.9 vs. 19%	1	2 vs. 5%	3 vs. 3%	14 vs. 5.9%	–
SES 2011	PRECOMBAT <sup>104</sup>	600	62	24	32	LM 100	61	Death, MI, stroke, or TVR	1	8.7 vs. 6.7% <sup>b</sup>	2	2.4 vs. 3.4%	1.7 vs. 1.0%	9.0 vs. 4.2%*	0.4 vs. 0.7%
EES 2015	BEST <sup>105</sup>	880	64	29	41	MV 100	60	Death, MI, or TVR	2	11.0 vs. 7.9%	5	6.6 vs. 5.0%	4.8 vs. 2.7%	13.4 vs. 6.6%	2.9 vs. 3.3%
BES 2016	NOBLE <sup>106</sup>	1201	66	22	15	LM 100	60	Death, MI, or TVR	5	15.4 vs. 7.2%	5	11.6 vs. 9.5%	6.9 vs. 1.9%* <sup>c</sup>	16.2 vs. 10.4%*	4.9 vs. 1.7%
EES 2016	EXCEL <sup>107</sup>	1905	66	24	30	LM 100	57	Death, MI, or stroke	3	15.4 vs. 14.7% <sup>b</sup>	3	8.2 vs. 5.9%	8.0 vs. 8.3%	13.4 vs. 6.6%*	2.3 vs. 2.9%

Age and EF are reported as means. \*P<0.05. BES: biolimus-eluting stents; BEST: Randomised Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease; DES: drug-eluting stents; EES: everolimus-eluting stent; EF: ejection fraction; EXCEL: Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; LM: left main coronary artery disease; MI: myocardial infarction; MV: multivessel coronary artery disease; NOBLE: Nordic-Baltic-British Left Main Revascularization Study; PES: paclitaxel-eluting stents; PRECOMBAT: Premier of Randomised Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; Revasc: revascularization; SES: sirolimus-eluting stents; SYNTAX: Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TVR: target vessel revascularization; Y: years. <sup>a</sup>Results are reported as percutaneous coronary intervention vs. coronary artery bypass grafting.

<sup>b</sup>Non-inferiority met. <sup>c</sup>Non-procedural MI (exclusion of periprocedural MI)



**Figure 3.** Aspects to be considered by the Heart Team for decision-making between percutaneous coronary intervention and coronary artery bypass grafting among patients with stable multivessel and/or left main coronary artery disease.

### 5.3.1 CRITERIA FOR DECISION-MAKING

Predicted surgical mortality, the anatomical complexity of CAD, and the anticipated completeness of revascularization are important criteria for decision-making with respect to the type of revascularization (CABG or PCI). Whether conservative therapy, PCI, or CABG is preferred should depend on the risk-benefit ratios of these treatment strategies, weighing up the risks of periprocedural complications (e.g. cerebrovascular events, blood transfusions, renal failure, new onset arrhythmias, or wound infections) against improvements in health-related quality of life, as well as long-term freedom from death, MI, or repeat revascularization.

#### 5.3.1.1 Predicted surgical mortality

To assess the predicted surgical mortality, the European System for Cardiac Operative Risk Evaluation (EuroSCORE II)

([www.euroscore.org/calc.html](http://www.euroscore.org/calc.html)) and the Society of Thoracic Surgeons (STS) score (<http://riskcalc.sts.org>) were both developed based on clinical variables to estimate the operative in-hospital or 30 day mortality risk<sup>108-110</sup> (**Supplementary Table 4**). Both scores have demonstrated their value in specific cohorts of patients undergoing CABG.<sup>111</sup> Calibration of the STS score is updated on a regular basis. It has been suggested that the STS score outperforms the EuroSCORE II when compared directly in a cohort of CABG patients,<sup>112</sup> although other studies have found comparable performance of both models.<sup>113,114</sup>

There are no established cut-offs for low predicted surgical mortality based on the EuroSCORE II or STS score. Thus, individualized treatment decisions are needed. These decisions should respect the range of predicted surgical risks in the major RCTs

that inform the choice of revascularization modality (Table 5). In these studies, the predicted surgical risk was assessed by the logistic EuroSCORE. Compared with the more recent EuroSCORE II, the logistic EuroSCORE has similar discrimination but poorer calibration and, thus, overestimates surgical mortality by roughly two-fold.<sup>115</sup>

**Table 5. Logistic EuroSCOREs in major randomized trials comparing percutaneous coronary intervention with coronary artery bypass grafting.**

Trial	EuroSCORE PCI	EuroSCORE CABG
SYNTAX	3.8±2.6	3.8±2.7
BEST	2.9±2.0	3.0±2.1
FREEDOM	2.7±2.4	2.8±2.5
PRECOMBAT	2.7±1.8	2.8±1.9
EXCEL	Not reported	Not reported
NOBLE	2 (2-4)	2 (2-4)

Numbers are presented as mean±SD or median (interquartile range). BEST: Randomised Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease; CABG: coronary artery bypass grafting; EuroSCORE: European System for Cardiac Operative Risk Evaluation; EXCEL : Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; NOBLE: Nordic-Baltic-British Left Main Revascularization Study; PCI: percutaneous coronary intervention; PRECOMBAT: Premier of Randomised Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; SYNTAX: Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery

Despite the usefulness of these scores, there is not a single risk model that provides perfect risk assessment because the scores are limited by (i) the specific definitions used or the methodology applied, (ii) the absence of important variables such as frailty, (iii) the practicability of calculation, (iv) a failure to reflect all relevant mortality and morbidity endpoints, and (v) limited external validation. Decision-making should not be solely dependent on risk scores. These scores should be used as a guide within the multi-disciplinary Heart Team discussion.

To combine clinical and anatomical risk estimation, the SYNTAX II score was retrospectively derived from the SYNTAX cohort<sup>127</sup> and subsequently externally validated.<sup>120,128,129</sup> Nevertheless, compared with the SYNTAX score, its value in assigning patients to PCI or CABG is less well investigated. The fact that the SYNTAX II score failed to predict the outcome of the EXCEL trial raises additional concern.<sup>130</sup>

### 5.3.1.2 Anatomical complexity of coronary artery disease

The SYNTAX score (<http://www.syntaxscore.com>) was prospectively developed for the SYNTAX trial to grade the anatomical complexity of coronary lesions in patients with LM or three-vessel disease (Table 6 and Supplementary Table 4).<sup>116</sup> In the cohort of the SYNTAX trial, and subsequently in external validation cohorts, the SYNTAX score was found to be an independent predictor of long-term major adverse cardiac and cerebrovascular

events (MACCE) and of death in patients treated with PCI but not CABG.<sup>117-120</sup>

In the SYNTAX trial, tertiles of SYNTAX score with low, intermediate, and high anatomical complexity stratified patients into those who had similar outcomes with both PCI and CABG and those who derived significant benefit from CABG.<sup>121-123</sup> In subsequent RCTs, the interaction of the strata of SYNTAX score with the effect of the randomized treatment was less pronounced and did not reach statistical significance.<sup>105-107</sup> However, in a recent collaborative individual patient pooled analysis of randomized trials including 11 518 patients,<sup>124</sup> the test for trend across the ordered tertiles of the SYNTAX score of the SYNTAX study was positive at  $P=0.0011$  (unpublished analysis), confirming the strata of the SYNTAX score as an effect modifier to be considered. There is concern about bias and inter-individual variability in calculating the SYNTAX score.<sup>125</sup> This should be minimized by adequate training.

### 5.3.1.3 Completeness of revascularization

The aim of myocardial revascularization is to minimize residual ischaemia. In support of this concept, the nuclear substudy of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial demonstrated an incremental benefit in reducing the risk of death and MI by reducing residual stress-induced ischaemia from >10% of the myocardium to ≤5%.<sup>86</sup>

In the SYNTAX trial, anatomical complete revascularization was defined as PCI or bypass of all epicardial vessels with a diameter exceeding ≥1.5 mm and a luminal reduction of ≥50% in at least one angiographic view.<sup>131</sup> A meta-analysis of 89 883 patients enrolled in RCTs and observational studies revealed a lower long-term mortality (RR 0.71, 95% CI 0.65-0.77,  $P<0.001$ ), MI (RR 0.78, 95% CI 0.68-0.90;  $P=0.001$ ), and repeat myocardial revascularization (RR 0.74, 95% CI 0.65-0.83;  $P<0.001$ ) by complete revascularization (based on anatomical definition in 87% of the patients) as compared with incomplete revascularization.<sup>132</sup> The benefit of complete revascularization was independent of the treatment modality. A more recent meta-analysis suggested enhanced benefit when complete revascularization is performed with state-of-the-art techniques in high-risk patients.<sup>133</sup> Likewise, in a *post hoc* analysis of the SYNTAX trial, anatomical incomplete revascularization was associated with inferior long-term outcomes after both CABG and PCI.<sup>131</sup> A residual SYNTAX score >8 after PCI was associated with significant increases in the 5-year risk of death and of the composite of death, MI, and stroke, and any residual SYNTAX score >0 was associated with the risk of repeat intervention.<sup>134</sup> In an observational study from the New York State registry that compared CABG with PCI using new-generation DES [everolimus-eluting stent (EES)] in 9 223 pairs of propensity-matched patients with multivessel CAD, the significantly higher risk of MI associated with PCI as compared with CABG was not seen among matched pairs of patients in which the PCI group had complete revascularization ( $P_{interaction}=0.02$ ).<sup>135</sup> Consistent findings were obtained in a pooled analysis of 3212 patients of the SYNTAX, BEST (Randomised Comparison of Coronary Artery Bypass Surgery

### Recommendations on criteria for the choice between coronary artery bypass grafting and percutaneous coronary intervention

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Assessment of surgical risk<sup>c</sup></b>		
It is recommended that the STS score is calculated to assess in-hospital or 30 day mortality, and in-hospital morbidity after CABG. <sup>112,114,138</sup>	I	B
Calculation of the EuroSCORE II score may be considered to assess in-hospital mortality after CABG. <sup>112</sup>	IIb	B
<b>Assessment of CAD complexity</b>		
In patients with LM or multivessel disease, it is recommended that the SYNTAX score is calculated to assess the anatomical complexity of CAD and the long-term risk of mortality and morbidity after PCI. <sup>117-124</sup>	I	B
When considering the decision between CABG and PCI, completeness of revascularization should be prioritized. <sup>131,132,134-136</sup>	IIa	B

EuroSCORE: European System for Cardiac Operative Risk Evaluation; CABG: coronary artery bypass grafting; CAD: coronary artery disease; LM: left main; PCI: percutaneous coronary intervention; STS: Society of Thoracic Surgeons; SYNTAX: Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence. <sup>c</sup>Level of evidence refers to prediction of outcomes.

### Recommendation for the type of revascularization in patients with stable coronary artery disease with suitable coronary anatomy for both procedures and low predicted surgical mortality<sup>d</sup>

Recommendations according to extent of CAD	CABG		PCI	
	Class <sup>a</sup>	Level <sup>b</sup>	Class <sup>a</sup>	Level <sup>b</sup>
<b>One-vessel CAD</b>				
Without proximal LAD stenosis.	IIb	C	I	C
With proximal LAD stenosis. <sup>68,101,139-144</sup>	I	A	I	A
<b>Two-vessel CAD</b>				
Without proximal LAD stenosis.	IIb	C	I	C
With proximal LAD stenosis. <sup>68,70,73</sup>	I	B	I	C
<b>Left main CAD</b>				
Left main disease with low SYNTAX score (0 - 22). <sup>69,121,122,124,145-148</sup>	I	A	I	A
Left main disease with intermediate SYNTAX score (23 - 32). <sup>69,121,122,124,145-148</sup>	I	A	IIa	A
Left main disease with high SYNTAX score (≥33). <sup>c 69,121,122,124,146-148</sup>	I	A	III	B
<b>Three-vessel CAD without diabetes mellitus</b>				
Three-vessel disease with low SYNTAX score (0 - 22). <sup>102,105,121,123,124,135,149</sup>	I	A	I	A
Three-vessel disease with intermediate or high SYNTAX score (>22). <sup>c 102,105,121,123,124,135,149</sup>	I	A	III	A
<b>Three-vessel CAD with diabetes mellitus</b>				
Three-vessel disease with low SYNTAX score 0-22. <sup>102,105,121,123,124,135,150-157</sup>	I	A	IIb	A
Three-vessel disease with intermediate or high SYNTAX score (>22). <sup>c 102,105,121,123,124,135,150-157</sup>	I	A	III	A

SYNTAX score calculation information is available at <http://www.syntaxscore.com>. CABG: coronary artery bypass grafting; CAD: coronary artery disease; LAD: left anterior descending coronary artery; PCI: percutaneous coronary intervention; SYNTAX: Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence. <sup>c</sup>PCI should be considered if the Heart Team is concerned about the surgical risk or if the patient refuses CABG after adequate counselling by the Heart Team. <sup>d</sup>For example, absence of previous cardiac surgery, severe morbidities, frailty, or immobility precluding CABG (also see Table 5).

and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease), and PRECOMBAT (Premier of Randomised Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) trials.<sup>136</sup> A mean SYNTAX score of 27 and an LVEF of 59% were obtained. In a propensity-matched analysis, mortality and the composite risk of death, MI, and stroke were significantly lower after PCI with complete vs. incomplete revascularization. After PCI with complete revascularization, the risk of death or of the composite of death, MI, or stroke was not significantly different from that after CABG with complete revascularization (adjusted HR 1.16, 95% CI 0.83-1.63, P=0.39, and 1.14, 95% CI 0.87-1.48, P=0.35, respectively), whereas these risks were significantly elevated after PCI with incomplete revascularization.

Functional complete revascularization is achieved when all lesions causing resting or stress-induced ischaemia are bypassed or treated by PCI. Given the limitations of non-invasive imaging techniques (see section 3), these lesions are best identified by FFR or iwFR during diagnostic angiography. For PCI, the FAME study demonstrated that the more restrictive selection of target lesions by functional guidance conferred superior long-term outcomes compared with anatomically guided lesion selection (see section 3).<sup>31</sup> In contrast, leaving functionally relevant lesions untreated resulted in a high rate of reinterventions in the FAME 2 study.<sup>33</sup> Based on the data of the FAME and FAME 2 studies, complete revascularization based on the functional definition is the preferred strategy for PCI.

The role of functional guidance for CABG is less clear.<sup>28,137</sup> One of the potential benefits of CABG is protection against

**Table 6. Guide for calculating the SYNTAX score.**

Steps	Variable assessed	Description
Step 1	Dominance	The weight of individual coronary segments varies according to coronary artery dominance (right or left). Co-dominance does not exist as an option in the SYNTAX score.
Step 2	Coronary segment	The diseased coronary segment directly affects the score as each coronary segment is assigned a weight depending on its location, ranging from 0.5 (i.e. the posterolateral branch) to 6 (i.e. left main in case of left dominance). <div data-bbox="493 385 1332 1095" style="text-align: center;"> <p><b>Right dominance</b></p> <p><b>Left dominance</b></p> <p><b>Weighting Factor</b></p> <ul style="list-style-type: none"> <li><span style="color: red;">■</span> +6</li> <li><span style="color: yellow;">■</span> +5</li> <li><span style="color: cyan;">■</span> +3.5</li> <li><span style="color: green;">■</span> +2.5</li> <li><span style="color: magenta;">■</span> +1.5</li> <li><span style="color: blue;">■</span> +1</li> <li><span style="color: grey;">■</span> +0.5</li> </ul> <p>©ESC 2018</p> </div>
Step 3	Diameter stenosis	The score of each diseased coronary segment is multiplied by two in case of a stenosis 50-99% and by five in case of total occlusion. In case of total occlusion, additional points will be added as follows: <ul style="list-style-type: none"> <li>– Age &gt;3 months or unknown +1</li> <li>– Blunt stump +1</li> <li>– Bridging +1</li> <li>– First segment visible distally +1 per non-visible segment</li> <li>– Side branch at the occlusion +1 if &lt;1.5 mm diameter +1 if both &lt;1.5 mm and ≥1.5 mm diameter +0 if ≥1.5 mm diameter (i.e. bifurcation lesion)</li> </ul>
Step 4	Trifurcation lesion	The presence of a trifurcation lesion adds additional points based on the number of diseased segments: <ul style="list-style-type: none"> <li>– 1 segment +3</li> <li>– 2 segments +4</li> <li>– 3 segments +5</li> <li>– 4 segments +6</li> </ul>
Step 5	Bifurcation lesion	The presence of a bifurcation lesion adds additional points based on the type of bifurcation according to the Medina classification:126 <ul style="list-style-type: none"> <li>– Medina 1,0,0-0,1,0-1,1,0 +1</li> <li>– Medina 1,1,1-0,0,1-1,0,1-0,1,1 +2</li> </ul> Moreover, the presence of a bifurcation angle <70° adds one additional point
Step 6	Aorto-ostial lesion	The presence of aorto-ostial lesion segments adds one additional point
Step 7	Severe tortuosity	The presence of severe tortuosity proximal of the diseased segment adds two additional points
Step 8	Lesion length	Lesion length >20 mm adds one additional point
Step 9	Calcification	The presence of heavy calcification adds two additional points
Step 10	Thrombus	The presence of thrombus adds one additional point
Step 11	Diffuse disease/ small vessels	The presence of diffusely diseased and narrowed segments distal to the lesion (i.e. when at least 75% of the length of the segment distal to the lesion has a vessel diameter <2 mm) adds one point per segment number

SYNTAX: Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery

disease progression in proximal segments, which may be diminished by restricting the bypass targets to functionally relevant lesions. This has to be weighed against the risk of bypass closure when native vessel flow is high. Thus, for ambiguous lesions, functional testing may also help guide the surgical revascularization strategy.

### 5.3.2 ISOLATED PROXIMAL LEFT ANTERIOR DESCENDING CORONARY ARTERY DISEASE

Comparing CABG and PCI among patients with isolated proximal LAD disease, the available evidence suggests similar outcomes in terms of death, MI, and stroke, but a higher risk of repeat revascularization with PCI.<sup>68,70,73,101,139-144</sup>

### 5.3.3 LEFT MAIN CORONARY ARTERY DISEASE

The available evidence from RCTs and meta-analyses comparing CABG with PCI using DES among patients with LM disease suggests equivalent results for the safety composite of death, MI, and stroke up to 5 years of follow-up.<sup>148</sup> A significant interaction with time is notable, providing early benefit for PCI in terms of MI and peri-interventional stroke, which is subsequently offset by a higher risk of spontaneous MI during long-term follow-up. The need for repeat revascularization is higher with PCI than with CABG.

The EXCEL trial compared CABG with PCI using new-generation DES (EES) among 1905 patients with significant LM disease.<sup>107</sup> At 3 years of follow-up, the primary endpoint of death, stroke, or MI occurred with similar frequency in the CABG and PCI group (14.7 vs. 15.4%; HR 1.00, 95% CI 0.79-1.26,  $P=0.98$ ). The pre-planned landmark analysis from 30 days to 3 years showed a significant difference for the primary endpoint in favour of CABG (7.9 vs. 11.5%,  $P=0.02$ ).

The NOBLE (Nordic-Baltic-British Left Main Revascularization Study) trial compared CABG with PCI using new-generation DES [biolimus-eluting stents (BES)] among 1201 patients with significant LM disease (mean SYNTAX score of 23).<sup>106</sup> At a median follow-up of 3.1 years, the primary endpoint of death, non-procedural MI, stroke, and repeat revascularization occurred more frequently in the PCI than the CABG group (29 vs. 19%; HR 1.48, 95% CI 1.11-1.96,  $P=0.007$ ).

A recent collaborative individual patient pooled analysis of randomized trials including 11 518 patients reviewed the currently available evidence from randomized trials comparing CABG with PCI for LM or multivessel disease.<sup>124</sup> The primary outcome was all-cause mortality. In the overall cohort, CABG was associated with a significant survival benefit during a mean follow-up of  $3.8\pm 1.4$  years (5 year all-cause mortality 11.2% after PCI vs. 9.2% after CABG; HR 1.20, 95% CI 1.06-1.37,  $P=0.0038$ ). There was a linear trend for HRs of death increasing with increasing SYNTAX tertiles [ $P=0.0011$  for trend (unpublished analysis)]. However, among 4478 patients with LM disease, those randomly assigned to CABG or PCI with a mean follow-up of  $3.4\pm 1.4$  years reported similar risks for the primary outcome all-cause mortality (PCI 10.7 vs. CABG 10.5%; HR 1.07, 95% CI 0.87-1.33,  $P=0.52$ ) at 5 years. There were no

significant differences in mortality between PCI and CABG in subgroup analyses according to SYNTAX scores. Nevertheless, in patients with a high SYNTAX score, a trend towards better survival was noted with CABG. The proportion of patients with a high SYNTAX score was limited in view of the inclusion criteria of the respective studies.

Current evidence indicates that PCI is an appropriate alternative to CABG in LM disease and low-to-intermediate anatomical complexity. Among patients with LM disease and low anatomical complexity, there is evidence that the outcomes with respect to major clinical endpoints are similar for PCI and CABG, resulting in a class I recommendation. Among patients with LM disease and high anatomical complexity, the number of patients studied in RCTs is low due to exclusion criteria; the risk estimates and CIs are imprecise, but suggest a trend towards better survival with CABG. Therefore, PCI in this setting cannot be endorsed as reflected by a class III recommendation. For PCI in LM with intermediate anatomical complexity, the previous class IIa recommendation was maintained in view of the incomplete 5 year follow-up of the two largest RCTs in this setting.

### 5.3.4 MULTIVESSEL CORONARY ARTERY DISEASE

The observation of a survival advantage of CABG over PCI has been consistent among patients with severe three-vessel CAD (intermediate to high SYNTAX score), and has been attributed at least in part to the placement of bypass grafts to the mid coronary vessels providing prophylaxis against the development of new proximal disease.

The BEST trial, comparing CABG with PCI using new-generation DES (EES) among patients with multivessel CAD (77% three-vessel CAD and 23% two-vessel disease, mean SYNTAX score 24), prematurely stopped enrolment after the inclusion of 880 patients due to slow recruitment.<sup>105</sup> At a median follow-up of 4.6 years, PCI was associated with a higher incidence of the primary endpoint (death, MI, and TVR) (15.3 vs. 10.6%; HR 1.47, 95% CI 1.01-2.13,  $P=0.04$ ) than CABG. The risk of death, MI, and stroke was not statistically different between the two treatment groups (11.9 vs. 9.5%; HR 1.26, 95% CI 0.84-1.89,  $P=0.26$ ), whereas repeat revascularization of any vessel (11.0 vs. 5.4%; HR 2.1, 95% CI 1.28-3.41,  $P=0.003$ ) but not target lesion revascularization (5.7 vs. 3.8%; HR 1.51, 95% CI 0.82-2.80,  $P=0.19$ ) was more frequent in the PCI group. CABG resulted in more complete revascularization (71.5 vs. 50.9%;  $P<0.001$ ) and a lower incidence of revascularization for new lesions (5.5 vs. 2.3%; HR 2.47, 95% CI 1.18-5.17,  $P=0.01$ ).

Consistent with findings in the overall cohort (see section 5.3.3), the collaborative individual patient pooled analysis found that in 7040 patients with multivessel disease, those assigned to CABG had significantly lower 5 year all-cause mortality than those assigned to PCI (PCI 11.5 vs. CABG 8.9%; HR 1.28, 95% CI 1.09-1.49,  $P=0.0019$ ).<sup>124</sup> Outcomes for the endpoint all-cause mortality were modified by two variables, diabetes and disease complexity, as assessed by the SYNTAX

score. Compared with patients without diabetes (8.7 vs. 8.0%; HR 1.08, 95% CI 0.86-1.36,  $P=0.49$ ), mortality was higher after PCI than CABG in patients with diabetes (15.5 vs. 10.0%; HR 1.48, 95% CI 1.19-1.84,  $P=0.0004$ ,  $P_{\text{interaction}}=0.045$ ). There was a gradient of risk with a stepwise increase in mortality for PCI according to SYNTAX score tertile (SYNTAX score 0-22: 10.5 vs. 8.4%; HR 1.11, 95% CI 0.77-1.62,  $P=0.57$ ; SYNTAX score 23-32: 14.0 vs. 9.5%; HR 1.50, 95% CI 1.09-2.08,  $P=0.0129$ ; SYNTAX score >32: 19.2 vs. 11.2%; HR 1.70, 95% CI 1.13-2.55,  $P=0.0094$ ).

An individual patient data pooled analysis of SYNTAX and BEST, comparing CABG with PCI using DES among 1275 patients with multivessel disease in the absence of diabetes (89% three-vessel CAD, mean SYNTAX score 26), reported a lower risk of death (6.0 vs. 9.3%; HR 0.65, 95% CI 0.43-0.98,  $P=0.04$ ) and MI (3.3 vs. 8.3%; HR 0.40, 95% CI 0.24-0.65,  $P<0.001$ ) in the CABG group at a median follow-up of 61 months.<sup>149</sup> The risk of death was not significantly different among patients with a low (0-22) SYNTAX score (6.0 vs. 7.5%,  $P=0.66$ ), whereas the benefit of CABG over PCI was greater in patients with an intermediate-to-high (>22) SYNTAX score (7.1 vs. 11.6%,  $P=0.02$ ). Another individual patient data pooled analysis of SYNTAX and BEST, comparing CABG with PCI using DES among 1166 patients with multivessel disease involving the proximal LAD (88% three-vessel CAD, mean SYNTAX score 28), reported a higher risk of the composite of death, MI, and stroke (16.3 vs. 11.5%; HR 1.43, 95% CI 1.05-1.96,  $P=0.02$ ), cardiac death, MI, and repeat revascularization in the PCI group at 5 years of follow-up.<sup>147</sup> Of note, outcomes were not significantly different for CABG and PCI for any endpoint except for MI among the subgroup of patients with low SYNTAX score (0-22).

The available evidence suggests that in multivessel CAD without diabetes and low anatomical complexity, PCI and CABG achieve similar long-term outcomes with respect to survival and the composite of death, MI, and stroke, justifying a class I recommendation for PCI. In patients with multivessel CAD and intermediate-to-high anatomical complexity, the two large trials using DES, SYNTAX and BEST, found a significantly higher mortality and a higher incidence of death, MI, and stroke with PCI in the absence of diabetes. Consistent results were also obtained for patients with multivessel CAD in the recent individual patient-level meta-analysis.<sup>124</sup> Thus, the previous class III recommendation for PCI in multivessel CAD and intermediate-to-high complexity was maintained.

#### 5.4 GAPS IN THE EVIDENCE

It remains to be determined whether revascularization by PCI improves prognosis in patients with SCAD. The ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) study (NCT01471522) is currently recruiting 5000 patients with SCAD and evidence of moderate-to-severe ischaemia detected by non-invasive imaging, who

are randomized before coronary angiography to medical therapy or an invasive strategy to detect differences in the primary endpoint of death or MI. Current techniques rely on coronary angiography and the detection of ischaemia-producing lesions. However, future adverse events are related at least in part to non-flow limiting, vulnerable plaques. Better identification of vulnerable plaques and the development of appropriate treatment strategies is needed. Along the same lines, the completeness and timing of revascularization are not well defined, and neither are the roles of residual ischaemia and lesions. Moreover, we need more research on the use of the SYNTAX and other scores for informing treatment allocation, as well as dedicated trials in specific subsets. Very long-term, extended follow-up (10 years) of trials comparing PCI and CABG, particularly in the setting of LM disease, will provide further insights into the relative merits of both revascularization techniques.

## 6 Revascularization in non-ST-elevation acute coronary syndrome

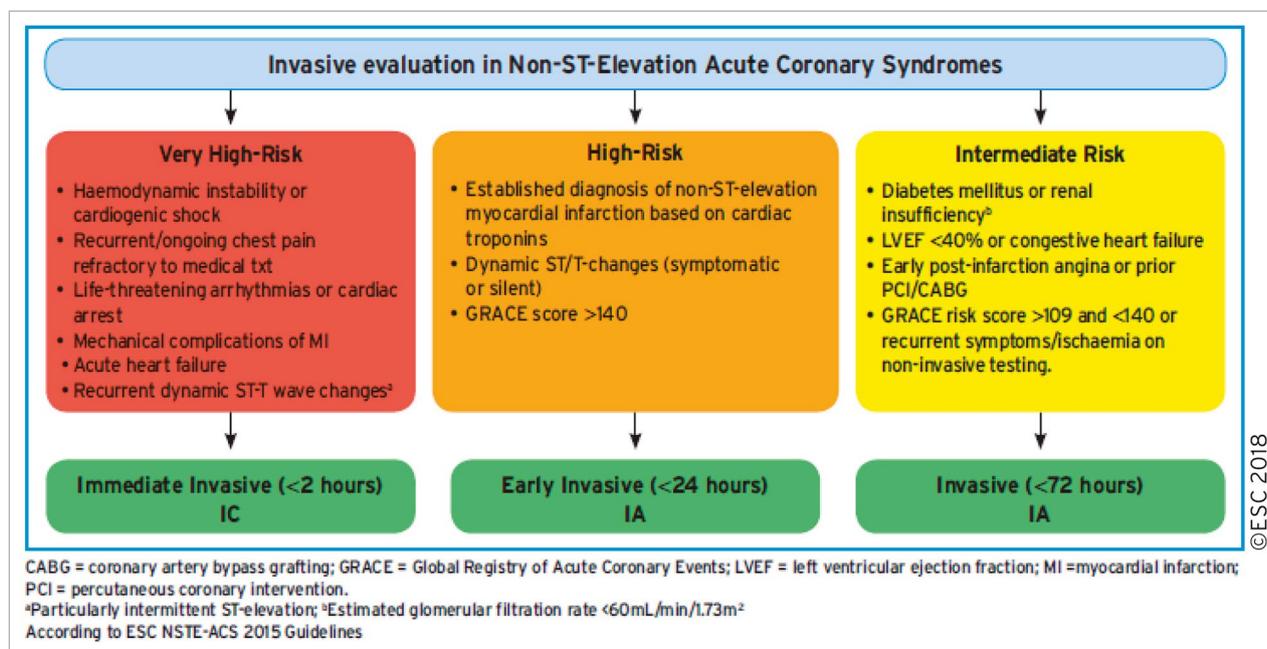
Myocardial revascularization in patients with non-ST-segment elevation ACS (NSTEMI-ACS) is addressed by prior Guidelines that are endorsed by the current Task Force.<sup>158</sup> In the present Guidelines, we discuss new evidence where previous recommendations require an update.

### 6.1 EARLY INVASIVE VS. CONSERVATIVE STRATEGY

An invasive strategy has become the standard of care for high-risk patients.<sup>158</sup> This approach allows prompt diagnosis of the underlying CAD, identification of the culprit lesion, guidance for antithrombotic management, and the assessment of the suitability of coronary anatomy for PCI or CABG. Numerous factors interplay in the decision-making process, including clinical presentation, comorbidities, risk stratification (**Figure 4**), and high-risk features specific for a revascularization modality such as frailty, cognitive status, estimated life expectancy, and the functional and anatomical severity of CAD.

Up to 40% of NSTEMI-ACS patients with obstructive CAD present with multiple complex plaques<sup>159-162</sup> and 25% with an acute occluded coronary artery,<sup>163</sup> so that identification of the culprit lesion may be challenging. Correlation with ECG or echo changes and the use of OCT in the 25% of NSTEMI-ACS patients with angiographically normal epicardial coronary arteries<sup>164-166</sup> may be helpful for identifying the culprit lesion, or rule out other mechanisms such as dissection or haematomas [MI with non-obstructive coronary arteries (MINOCA)].<sup>167-169</sup>

A routine invasive strategy in NSTEMI-ACS has been shown to improve clinical outcomes,<sup>170</sup> and benefit was mainly confined to biomarker-positive patients<sup>171</sup> and patients with other high-risk features as defined in **Figure 4**. Of importance, the use of a radial approach, new-generation DES, and more effective P2Y<sub>12</sub>-inhibitors were not available or broadly implemented in these trials, and led to a magnified benefit in frail ACS populations.<sup>172,173</sup>



**Figure 4.** Selection of non-ST-elevation acute coronary syndrome treatment strategy and timing according to initial risk stratification.

## 6.2 TIMING OF ANGIOGRAPHY AND INTERVENTION

The current recommendations on the timing of angiography and intervention, as defined in **Figure 4**, are based on evidence discussed in detail by the prior Guidelines on NSTEMI-ACS.<sup>158</sup> Specifically, a reduction in recurrent or refractory ischaemia and length of hospital stay was found with early intervention.<sup>174,175</sup> More recently, an updated collaborative meta-analysis on individual published and unpublished data (n=5324 patients with a median follow-up of 180 days) suggested that early intervention might also be associated with decreased mortality.<sup>176</sup> This meta-analysis showed a statistical trend towards decreased mortality with an early invasive strategy compared with a delayed invasive strategy in unselected patients with NSTEMI-ACS (HR 0.81, 95% CI 0.64-1.03, P=0.088). The survival benefit of the early invasive strategy appeared more pronounced in high-risk subsets, including elevated cardiac biomarkers at baseline (HR 0.76, 95% CI 0.58-0.996), diabetes (HR 0.67, 95% CI 0.45-0.99), a Global Registry of Acute Coronary Events risk score >140 (HR 0.70, 95% CI 0.52-0.95), and age 75 years or older (HR 0.65, 95% CI 0.46-0.93), although tests for interaction were inconclusive.

## 6.3 TYPE OF REVASCULARIZATION

### 6.3.1 PERCUTANEOUS CORONARY INTERVENTION

#### 6.3.1.1 Technical aspects

Implantation of new-generation DES is the standard treatment strategy even when dual antiplatelet therapy (DAPT) cannot be sustained beyond 1 month post-intervention<sup>173,177-179</sup> (see section 17), and the radial approach has also become the standard of care.<sup>172</sup> DAPT is recommended for 12 months irrespective of stent type, while in patients at high ischaemic risk not experiencing

bleeding events, DAPT may be extended (see section 17). There is no evidence for any additional benefit of thrombectomy in patients undergoing PCI in the setting of NSTEMI-ACS.<sup>180</sup> While FFR is considered the invasive gold standard for the functional assessment of lesion severity in SCAD, it has been shown to be feasible, reliable, safe, and effective in NSTEMI-ACS patients with multivessel disease, although its prognostic value is unclear.<sup>22,137,181</sup>

#### 6.3.1.2 Revascularization strategies and outcomes

Complete revascularization of significant lesions should be attempted in multivessel disease NSTEMI-ACS patients, given that it was mandated in trials testing early vs. late intervention<sup>171,182,183</sup> and that the prognosis of patients with incomplete revascularization is known to be worse.<sup>131,184</sup> In addition, it seems that complete one-stage revascularization is associated with better clinical outcome than multistage PCI.<sup>185</sup> The risk of periprocedural complications of PCI defined as MI or myocardial injury, as well as that of long-term ischaemia, remains higher in NSTEMI-ACS than in stable patients.<sup>186,187</sup> For ACS patients who have undergone PCI, revascularization procedures represent the most frequent, most costly, and earliest causes for rehospitalization.<sup>188,189</sup> As in ST-elevation myocardial infarction (STEMI), routine treatment of non-culprit lesions during the primary intervention by PCI is harmful in NSTEMI-ACS patients with cardiogenic shock, as shown by the recently published CULPRIT-SHOCK (Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock) trial (see section 7.3).<sup>190</sup>

#### 6.3.2 CORONARY ARTERY BYPASS GRAFTING

Approximately 5-10% of NSTEMI-ACS patients require CABG,<sup>191</sup> and they represent a challenging subgroup given their high-risk characteristics compared with patients undergoing elective

CABG.<sup>192</sup> In the absence of randomized data, optimal timing for non-emergent CABG in NSTEMI-ACS patients should be determined individually. The risk of ischaemic events possibly related to suboptimal antiplatelet therapy while awaiting surgery is <0.1%, while that of perioperative bleeding complications associated with platelet inhibitors is >10%.<sup>193</sup> In patients with ongoing ischaemia or haemodynamic instability with an indication for CABG, emergency surgery should be performed and not postponed as a consequence of antiplatelet treatment exposure.

### 6.3.3 PERCUTANEOUS CORONARY INTERVENTION VS. CORONARY ARTERY BYPASS GRAFTING

There is no randomized comparison of PCI vs. CABG in the specific setting of NSTEMI-ACS. The currently available evidence indirectly suggests that the criteria applied to patients with SCAD to guide the choice of revascularization modality should be applied to stabilized patients with NSTEMI-ACS.<sup>100,121,150,194</sup> Recent individual-patients data analysis from the BEST, PRECOMBAT, and SYNTAX studies compared the outcome of CABG with that of PCI in 1246 patients with stabilized NSTEMI-ACS and multivessel or LM disease.<sup>194</sup> The 5 year incidence of the primary outcome – the composite of death, MI, or stroke – was significantly lower with CABG than with PCI (13.4 vs. 18%, P=0.036). The findings of this meta-analysis were consistent with the main findings of the studies included, thus supporting the concept that the principles of SCAD should apply to stabilized patients with NSTEMI-ACS as well.

For complex cases, Heart Team discussion and use of the SYNTAX score are recommended,<sup>195</sup> given its ability to predict death, MI, and revascularization in patients with NSTEMI-ACS and

multivessel disease undergoing PCI. In patients with multivessel disease and diabetes in particular, recent evidence suggests a greater benefit of CABG vs. PCI.<sup>196</sup>

### 6.4 GAPS IN THE EVIDENCE

In the setting of NSTEMI-ACS, there are no dedicated prospective studies on the revascularization strategy with multivessel disease. Thus, current recommendations on the choice of lesions to be treated and treatment modality (PCI or CABG) are based on an analogy to findings obtained in SCAD or STEMI. Likewise, the prognostic role of FFR and iwFR in guiding myocardial revascularization needs additional clarification.

## 7 Revascularization in ST-segment elevation myocardial infarction

Myocardial revascularization in patients with STEMI is addressed by the 2017 ESC Guidelines on STEMI. After reviewing the subsequent literature, the current Task Force endorses most recommendations of these Guidelines.<sup>198</sup>

### 7.1 TIME DELAYS

Delays in the timely implementation of reperfusion therapy are key issues in the management of STEMI. Detailed recommendations on timelines, logistics, and pre-hospital management have been provided in the recent ESC STEMI Guidelines (**Figure 5**).<sup>198</sup>

A recent analysis of 12 675 STEMI patients in the FITT-STEMI (Feedback Intervention and Treatment Times in ST-Elevation Myocardial Infarction) trial emphasizes the strong impact of time delays on mortality, particularly in STEMI patients with cardiogenic shock or out-of-hospital cardiac arrest.<sup>199</sup> In shock without out-of-hospital cardiac arrest, every 10 min treatment delay between 60-180 min from the first medical contact resulted in 3.3 additional deaths per 100 PCI-treated patients, and in 1.3 additional deaths after out-of-hospital cardiac arrest without cardiogenic shock. In stable STEMI patients, time delays were substantially less relevant (0.3 additional deaths per 100 PCI-treated patients for every 10 min delay between 60-180 min from the first medical contact). Thus, high-risk STEMI patients with cardiogenic shock or out-of-hospital cardiac arrest are those who benefit most from expediting all steps of the care pathway.

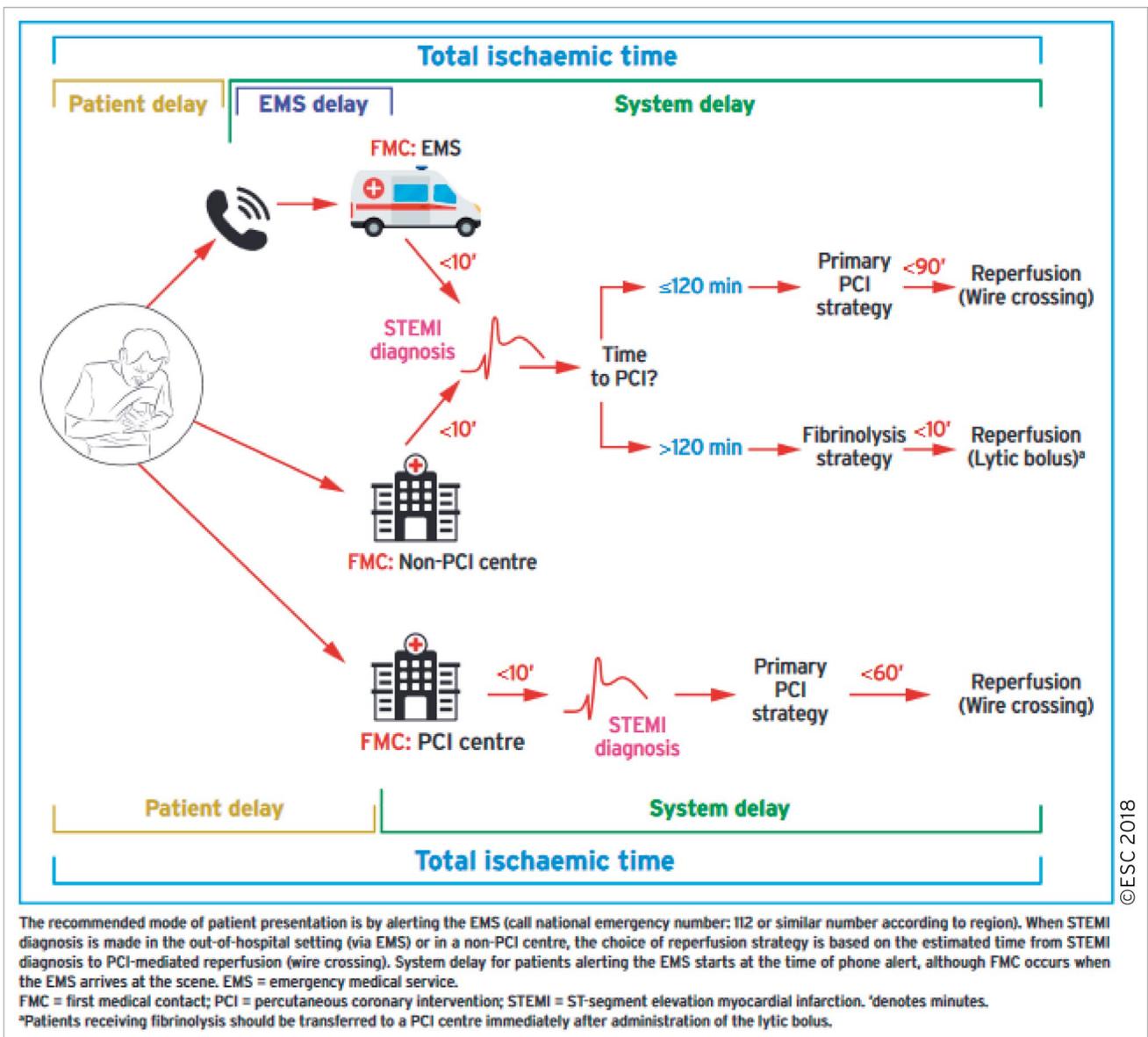
### 7.2 SELECTION OF REPERFUSION STRATEGY

Primary PCI, defined as percutaneous catheter intervention in the setting of STEMI without previous fibrinolysis, is the preferred reperfusion strategy. It has replaced fibrinolysis in patients with STEMI, provided it can be performed in a timely manner in high-volume PCI centres with experienced operators and 24 h/7 days a week catheterization laboratory activation.<sup>198,200,201</sup> In settings where primary PCI cannot be performed in a timely fashion, fibrinolysis should be administered as soon as possible. If first medical contact (FMC) is out-of-hospital, lysis should be implemented pre-hospital (e.g. in the ambulance) (**Figure 5**).<sup>202-206</sup> It should be followed by transfer to PCI-capable centres for

### Recommendations for invasive evaluation and revascularization in non-ST-elevation acute coronary syndrome

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Urgent coronary angiography (<2 h) is recommended in patients at very high ischaemic risk (Figure 4). <sup>197</sup>	I	C
An early invasive strategy (<24 h) is recommended in patients with at least one high-risk criterion (Figure 4). <sup>164,174,176</sup>	I	A
An invasive strategy (<72 h after first presentation) is indicated in patients with at least one intermediate-risk criterion (Figure 4) or recurrent symptoms. <sup>170,171</sup>	I	A
It is recommended to base the revascularization strategy ( <i>ad hoc</i> culprit lesion PCI/multivessel PCI/CABG) on the clinical status and comorbidities, as well as the disease severity [i.e. the distribution and angiographic lesion characteristics (e.g. SYNTAX score)], according to the principles for SCAD. <sup>c 194</sup>	I	B
In cardiogenic shock, routine revascularization of non-IRA lesions is not recommended during primary PCI. <sup>190</sup>	III	B

CABG: coronary artery bypass grafting; IRA: infarct-related artery; NSTEMI-ACS: non-ST-elevation acute coronary syndrome; PCI: percutaneous coronary intervention; SCAD: stable coronary artery disease; SYNTAX: Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence. <sup>c</sup>May apply to stabilized NSTEMI-ACS patients.



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Figure 5. Modes of patient's medical contact, components of ischaemia time, and flowchart for reperfusion strategy selection.

routine coronary angiography in all patients, and should be performed without delay for rescue PCI in the case of unsuccessful fibrinolysis or within 2-24 h after bolus administration.<sup>198</sup> Emergency CABG may be indicated in selected STEMI patients unsuitable for PCI.

### 7.3 PRIMARY PERCUTANEOUS CORONARY INTERVENTION

Key points for optimizing and guiding primary PCI are summarized below.

The infarct-related artery (IRA) should be systematically treated during the initial intervention. Patients with extensive CAD in vessels remote from the IRA have an adverse prognosis following primary PCI.<sup>207</sup> Staged PCI in patients with multivessel disease and no haemodynamic compromise is an independent predictor of survival, and more frequent ischaemic events have been reported

in direct vs. staged revascularization of STEMI patients with multivessel disease.<sup>208-210</sup>

Four major randomized trials-PRAMI (Preventive Angioplasty in Acute Myocardial Infarction),<sup>211</sup> CvLPRIT (Complete Versus Lesion-Only Primary PCI trial),<sup>212</sup> DANAMI-3-PRIMULTI (The Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: PRImary PCI in MULTIVessel Disease),<sup>213</sup> and Compare-Acute<sup>214</sup>-have consistently shown a benefit of complete revascularization (performed immediately or staged) as compared with IRA-only PCI in patients with STEMI and multivessel disease (for details see the **Supplementary Data**). A recent meta-analysis of 10 trials has shown that complete revascularization was associated with a lower risk of MACE (RR 0.57, 95% CI 0.42-0.77), due to a lower risk of urgent revascularization (RR 0.44, 95% CI 0.30-0.66), with no significant difference

in mortality (RR 0.76, 95% CI 0.52-1.12) or MI (RR 0.54, 95% CI 0.23-1.27).<sup>215</sup> This meta-analysis did not include Compare-Acute. Yet, similar to earlier studies, the benefit of complete revascularization over culprit-only revascularization seen in Compare-Acute was driven by a lower need for unplanned reintervention, whereas the incidences of death and recurrent MI were similar between the two strategies.<sup>214</sup>

Most of the studies support the concept of full revascularization either during the initial hospital stay for STEMI or a staged admission,<sup>215</sup> but it remains to be determined how clinicians can identify lesions that should be revascularized beyond the culprit lesion and whether complete revascularization should be performed in single- or multi-stage procedures. Moreover, there is a lack of evidence on the optimal timing of staged procedures. In most of the studies, staged procedures were performed during the initial hospital stay. At present, one-stage multivessel PCI during STEMI without cardiogenic shock should be considered in patients in the presence of multiple, critical stenoses or highly unstable lesions (angiographic signs of possible thrombus or lesion disruption), and if there is persistent ischaemia after PCI on the supposed culprit lesion.

In patients with multivessel disease and AMI with cardiogenic shock, the recently published CULPRIT-SHOCK trial showed that a strategy with PCI of the culprit lesion only with possible staged revascularization determined a lower 30 day risk of the composite of all-cause mortality or severe renal failure compared with immediate multivessel PCI.<sup>190</sup> This was driven by a significant risk reduction in 30 day all-cause mortality by the culprit lesion-only strategy compared with immediate multivessel PCI (43.3 vs. 51.6%; HR 0.84, 95% CI 0.72-0.98, P=0.03). These findings need to be interpreted in light of a low 12.5% (43 out of 344 patients) crossover rate from culprit lesion-only to immediate multivessel PCI based on physicians' judgment. Based on these findings, culprit lesion-only PCI is recommended as the default strategy in patients with AMI with cardiogenic shock. A more detailed discussion of the revascularization strategy in MI patients with cardiogenic shock is found in the **Supplementary Data**.

In patients with STEMI, DES (in particular new-generation DES) have demonstrated better efficacy as compared with BMS and should be used as the default strategy in STEMI patients, even when DAPT cannot be sustained beyond 1 month.<sup>177,178,216-218</sup> (see section 16.1.2). As discussed in section 16.4, radial access is preferred over femoral access.

Delaying stenting in primary PCI has been investigated as an option to reduce microvascular obstruction (MVO) and preserve microcirculatory function in two small trials with conflicting results.<sup>219,220</sup> More recently, in the larger deferred vs. conventional stent implantation in patients with STEMI [The Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: DEFERred stent implantation in connection with primary PCI (DANAMI 3-DEFER)] trial in 1215 STEMI patients, there was no effect on the primary clinical outcome (composite of death, non-fatal MI, or ischaemia-driven revascularization of non-IRA lesions) over a median follow-up

of 42 months.<sup>221</sup> Routine deferred stenting was associated with a higher risk of TVR.

Thrombus aspiration has been proposed as an adjunct during primary PCI to further improve epicardial and myocardial reperfusion by the prevention of distal embolization of thrombotic material and plaque debris.<sup>222</sup> Two landmark RCTs, which were adequately powered to detect the superiority of routine manual thrombus aspiration vs. conventional PCI, showed no benefit on clinical outcomes of the routine aspiration strategy overall or in any subgroup of patients indicating high thrombotic risk.<sup>223-226</sup> A safety concern emerged in TOTAL (Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI) trial with an increase in the risk of stroke.<sup>225,227</sup> Taken together, these results suggest that the routine use of thrombus aspiration is not indicated. In the high-thrombus burden subgroup, the trend towards reduced cardiovascular death and increased stroke/transient ischaemic attack (TIA) provides a rationale for future trials of improved thrombus aspiration technologies in this high-risk subgroup (although statistical tests did not support significant subgroup interaction).<sup>228</sup>

#### 7.4 PERCUTANEOUS CORONARY INTERVENTION AFTER THROMBOLYSIS AND IN PATIENTS WITH LATE DIAGNOSIS

The benefits of early, routine PCI after thrombolysis were seen in the absence of an increased risk of adverse events (stroke or major bleeding). Based on data from the four most recent trials, all of which had a median delay between the start of thrombolysis and angiography of 2-6 h, a time frame of 2-24 h after successful lysis is recommended.<sup>206,229-231</sup> In cases of failed fibrinolysis, or if there is evidence of re-occlusion or reinfarction with recurrence of ST-segment elevation, the patient should undergo immediate coronary angiography and rescue PCI.<sup>232</sup> Patients presenting between 12 and 48 h after the onset of symptoms, even if pain free and with stable haemodynamics, may still benefit from early coronary angiography and possibly PCI.<sup>233,234</sup> In patients presenting days after the acute event with a completed MI, only those with recurrent angina or documented residual ischaemia – and proven viability on non-invasive imaging in a large myocardial territory – may be considered for revascularization when the infarct artery is occluded. Routine late PCI of an occluded IRA after MI in stable patients has no incremental benefit over medical therapy.<sup>235</sup>

#### 7.5 GAPS IN THE EVIDENCE

Patients undergoing primary PCI benefit from full revascularization, but the optimal timing of treatment of the non-culprit lesion is not known. More studies evaluating the assessment of non-culprit lesions by FFR or iwFR at the time of acute PCI, and studies investigating whether intravascular imaging guidance of primary PCI can improve the outcomes of STEMI patients, are needed. Future trials of improved thrombus aspiration technologies may address the role of this strategy in patients with high-risk features, such as large thrombus burden.<sup>228</sup>

**Primary percutaneous coronary intervention for myocardial reperfusion in ST-elevation myocardial infarction: indications and logistics**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Indication</b>		
Reperfusion therapy is indicated in all patients with time from symptom onset <12 h duration and persistent ST-segment elevation. <sup>200,201,236</sup>	I	A
In the absence of ST-segment elevation, a primary PCI strategy is indicated in patients with suspected ongoing ischaemic symptoms suggestive of MI and at least one of the following criteria present: – haemodynamic instability or cardiogenic shock – recurrent or ongoing chest pain refractory to medical treatment – life-threatening arrhythmias or cardiac arrest – mechanical complications of MI – acute heart failure – recurrent dynamic ST-segment or T-wave changes, particularly with intermittent ST-segment elevation.	I	C
A primary PCI strategy is recommended over fibrinolysis within the indicated time frames. <sup>200,201,237,238</sup>	I	A
In patients with time from symptom onset >12 h, a primary PCI strategy is indicated in the presence of ongoing symptoms or signs suggestive of ischaemia, haemodynamic instability, or life-threatening arrhythmias.	I	C
A routine primary PCI strategy should be considered in patients presenting late (12-48 h) after symptom onset. <sup>233,234,239</sup>	Ila	B
<b>Logistics</b>		
It is recommended that the pre-hospital management of STEMI patients should be based on regional networks that are designed to deliver reperfusion therapy effectively in a timely fashion, and to offer primary PCI to as many patients as possible. <sup>240,241</sup>	I	B
It is recommended that all EMS, emergency departments, coronary care units, and catheterization laboratories have a written updated STEMI management protocol, preferably shared within geographical networks.	I	C
It is recommended that primary PCI-capable centres deliver a 24 h/7 day service and ensure that primary PCI is performed as fast as possible. <sup>242-244</sup>	I	B
It is recommended that patients transferred to a PCI-capable centre for primary PCI bypass the emergency department and CCU/ICCU, and are transferred directly to the catheterization laboratory. <sup>245-247</sup>	I	B

CCU: coronary care unit; EMS: emergency medical services; ICCU: intensive coronary care unit; MI: myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

**Primary percutaneous coronary intervention for myocardial reperfusion in ST-elevation myocardial infarction: procedural aspects (strategy and technique)**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Strategy</b>		
Routine revascularization of non-IRA lesions should be considered in patients with multivessel disease before hospital discharge. <sup>211-214</sup>	Ila	A
CABG should be considered in patients with ongoing ischaemia and large areas of jeopardized myocardium if PCI of the IRA cannot be performed.	Ila	C
In cardiogenic shock, routine revascularization of non-IRA lesions is not recommended during primary PCI. <sup>190</sup>	III	B
<b>Technique</b>		
Routine use of thrombus aspiration is not recommended. <sup>223-226,228</sup>	III	A

CABG: coronary artery bypass grafting; IRA: infarct-related artery; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

**8 Myocardial revascularization in patients with heart failure**

**8.1 CHRONIC HEART FAILURE**

**8.1.1 RECOMMENDATIONS FOR MYOCARDIAL REVASCLARIZATION IN PATIENTS WITH CHRONIC HEART FAILURE**

When compared with medical therapy alone, coronary revascularization is superior in improving survival in patients with HF

of ischaemic origin and is recommended in clinical practice.<sup>81,248</sup> However, the optimal revascularization strategy is not defined. The choice between CABG and PCI should be made by the Heart Team after careful evaluation of the patient’s clinical status and coronary anatomy, expected completeness of revascularization (see section 5.3.1.3), myocardial viability, coexisting valvular disease, and comorbidities. Considerations relating to the need for viability testing prior to revascularization are discussed in section 3.

Randomized clinical trial data comparing revascularization with medical therapy exists only for CABG in the setting of the STICH trial.<sup>81</sup> One analysis from this trial showed that CABG can be performed with acceptable 30 day mortality rates (5.1%) in patients with LV dysfunction (LVEF ≤35%).<sup>249</sup> Extended follow-up in the STICH Extension Study (STICHES) supports a significant survival benefit of CABG combined with medical therapy vs. medical therapy alone in a 10 year observation period.<sup>81</sup>

There are currently no dedicated randomized clinical trials comparing PCI vs. medical therapy in patients with HF with reduced EF (HFrEF). In addition, CABG vs. PCI randomized trials have excluded patients with severe HF. In one prospective registry including 4616 patients with multivessel disease and severe HFrEF, propensity score-matched comparison revealed similar survival (mean follow-up 2.9 years) with PCI (using EES) vs. CABG.<sup>250</sup> PCI was associated with a higher risk of MI, particularly in patients with incomplete revascularization, and repeat revascularization. CABG was associated with a higher risk of stroke. The conclusion of the study was that multivessel

PCI can be a valuable option in HF patients if complete revascularization is possible. A systematic review of studies comparing revascularization with medical therapy in patients with an EF  $\leq 40\%$  showed that there was a significant mortality reduction with CABG (HR 0.66, 95% CI 0.61-0.72,  $P < 0.001$ ) and PCI (HR 0.73, 95% CI 0.62-0.85,  $P < 0.001$ ) vs. medical therapy, though these findings are limited by the predominantly observational nature of the included studies and missing information on the completeness of revascularization.<sup>248</sup>

A recent observational study investigated outcomes with PCI or CABG for multivessel CAD and LV dysfunction in 1738 propensity-matched patients with diabetes mellitus.<sup>251</sup> Similar to the findings in the absence of LV dysfunction, when CABG was compared with PCI it was associated with a significantly lower risk of MACE, which included a significant reduction in mortality. Event curves separated early during the first year and continued to separate out to 12 years.

PCI should be considered in older patients without diabetes in whom complete revascularization can be achieved, whereas CABG is preferred in younger patients with more extensive CAD or those with diabetes. In patients with diabetes and LV moderate or severe dysfunction (EF  $< 50\%$ ), CABG is associated with better long-term survival and reduced incidence of MACCE.<sup>250,251</sup>

### 8.1.2 VENTRICULAR RECONSTRUCTION AND ANEURYSM RESECTION

The aim of surgical ventricular reconstruction (SVR) is to restore physiological volume, and achieve an elliptical shape of the LV, by scar resection and LV wall reconstruction on a mannequin of pre-defined size. The aim of ventricular aneurysmectomy is to remove fibrous scars in cases of severe dilatation, thrombus formation, or as a source of life-threatening ventricular arrhythmias.

The STICH trial revealed no difference in the primary outcome (total mortality or cardiac hospitalization) between patients randomly allocated to CABG vs. combined CABG and SVR.<sup>252</sup> Subgroup analyses of patients with a less dilated LV and better LVEF showed benefit from SVR.<sup>253</sup> In the STICH trial, a post-operative LV end-systolic volume index  $\leq 70$  mL/m<sup>2</sup>, after CABG plus SVR, resulted in improved survival compared with CABG alone.<sup>252,254</sup> In experienced centres, SVR may be done at the time of CABG if HF symptoms are more predominant than angina, and if myocardial scar and moderate LV remodelling are present.

## 8.2 ACUTE HEART FAILURE AND CARIOGENIC SHOCK

Acute myocardial ischaemia in the setting of AMI is the antecedent event for the majority of patients with cardiogenic shock undergoing percutaneous revascularization. Mechanical complications – such as papillary muscle rupture with severe mitral valve regurgitation, ventricular septal defect, or free wall rupture – are additional precipitating causes.

### 8.2.1 REVASCULARIZATION

The SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial demonstrated that in patients with cardiogenic shock complicating AMI, emergency

### Recommendations on revascularizations in patients with chronic heart failure and systolic left ventricular dysfunction (ejection fraction $\leq 35\%$ )

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
In patients with severe LV systolic dysfunction and coronary artery disease suitable for intervention, myocardial revascularization is recommended. <sup>81,250</sup>	I	B
CABG is recommended as the first revascularization strategy choice in patients with multivessel disease and acceptable surgical risk. <sup>68,81,248,255</sup>	I	B
In patients with one- or two-vessel disease, PCI should be considered as an alternative to CABG when complete revascularization can be achieved.	IIa	C
In patients with three-vessel disease, PCI should be considered based on the evaluation by the Heart Team of the patient's coronary anatomy, the expected completeness of revascularization, diabetes status, and comorbidities.	IIa	C
LV aneurysmectomy during CABG should be considered in patients with NYHA class III/IV, large LV aneurysm, large thrombus formation, or if the aneurysm is the origin of arrhythmias.	IIa	C
Surgical ventricular restoration during CABG may be considered in selected patients treated in centres with expertise. <sup>252-254,256,257</sup>	IIb	B

CABG: coronary artery bypass grafting; LV: left ventricular; NYHA: New York Heart Association; PCI: percutaneous coronary intervention. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

revascularization with PCI or CABG improved long-term survival when compared with initial intensive medical therapy. All-cause mortality at 6 months was lower in the group assigned to revascularization than in the medically treated patients (50.3 vs. 63.1%, respectively; RR 0.80, 95% CI 0.65-0.98,  $P=0.03$ ).<sup>258</sup>

The revascularization strategy for patients with cardiogenic shock and multivessel disease is addressed in section 7.

A subanalysis of the SHOCK trial comparing patients treated with CABG or PCI showed similar survival rates between the two subgroups.<sup>259</sup> There were more patients with diabetes (48.9 vs. 26.9%;  $P=0.02$ ), three-vessel disease (80.4 vs. 60.3%;  $P=0.03$ ), and LM coronary disease (41.3 vs. 13.0%;  $P=0.001$ ) in the CABG group. The findings of this non-randomized comparison suggest that CABG should be considered in patients with cardiogenic shock who have suitable anatomy, particularly if successful PCI is not feasible.

### 8.2.2 MECHANICAL CIRCULATORY SUPPORT

Short-term MCS devices that are currently available are the intra-aortic balloon pump (IABP), veno-arterial extracorporeal membrane oxygenation (ECMO), and percutaneous left ventricular assist devices (pLVADs). Short-term MCS may be considered in refractory cardiogenic shock depending on patient age, comorbidities, neurological function, and the prospects for long-term survival and quality of life.

#### 8.2.2.1 Intra-aortic balloon pump

IABPs are low-cost devices that are easy to insert and remove. They moderately increase cardiac output and coronary and

cerebral perfusion, while decreasing ventricular workload. In patients with cardiogenic shock complicating acute MI, the IABP-SHOCK II (Intraaortic Balloon Pump in Cardiogenic Shock II) randomized trial (600 patients) showed that the use of IABPs did not reduce 30 day mortality and that there was no evidence of long-term benefit.<sup>260,261</sup> A recent Cochrane review of seven trials (790 patients) showed that IABPs may have a beneficial effect on some haemodynamic parameters but did not result in survival benefits.<sup>262</sup> Thus, the routine use of IABPs in patients with cardiogenic shock complicating acute MI is not recommended.

**8.2.2.2 Extracorporeal membrane oxygenation**

Veno-arterial ECMO (VA-ECMO), also known as extracorporeal life support (ECLS), in its current form is a modified form of cardiopulmonary bypass. It decompresses the venous system; increases coronary, cerebral, and peripheral perfusion; and also provides supplementary blood oxygenation. When performed percutaneously, it does not allow for LV decompression and leads to increasing LV afterload.

In patients with cardiac arrest, evidence from observational trials supports better survival in patients treated with VA-ECMO compared with those without.<sup>263</sup> When compared with IABP, VA-ECMO provides superior circulatory support.<sup>264,265</sup> Moreover, a meta-analysis of observational studies suggested that in patients with cardiogenic shock post-ACS, VA-ECMO showed a 33% higher 30 day survival compared with IABP [95% CI 14-52%, P <0.001; number needed to treat (NNT) 13].<sup>263</sup> However, the low number of patients included in the analysed studies and the non-random treatment allocation are important limitations.

**8.2.2.3 Percutaneous left ventricular assist devices**

The majority of clinical experience with currently available pLVADs is limited to two types of device: (i) a transaortic micro-axial pump (Impella) that directly unloads the LV providing 2.5-5 L/min blood flow and (ii) a transeptal centrifugal assist device (TandemHeart) that unloads the LV via a cannula introduced into the left atrium through a transeptal puncture.

A recent meta-analysis on MCS in cardiogenic shock included four randomized trials investigating the efficacy and safety of pLVADs vs. IABP, and demonstrated similar short-term mortality despite initial beneficial effects on arterial blood pressure and peripheral perfusion, measured by serum lactate levels.<sup>266</sup> In all trials, a higher rate of bleeding from vascular access sites and a significantly higher incidence of limb ischaemia following pLVAD was noted. Similar outcomes were noted in an RCT of high-risk PCI in patients with impaired LV function. The 30 day incidence of major adverse events was not different for patients with pLVAD vs. IABP.<sup>267</sup>

In summary, the evidence for pLVAD is insufficient to provide a recommendation on its clinical use in cardiogenic shock.

**8.2.2.4 Surgically implanted left ventricular assist devices**

There are limited data on surgically-implanted LV assist device (LVAD) therapy in patients with AMI and cardiogenic shock. One multicentre registry showed that despite being more critically ill

prior to implantation, patients with acute MI managed with LVAD had outcomes similar to other LVAD populations.<sup>268</sup>

A suggested algorithm for the management of patients with cardiogenic shock is shown in **Figure 6**.

**8.3 GAPS IN THE EVIDENCE**

There is no RCT comparing revascularization with PCI vs. CABG in patients with HF.

There is limited evidence on the role of active MCS in patients with cardiogenic shock compared with standard therapy.

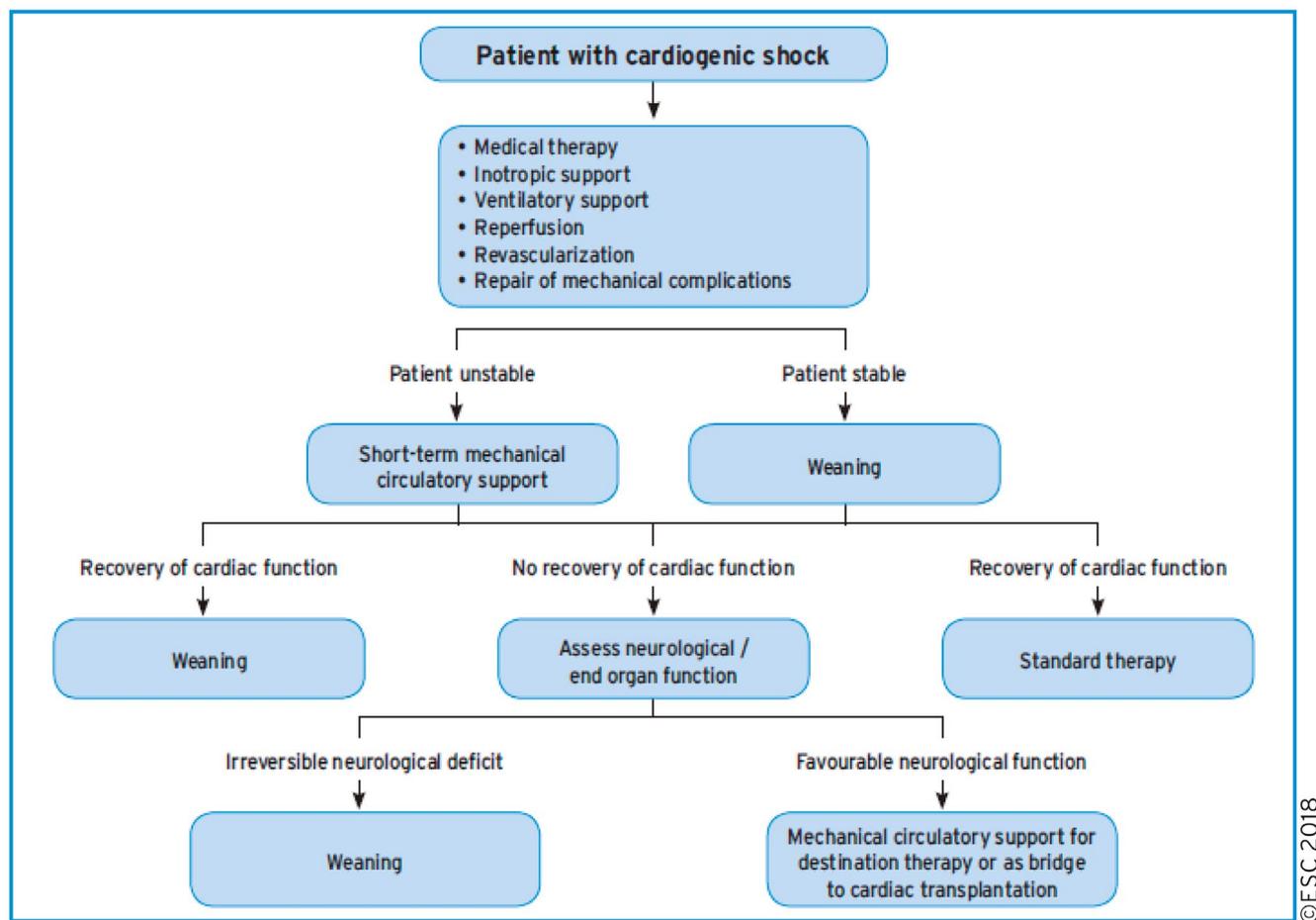
Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Emergency coronary angiography is indicated in patients with acute heart failure or cardiogenic shock complicating ACS. <sup>258,269</sup>	I	B
Emergency PCI of the culprit lesion is indicated for patients with cardiogenic shock due to STEMI or NSTEMI-ACS, independent of time delay of symptom onset, if coronary anatomy is amenable to PCI. <sup>258</sup>	I	B
Emergency CABG is recommended for patients with cardiogenic shock if the coronary anatomy is not amenable to PCI. <sup>258</sup>	I	B
In cases of haemodynamic instability, emergency surgical or catheter-based repair of mechanical complications of ACS is indicated, as decided by the Heart Team.	I	C
In selected patients with ACS and cardiogenic shock, short-term mechanical circulatory support may be considered, depending on patient age, comorbidities, neurological function, and the prospects for long-term survival and predicted quality of life.	IIb	C
Routine use of IABPs in patients with cardiogenic shock due to ACS is not recommended. <sup>260-262</sup>	III	B

ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; IABP: intra-aortic balloon pump; NSTEMI-ACS: non-ST-elevation acute coronary syndrome; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence

**9 Revascularization in patients with diabetes**

Patients with diabetes mellitus have a higher prevalence of CAD, which often manifests earlier in life and confers a substantially worse prognosis than for patients without diabetes.<sup>270</sup> Patients with diabetes who have suffered an MI have a worse prognosis, particularly those requiring treatment with insulin, and the presence of diabetes amplifies the risk of any cardiovascular event.<sup>271</sup> Diabetes mellitus is present in 25-30% of patients admitted with ACS and in up to 40% of patients undergoing CABG.<sup>272</sup>

The anatomical pattern of CAD in patients with diabetes clearly influences their prognosis and response to revascularization. Angiographic studies have demonstrated that patients with diabetes are more likely to have LM disease and multivessel CAD, with more diffuse disease involving smaller vessels.<sup>273</sup> In addition, patients with diabetes have a greater atherosclerotic burden and an increased number of lipid-rich plaques, which are prone to



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Figure 6. Algorithm for the management of patients with cardiogenic shock.

rupture,<sup>274,275</sup> and those with unstable angina have more fissured plaques and intracoronary thrombi.<sup>276</sup> Patients with diabetes undergoing revascularization, either with CABG or PCI, are at greater risk of kidney injury than patients without diabetes.

### 9.1 EVIDENCE FOR MYOCARDIAL REVASCUARIZATION

In patients with diabetes, the indications for myocardial revascularization are the same as those in patients without diabetes (see sections 5, 6, and 7). A meta-analysis of nine RCTs with 9904 ACS patients did not show an interaction between diabetic status and the benefit from invasive management and revascularization.<sup>277</sup> Yet, absolute risk reductions were larger in the diabetic subsets compared with non-diabetic subsets. Consistent with the findings in the absence of diabetes, the adverse impact of incomplete revascularization in patients with diabetes was also demonstrated in the BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial.<sup>278</sup>

Data from randomized trials on revascularization in patients with diabetes are summarized in **Supplementary Table 5**.

### 9.2 TYPE OF MYOCARDIAL REVASCUARIZATION

The selection of the optimal myocardial revascularization strategy for patients with diabetes and multivessel CAD requires

particular consideration. The recommendations are provided in section 5.

#### 9.2.1. RANDOMIZED CLINICAL TRIALS

The FREEDOM trial compared elective revascularization with CABG or PCI with first-generation DES (94%) in 1900 patients with diabetes (6% of the screened population) with multivessel disease but without LM stenosis.<sup>150</sup> The primary endpoint of any-cause death, non-fatal MI, or stroke at 5 years occurred in 26.6% in the PCI group, compared with 18.7% in the CABG group (absolute difference 7.9%, 95% CI 3.3-12.5%,  $P=0.005$ ). The incidences of death (16.3% in the PCI group vs. 10.9% in the CABG group; absolute difference 5.4%, 95% CI 1.5-9.2%,  $P=0.049$ ) and MI (13.9% in the PCI group vs. 6.0% in the CABG group,  $P<0.001$ ) were higher in the PCI group, but the incidence of stroke was lower (2.4 vs. 5.2%;  $P=0.03$ ). Within the FREEDOM trial at 5 years, patients with diabetes treated with insulin had higher event rates, but there was no significant interaction of treatment and insulin requirement for the primary endpoint ( $P_{\text{interaction}}=0.40$ ), even after adjusting for SYNTAX score: the NNT with CABG vs. PCI to prevent one event was 12.7 for insulin-treated patients and 13.2 in those not requiring insulin.<sup>279</sup>

VACARDS (Veterans Affairs Coronary Artery Revascularization in Diabetes Study) compared CABG with PCI in patients with

diabetes and extensive CAD in the USA.<sup>154</sup> Only 198 patients with diabetes were randomized due to early termination of the study. The combined risk of death or non-fatal MI was 18.4% for the CABG arm and 25.3% for the PCI arm (HR 0.89, 95% CI 0.47-1.71,  $P < 0.05$ ).<sup>154</sup>

In the CARDia (Coronary Artery Revascularization in Diabetes) trial, 510 patients with diabetes and multivessel or complex single-vessel CAD were randomly assigned to either CABG or PCI, with the use of either BMS or DES and routine use of abciximab.<sup>156</sup> There were no differences between CABG and PCI for the primary endpoint of 1 year composite of death, MI, or stroke, but the trial was underpowered to detect these differences. However, repeat revascularization was more likely to occur in patients treated with PCI ( $P < 0.001$ ).<sup>156</sup>

In the subset of 452 patients with diabetes and multivessel CAD who were enrolled in the SYNTAX trial, there were no differences in the composite safety endpoint of all-cause death, stroke, and MI at 5 year follow-up.<sup>155</sup> However, the need for repeat revascularization (HR 2.01, 95% CI 1.04-3.88,  $P < 0.001$ ) was significantly more frequent in patients with diabetes treated with PCI than in those who underwent CABG.<sup>155,275</sup>

Patients with diabetes had a higher rate of repeat revascularization after PCI when compared with CABG in the low ( $\leq 22$ ) (38.5 vs. 18.5%, respectively,  $P = 0.014$ ) and intermediate (23-33) (27 vs. 13.4%, respectively,  $P = 0.049$ ) SYNTAX score tertiles. Further analyses according to treatment with either oral hypoglycaemic agents or insulin showed that the MACCE rate was significantly greater after PCI in both the oral hypoglycaemic agent group (PCI 40.4 vs. CABG 26.4%,  $P = 0.022$ ) and the insulin-dependent group (PCI 56.2 vs. CABG 32.6%,  $P = 0.002$ ). A higher incidence of cardiac death was noted in the insulin-dependent patients treated with PCI (PCI 18.8 vs. CABG 7.1%,  $P = 0.023$ ).

In the SYNTAX trial, diabetes was not an independent predictor of outcomes once the SYNTAX score was entered into the multivariable model.<sup>127</sup> Consequently, the SYNTAX 2 score does not include diabetes as one of the eight variables that impacts on the preferential selection of revascularization modality.<sup>127</sup> Conflicting data were seen in a patient-level pooled analysis of 6081 patients treated with stents (75% newer generation DES), stratified according to diabetes status and SYNTAX score.<sup>157</sup> After Cox regression adjustment, SYNTAX score and diabetes were both associated with MACE ( $P < 0.001$  and  $P = 0.0028$ , respectively). At 2 years, patients with diabetes had higher MACE (HR 1.25, 95% CI 1.03-1.53,  $P = 0.026$ ) and TVR, and similar death and MI rates.<sup>157</sup>

In the BEST trial, patients with diabetes treated with PCI had a higher rate of the primary endpoint of death, MI, or TVR compared with CABG (EES:  $n = 177$ ; CABG:  $n = 186$ ) (19.2 vs. 9.1%,  $P = 0.007$ ) (see section 5).<sup>105</sup>

### 9.2.2 META-ANALYSIS OF CORONARY ARTERY BYPASS GRAFTING VS. PERCUTANEOUS CORONARY INTERVENTION IN PATIENTS WITH DIABETES

A meta-analysis – restricted to four RCTs covering 3052 patients – compared PCI with the use of early-generation DES vs. CABG in

patients with diabetes and multivessel CAD. It suggested a higher risk of death and MI with revascularization by early-generation DES (RR 1.51, 95% CI 1.09-2.10;  $P < 0.01$ ), but a lower risk of stroke (2.3 vs. 3.8%; RR 0.59, 95% CI 0.39- 0.90;  $P < 0.01$ ).<sup>152</sup> A sensitivity analysis revealed that this superiority of CABG over early-generation DES for the endpoint MACCE was most pronounced among patients with a high SYNTAX score. A network meta-analysis had suggested that the survival benefit of CABG over PCI in patients with diabetes might be lost when using EES,<sup>151</sup> though this was not confirmed in a subsequent meta-analysis that also included the direct comparison between EES and CABG in the subset of BEST.<sup>153</sup>

In a collaborative, individual patient data pooled analysis of 11 518 patients with multivessel or LM disease randomized to CABG or PCI with stents, all-cause death was significantly different after CABG (9.2%) and PCI (11.2%) ( $P = 0.0038$ ), which was evident in patients with diabetes (10.7 vs. 15.7%, respectively;  $P = 0.0001$ ) but not in patients without diabetes (8.4 vs. 8.7%, respectively;  $P = 0.81$ ) (Pinteraction=0.0077).<sup>124</sup> Similar results were found in the subgroup of 7040 patients with multivessel disease (Pinteraction=0.0453), while the interaction with diabetes was not significant in the 4478 patients with LM disease (Pinteraction=0.13).

A recent population-based analysis has confirmed the benefit of CABG compared with PCI in patients with diabetes when patients present with an ACS.<sup>196</sup> Consequently, overall current evidence continues to favour CABG as the revascularization modality of choice for patients with diabetes and multivessel disease. When patients present with a comorbidity that increases surgical risk, the choice of revascularization method is best decided by multidisciplinary individualized risk assessment.

## 9.3 REVASCULARIZATION WITH THE USE OF PERCUTANEOUS CORONARY INTERVENTION

For the reasons discussed above, PCI in patients with diabetes is often more complex than PCI in the absence of diabetes. Nevertheless, irrespective of diabetic status, the same principles apply as discussed in section 16. Placement of a new-generation DES is the default strategy.

## 9.4 ANTITHROMBOTIC PHARMACOTHERAPY

In the current context of the use of oral P2Y<sub>12</sub>-inhibitors, there is no indication that antithrombotic pharmacotherapy should differ between diabetics and patients without diabetes who are undergoing revascularization. For detailed discussion refer to section 17.

## 9.5 METFORMIN

There is a theoretical risk of lactic acidosis and deteriorating renal function in patients treated with metformin who are exposed to iodinated contrast media.<sup>280</sup> Consequently, it is generally recommended that in elective cases, metformin should be withheld before angiography or PCI for 48 h, as the plasma half-life of metformin is 6.2 h,<sup>280</sup> and reintroduced 48 h later. However,

clinical experience suggests that the actual risk of lactate acidosis is very small, and that checking renal function after angiography in patients on metformin and withholding the drug when renal function deteriorates appears to be an acceptable alternative.<sup>280</sup> In patients with renal failure, metformin should be stopped before the procedure. Accurate recognition of metformin-associated lactic acidosis based on arterial pH <7.35, blood lactate >5 mmol/L (45 mg/dL), and detectable plasma metformin concentration should prompt the initiation of haemodialysis.

#### Recommendation for patients on metformin

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended to check renal function if patients have taken metformin immediately before angiography and withhold metformin if renal function deteriorates.	I	C

<sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

### 9.6 GAPS IN THE EVIDENCE

Following successful revascularization, the rate of events during follow-up remains high in patients with diabetes, independent of the mode of revascularization. Future research should be focused on identifying new disease-modifying therapies to influence the progression of vascular disease in this high-risk cohort.

## 10 Revascularization in patients with chronic kidney disease

### 10.1 EVIDENCE BASE FOR REVASCULARIZATION AND RECOMMENDATIONS

Myocardial revascularization in patients with chronic kidney disease (CKD), specifically National Kidney Foundation stage 3 or higher, is addressed by the 2014 ESC/EACTS Guidelines on myocardial revascularization. After reviewing the subsequent literature, the current Task Force has not found any evidence to support a major update. A recent *post hoc* analysis of the SYNTAX trial on patients with CKD confirms the principles for allocating patients to PCI or CABG,<sup>281</sup> as discussed in section 5 of this document.

### 10.2 PREVENTION OF CONTRAST-INDUCED NEPHROPATHY

The risk of contrast-induced nephropathy (CIN) depends on patient-related factors, such as CKD, diabetes mellitus, congestive HF, haemodynamic instability, reduced plasma volume, female sex, advanced age, anaemia, and periprocedural bleeding, as well as on the type and volume of contrast administered.<sup>282-288</sup> When the ratio of total contrast volume (in mL) to glomerular filtration rate (in mL/min) exceeds 3.7, the risk of CIN increases significantly.<sup>287,288</sup>

Adequate hydration remains the mainstay of CIN prevention.<sup>289-294</sup> High-dose statins, as indicated for secondary prevention irrespective of the risk of CIN are also beneficial.<sup>293</sup> All other strategies for the prevention of CIN do not have sufficient evidence to justify a recommendation in favour or against.<sup>293,294</sup> For more detailed discussion refer to the **Supplementary Data**.

### 10.3 GAPS IN THE EVIDENCE

Thus far, patients with CKD have been excluded from randomized trials on myocardial revascularization, hence current data are based on observational studies only. A randomized trial on optimal long-term revascularization strategies in patients with moderate-to-severe stress-induced ischaemia and severe CKD is currently ongoing (ISCHEMIA-CKD, <https://clinicaltrials.gov/ct2/show/NCT01985360>). Moreover, additional randomized evidence on optimal strategies for CIN prevention is needed.

#### Recommendations for the prevention of contrast-induced nephropathy

Recommendations	Dose	Class <sup>a</sup>	Level <sup>b</sup>
<b>Patients undergoing coronary angiography or MSCT</b>			
It is recommended that all patients are assessed for the risk of contrast-induced nephropathy.		I	C
Adequate hydration is recommended.		I	C
<b>Patients with moderate or severe CKD (National Kidney Foundation stages 3b and 4)</b>			
Use of low-osmolar or iso-osmolar contrast media is recommended. <sup>284-286</sup>		I	A
It is recommended that the volume of contrast media be minimized. <sup>287,288</sup>	Total contrast volume/GFR <3.7. <sup>c</sup>	I	B
In statin-naïve patients, pre-treatment with high-dose statins should be considered. <sup>293</sup>	Rosuvastatin 40/20 mg or atorvastatin 80 mg.	IIa	A
Pre- and post-hydration with isotonic saline should be considered if the expected contrast volume is >100 mL.	1 mL/kg/h 12 h before and continued for 24 h after the procedure (0.5 mL/kg/h if LVEF ≤35% or NYHA >2).	IIa	C
As an alternative to the pre- and post-hydration regimen, tailored hydration regimens may be considered. <sup>295-297</sup>		IIb	B
<b>Patients with severe CKD (National Kidney Foundation stage 4)</b>			
Prophylactic haemofiltration 6 h before complex PCI may be considered. <sup>298-300</sup>	Fluid replacement rate 1000 mL/h without negative loss and saline hydration continued for 24 h after the procedure.	IIb	B
Haemodialysis is not recommended as a preventive measure. <sup>300,301</sup>		III	B

CKD: chronic kidney disease; GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction; MSCT: multi-slice computed tomography; NYHA: New York Heart Association; PCI: percutaneous coronary angiography. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

<sup>c</sup>Example: 370 mL of contrast medium in a patient with a GFR of 100 mL/min will yield a ratio of 3.7. <sup>d</sup>Options are: infusion of normal saline adjusted to central venous pressure<sup>295</sup> or furosemide with matched infusion of normal saline<sup>296,297</sup> (for details see the **Supplementary Data**).

## 11 Revascularization in patients requiring valve interventions

### 11.1 PRIMARY INDICATION FOR VALVE INTERVENTIONS

Myocardial revascularization in patients undergoing primary valve interventions, either by surgery or transcatheter routes, is addressed by the 2014 ESC/EACTS Guidelines on myocardial revascularization. After reviewing the subsequent literature, the current Task Force endorses the recommendations of the 2014 Guidelines and has not found any evidence to support a major update. These recommendations are included below for ease of reference. Of note, the available evidence on invasive functional assessment of CAD (with FFR or iwFR) in patients with severe aortic stenosis (AS) is limited to a few small-scale observational studies. These studies support the feasibility of FFR and iwFR in this setting.<sup>302-304</sup> Notwithstanding, the available evidence is insufficient to support the use of invasive functional assessment of coronary lesions in patients with AS, particularly in consideration of the altered haemodynamic condition related to the presence of AS. Therefore, the Task Force is in consensus that indications for myocardial revascularization based on angiographic assessment of CAD should be maintained, consistent with the 2014 ESC/ EACTS Guidelines on myocardial revascularization and the 2017 ESC/EACTS Guidelines for the management of valvular heart disease.<sup>305</sup>

### 11.2 PRIMARY INDICATION FOR MYOCARDIAL REVASCULARIZATION

#### 11.2.1 AORTIC VALVE DISEASE

The recommendations for patients undergoing CABG for the clinically leading problem of CAD, who also have coexisting severe aortic stenosis or regurgitation, remain unchanged from those of the 2014 Guidelines and support replacement of the aortic valve.<sup>305</sup> However, in the current era of rapid developments in transcatheter valve implantation technologies, a decision regarding replacement of the aortic valve for moderate stenosis/regurgitation should be carefully considered on a case-by-case basis in discussion with the Heart Team. The patient's age, type of prosthesis, pathogenesis of aortic stenosis/regurgitation, aortic annular size, predicted size of implanted valve, transcatheter aortic valve implantation (TAVI) access routes, and technical feasibility of a TAVI procedure in the future in case of disease progression should all be taken into account.<sup>306</sup>

#### 11.2.2 MITRAL VALVE DISEASE

Patients with concomitant severe primary mitral regurgitation (MR) should undergo mitral valve repair at the time of CABG in keeping with guidance for the surgical repair of primary MR.<sup>305</sup> There is also consensus based on expert opinion on the surgical repair of severe secondary MR at the time of CABG.<sup>305,307</sup> However, considerable controversy exists about the treatment of moderate secondary or ischaemic MR in patients undergoing CABG. Until the publication of 2 year outcomes of the CTSN (Cardiothoracic Surgical Trials Network) randomized trial on treatment of 'moderate' ischaemic MR, the literature in this field was limited to small single-centre randomized trials, observational studies, and case series, and failed to provide clear direction. The CTSN trial showed that addition of

surgical mitral valve repair to CABG made no significant difference to survival, overall reduction of adverse events, or LV reverse remodelling at 2 years.<sup>308,309</sup> Increased length of intensive care and hospital stay and perioperative morbidity, including neurological complications and supraventricular arrhythmias, were reported in the CTSN and other randomized trials in this group of patients.<sup>308-310</sup> Because the CTSN trial used a very broad definition of moderate MR, including an effective regurgitant orifice area (EROA)  $\leq 0.2$  cm<sup>2</sup> plus additional criteria, no firm conclusions can be drawn concerning patients with an EROA  $>0.2$  cm<sup>2</sup>. Observational data suggest that in secondary MR, an EROA  $>0.2$  cm<sup>2</sup> and regurgitant volume  $>30$  mL indicates greater risk of cardiovascular events.<sup>311,312</sup> In the absence of dedicated trials in this setting, the decision to combine mitral valve surgery with CABG in patients with an EROA  $>0.2$  cm<sup>2</sup> and regurgitant volume  $>30$  mL needs to be made on a case-by-case basis by the Heart Team. For a more detailed discussion of this issue, please refer to the **Supplementary Data**.

### 11.3 GAPS IN THE EVIDENCE

In patients with concomitant valvular and coronary disease, the possibility of future transcatheter therapy for the aortic and mitral valves has made a significant impact on decision-making for patients with predominantly coronary disease with moderate valve lesions. However, there is currently little evidence on this topic.

#### Recommendations for combined valvular and coronary interventions

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Primary valve intervention and coronary revascularization</b>		
CABG is recommended in patients with a primary indication for aortic/mitral valve surgery and coronary artery diameter stenosis $>70\%$ .	I	C
CABG should be considered in patients with a primary indication for aortic/mitral valve surgery and coronary artery diameter stenosis of 50-70%.	Ila	C
PCI should be considered in patients with a primary indication to undergo TAVI and coronary artery diameter stenosis $>70\%$ in proximal segments.	Ila	C
PCI should be considered in patients with a primary indication to undergo transcatheter mitral valve interventions and coronary artery diameter stenosis $>70\%$ in proximal segments.	Ila	C
<b>Primary myocardial revascularization and valve intervention</b>		
SAVR is indicated in patients with severe AS undergoing CABG, or surgery of the ascending aorta or another valve.	I	C
Mitral valve surgery is indicated in patients with severe secondary MR undergoing CABG and LVEF $>30\%$ .	I	C
Mitral valve surgery should be considered in symptomatic patients with severe secondary MR and LVEF $<30\%$ , but with evidence of myocardial viability and an option for surgical revascularization.	Ila	C

AS: aortic stenosis; CABG: coronary artery bypass grafting; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; PCI: percutaneous coronary intervention; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

The need for and timing of PCI in patients undergoing TAVI is also an area with limited evidence. The long-term outcomes of patients with concomitant surgical repair of ischaemic MR are also awaited.

## 12 Associated peripheral artery diseases

### 12.1 PREVENTION OF STROKE ASSOCIATED WITH CAROTID ARTERY DISEASE AND MYOCARDIAL REVASCUARIZATION

The early risk of stroke after myocardial revascularization is higher after CABG than after PCI.<sup>313</sup> After 30 days, stroke rates between revascularization techniques were similar in a recent individual patient data meta-analysis of 11 randomized trials.<sup>313</sup>

Ischaemic stroke after CABG is multifactorial: thrombo-embolism from the aorta, its branches, or the heart; atrial arrhythmias; inflammatory pro-thrombogenic milieu; lower levels of antiplatelet therapy perioperatively; and haemodynamic instability. However, the most consistent predictor of perioperative stroke is previous stroke or TIA. There is no strong evidence that carotid artery stenosis is a significant cause of perioperative stroke except for bilateral severe carotid bifurcation stenosis.<sup>314</sup> Therefore, indications for preoperative carotid bifurcation screening by duplex ultrasound are limited.<sup>315</sup> Also, there is no evidence that prophylactic revascularization of unilateral asymptomatic carotid stenoses in CABG candidates reduces the risk of perioperative stroke. It may be reasonable to restrict prophylactic carotid revascularization to patients at highest risk of post-operative stroke, i.e. patients with severe bilateral lesions or a history of prior stroke/TIA.<sup>316</sup> Hence, the indication for revascularization, and the choice between carotid endarterectomy or carotid artery stenting in these patients, should be made by a multidisciplinary team including a neurologist.

The 2017 Guidelines on the diagnosis and treatment of peripheral arterial diseases in collaboration with the European Society of Vascular Surgery cover the screening for and management of carotid artery disease in patients scheduled for CABG, including screening, indications, and the timing and type of carotid revascularization.<sup>317</sup> Its recommendations are reproduced here.

Particularly for patients at high risk for perioperative stroke after CABG, such as elderly patients or patients with previous TIA/stroke, specific preventive measures have been suggested. CT scan screening of the ascending aorta/arch atheroma has been proposed to better assess risk stratification and guide the surgical strategy in elderly patients.<sup>318</sup> It is recommended that acetylsalicylic acid is restarted 6 h, or at the latest 24 h, after surgery, and that clopidogrel or ticagrelor are added in patients with ACS. New-onset atrial fibrillation (AF) is associated with a risk of stroke that increased two-to-three times after CABG. Its management is discussed in section 14.

### 12.2 ASSOCIATED CORONARY AND PERIPHERAL ARTERY DISEASES

Of all patients with CAD, 7-16% have lower extremity artery disease (LEAD), which is associated with a worse prognosis, even if it remains frequently asymptomatic, masked by cardiac symptoms. On the other hand, in patients with LEAD, CAD is present

in up to 70% of patients.<sup>317</sup> The choice between CABG and PCI is controversial and, in the absence of solid data, it should follow a multidisciplinary approach.<sup>127</sup> In patients undergoing CABG,

#### Recommendations on the management of carotid stenosis in patients undergoing coronary artery bypass grafting

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
In patients scheduled for CABG, it is recommended that the indication (and if so the method and timing) for carotid revascularization be individualized after discussion within a multidisciplinary team, including a neurologist.	I	C
In patients scheduled for CABG, with recent (<6 months) history of TIA/stroke:		
– Carotid revascularization should be considered in patients with 50-99% carotid stenosis. <sup>319,320</sup>	IIa	B
– Carotid revascularization with CEA should be considered as first choice in patients with 50-99% carotid stenosis. <sup>319,320</sup>	IIa	B
– Carotid revascularization is not recommended in patients with carotid stenosis <50%.	III	C
In neurologically asymptomatic patients scheduled for CABG:		
– Carotid revascularization may be considered in patients with bilateral 70-99% carotid stenosis or 70-99% carotid stenosis and contralateral occlusion.	IIb	C
– Carotid revascularization may be considered in patients with a 70-99% carotid stenosis, in the presence of one or more characteristics that may be associated with an increased risk of ipsilateral stroke, <sup>c</sup> in order to reduce stroke risk beyond the perioperative period.	IIb	C
– Routine prophylactic carotid revascularization in patients with a 70-99% carotid stenosis is not recommended.	III	C

CABG: coronary artery bypass grafting; CEA: carotid endarterectomy; TIA: transient ischaemic attack. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence. <sup>c</sup>Contralateral TIA/stroke, ipsilateral silent infarction on cerebral imaging, intraplaque haemorrhage or lipid-rich necrotic core on magnetic resonance angiography, or any of the following ultrasound imaging findings: stenosis progression (>20%), spontaneous embolization on transcranial Doppler, impaired cerebral vascular reserve, large plaques, echolucent plaques, or increased juxta-luminal hypoechoic area.<sup>317</sup>

#### Preoperative strategies to reduce the incidence of stroke in patients undergoing coronary artery bypass grafting

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
In patients undergoing CABG, carotid DUS is recommended in patients with recent (<6 months) history of stroke/TIA. <sup>321,322</sup>	I	B
In patients with no recent (<6 months) history of TIA/stroke, carotid DUS may be considered before CABG in the following cases: age ≥70 years, multivessel coronary artery disease, concomitant LEAD, or carotid bruit. <sup>321,322</sup>	IIb	B
Screening for carotid stenosis is not indicated in patients requiring urgent CABG with no recent stroke/TIA.	III	C

CABG: coronary artery bypass grafting; DUS: duplex ultrasound; LEAD: lower extremity artery disease; TIA: transient ischaemic attack. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

the saphenous vein should be preserved or harvested guided by the results of clinical examination including the ankle-brachial index. In addition, inter-arm blood pressure asymmetry should lead to the investigation of subclavian artery stenosis. Further details are provided in the 2017 peripheral arterial diseases Guidelines.<sup>317</sup>

## 13 Repeat revascularization

### 13.1 EARLY GRAFT FAILURE

Early graft failure after CABG is reported in up to 12% of grafts, as evaluated by intraoperative angiography.<sup>323</sup> However, only a minority (around 3%) are clinically apparent. Graft failure can be due to conduit defects, anastomotic technical errors, poor native vessel run-off, or competitive flow with the native vessel. When clinically relevant, acute graft failure may result in MI with consequently increased mortality and major cardiac events. The suspicion of early graft failure should arise in the presence of ECG signs of ischaemia, ventricular arrhythmias, biomarker changes, new wall motion abnormalities, or haemodynamic instability.<sup>324,325</sup> Owing to the low specificity of ECG changes and echocardiographic wall motion abnormalities during the post-operative course, and the delay in the appearance of biomarker changes, a careful assessment of all variables will influence decision-making for angiographic evaluation.

Perioperative angiography is recommended in cases of suspected severe myocardial ischaemia to detect its cause and aid decision-making on the most appropriate treatment.<sup>323,325,326</sup> In symptomatic patients, early post-operative graft failure can be identified as the cause of ischaemia in 40-80% of cases.<sup>324,326-328</sup> The optimal treatment strategy in patients with acute graft failure should be decided by *ad hoc* consultation between the cardiovascular surgeon and the interventional cardiologist, on the basis of the patient's clinical condition and the extent of myocardium at risk. In the case of early post-operative graft failure, emergency *ad hoc* PCI may limit the extent of infarction, if technically feasible. The target for PCI is the native vessel or the internal mammary artery (IMA) graft, while the acutely occluded saphenous vein graft (SVG) and any anastomotic site should be avoided, if possible, due to concerns regarding embolization or perforation. Redo surgery should be favoured if the anatomy is unsuitable for PCI, if several important grafts are occluded, or in the case of clear anastomotic errors. In asymptomatic patients, repeat revascularization should be considered if the artery is of an appropriate size and supplies a large territory of myocardium.

Further details on the diagnosis and management of perioperative MI are provided in a recent ESC position paper.<sup>329</sup>

### 13.2 ACUTE PERCUTANEOUS CORONARY INTERVENTION FAILURE

The need for urgent surgery to manage PCI-related complications is uncommon (<1%) and only required in patients with major complications that cannot be adequately resolved by percutaneous techniques.<sup>330,331</sup> The need for emergency CABG is mainly confined to patients with a large, evolving MI due to iatrogenic vessel

occlusion that cannot be salvaged percutaneously, or in patients with recurrent cardiac tamponade after pericardiocentesis following PCI-related vessel rupture.<sup>330,332,333</sup>

### 13.3 DISEASE PROGRESSION AND LATE GRAFT FAILURE

Ischaemia after CABG may be due to the progression of disease in native vessels or *de novo* disease of bypass grafts.<sup>334</sup> Repeat revascularization in these patients is indicated in the presence of significant symptoms despite medical treatment, and in asymptomatic patients with objective evidence of large myocardial ischaemia (>10% of the LV).<sup>32,87</sup>

#### 13.3.1 REDO CORONARY ARTERY BYPASS GRAFTING OR PERCUTANEOUS CORONARY INTERVENTION

PCI in patients with prior CABG has worse acute and long-term outcomes than in patients without prior CABG.<sup>335,336</sup> Likewise, redo CABG has a two- to four-fold increased mortality compared with first-time CABG, and repeat CABG is generally performed infrequently.<sup>334,337-339</sup> There are limited data comparing the efficacy of PCI vs. redo CABG in patients with previous CABG. The proportion of patients undergoing PCI, redo CABG, or conservative treatment differs significantly between studies; in one study, PCI was favoured in 50% of patients with only 22% undergoing redo CABG, while another study favoured CABG in 67% of patients.<sup>340,341</sup> In the AWESOME (Angina With Extremely Serious Operative Mortality Evaluation) RCT and registry, overall 3 year mortality was comparable between redo CABG and PCI.<sup>341,342</sup> A more recent study also found comparable rates of death and MI between redo CABG and PCI, although there were significantly more repeat revascularizations with PCI.<sup>341,343</sup>

In view of the higher risk of procedural mortality with redo CABG and the similar long-term outcome, PCI is the preferred revascularization strategy in patients with amenable anatomy.<sup>340</sup> PCI via the bypassed native artery should be the preferred approach. If PCI in the native vessel fails or is not an option, PCI in the diseased SVG should be considered. CABG should be considered for patients with extensively diseased or occluded bypass grafts and diffuse native vessel disease, especially in the absence of patent arterial grafts.<sup>340</sup> The IMA is the conduit of choice for revascularization during redo CABG if not previously used, or can be salvaged and reused in specific cases.<sup>344,345</sup>

#### 13.3.2 PERCUTANEOUS CORONARY INTERVENTION FOR SAPHENOUS VEIN GRAFT LESIONS

PCI in SVGs is associated with an increased risk of distal coronary embolization, frequently resulting in periprocedural MI.<sup>346</sup> PCI of *de novo* SVG stenosis is considered a high-risk intervention because SVG atheroma is friable and more prone to distal embolization. Several different approaches have been evaluated to prevent the distal embolization of particulate debris, including distal occlusion/aspiration, proximal occlusion, suction, filter devices, or covered stents. Distal protection devices using filters have shown the most encouraging results. However, although a single randomized trial supports the use of distal embolic protection during SVG PCI, observational studies including data from large-scale registries are

conflicting.<sup>347-349</sup> Outcomes from studies with other devices used for SVG PCI are not sufficient to recommend its use.<sup>350-353</sup>

Based on data from a small number of randomized trials, implantation of DES in SVG lesions is associated with a lower risk of repeat revascularization than with BMS at 1 year follow-up.<sup>354-356</sup> In the only trial powered for a clinical endpoint – the ISAR-CABG (Is Drug-Eluting-Stenting Associated with Improved Results in Coronary Artery Bypass Grafts) trial<sup>354</sup> – the primary endpoint of death, MI, and target lesion revascularization was significantly reduced with DES vs. BMS. However, at 5 year follow-up, the advantage of DES over BMS was lost due to a higher incidence of target lesion revascularization between years 1 and 5 in patients treated with DES.<sup>357</sup> Longer-term follow-up of the two smaller trials is available; one suggested sustained superiority of DES over BMS, while the other suggested loss of the efficacy advantage of the DES.<sup>358,359</sup>

### 13.4 REPEAT PERCUTANEOUS CORONARY INTERVENTION

Recurrence of symptoms or ischaemia after PCI is the result of restenosis, incomplete initial revascularization, or disease progression.<sup>334</sup> Patients may require repeat PCI due to late and very late stent thrombosis.

#### 13.4.1 RESTENOSIS

Restenosis associated with angina or ischaemia should be treated by repeat revascularization, and repeat PCI remains the strategy of

choice for most of these patients. In this setting, the results from DES are superior to those obtained with balloon angioplasty, BMS implantation, or brachytherapy.<sup>360-364</sup>

For restenosis within BMS, drug-coated balloon (DCB) proved superior to plain balloon angioplasty<sup>365-367</sup> and comparable to first-generation DES.<sup>365,366,368-372</sup> One trial showed inferior angiographic outcomes in comparison to new-generation DES,<sup>373</sup> while a second trial showed comparable outcomes.<sup>374</sup> For restenosis within DES, DCBs also proved superior to plain balloon angioplasty<sup>367,369,371</sup> and comparable to first-generation DES.<sup>371</sup> In one study, DCBs were inferior to new-generation DES in terms of the primary angiographic outcome measure.<sup>375</sup> In a more recent study, including patients with any type of in-stent restenosis, outcomes between DCB and repeat stenting with new-generation DES were comparable.<sup>376</sup> A single randomized trial of patients undergoing DCB for restenosis within DES showed superior angiographic outcomes in patients who underwent lesion preparation with scoring balloons vs. standard angioplasty balloons.<sup>377</sup>

Network meta-analysis suggests that repeat stenting with new-generation DES (with EES) and DCB are ranked first and second as the highest efficacy treatments.<sup>378,379</sup> The superior angiographic antirestenotic efficacy of new-generation DES should be weighed against a possible excess of long-term adverse events with repeat stenting during longer-term follow-up of these trials.<sup>380,381</sup> However, observations in relation to clinical events must

#### Recommendations on repeat revascularization

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Early post-operative ischaemia and graft failure</b>		
Coronary angiography post-CABG is recommended for patients with: – symptoms of ischaemia and/or abnormal biomarkers suggestive of perioperative MI – ischaemic ECG changes indicating large area of risk – new significant wall motion abnormalities – haemodynamic instability.	I	C
It is recommended that either emergency reoperation or PCI is decided upon by <i>ad hoc</i> consultation in the Heart Team, based on the feasibility of revascularization, area at risk, comorbidities, and clinical status.	I	C
<b>Disease progression and late graft failure</b>		
Repeat revascularization is indicated in patients with a large area of ischaemia or severe symptoms despite medical therapy. <sup>84,334</sup>	I	B
If considered safe, PCI should be considered as first choice over CABG.	IIa	C
<b>Procedural aspects of the revascularization modalities</b>		
<b>CABG</b>		
IMA is the conduit of choice for redo CABG in patients in whom the IMA was not used previously. <sup>344</sup>	I	B
Redo CABG should be considered for patients without a patent IMA graft to the LAD. <sup>340,341,344</sup>	IIa	B
<b>PCI</b>		
Distal protection devices should be considered for PCI of SVG lesions. <sup>348,350,351</sup>	IIa	B
PCI of the bypassed native artery should be considered over PCI of the bypass graft.	IIa	C
<b>Restenosis</b>		
DES are recommended for the treatment of in-stent restenosis of BMS or DES. <sup>373,375,378,379</sup>	I	A
Drug-coated balloons are recommended for the treatment of in-stent restenosis of BMS or DES. <sup>373,375,378,379</sup>	I	A
In patients with recurrent episodes of diffuse in-stent restenosis, CABG should be considered by the Heart Team over a new PCI attempt.	IIa	C
IVUS and/or OCT should be considered to detect stent-related mechanical problems leading to restenosis.	IIa	C

BMS: bare-metal stent; CABG: coronary artery bypass grafting; DES: drug-eluting stent; ECG: electrocardiogram; IMA: internal mammary artery; IVUS: intravascular ultrasound; LAD: left anterior descending artery; MI: myocardial infarction; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; SVG: saphenous vein graft. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

be interpreted with caution, as none of the trials was powered for clinical endpoints and the comparator stent in studies with long-term follow-up was an early-generation DES.

The use of intracoronary imaging provides unique insights into the underlying mechanisms of in-stent restenosis (see section 16.2). OCT is able to detect the presence of neoatherosclerosis in a significant number of these patients. Underexpanded stents should be aggressively tackled with high-pressure dilatations using non-compliant balloons. The optimization of the final results remains crucial during reinterventions for in-stent restenosis and, in this regard, the use of intracoronary imaging may be particularly helpful. Outcomes of patients with in-stent restenosis after DES are poorer than those in patients with BMS in-stent restenosis, independently of the therapeutic modality.<sup>382</sup> In patients with recurrent episodes of diffuse in-stent restenosis in large vessels – and in those with associated multivessel disease, especially in the presence of other complex lesions such as chronic total occlusions – CABG should be considered before a new PCI attempt.

#### 13.4.2 DISEASE PROGRESSION

Patients with symptomatic disease progression after PCI account for up to 50% of reinterventions.<sup>383,384</sup> They should be managed using criteria similar to those applied to patients without previous revascularization.

#### 13.4.3 STENT THROMBOSIS

Although stent thrombosis is very rare, particularly since the advent of new-generation DES, it may have devastating clinical

consequences. Stent thrombosis usually presents as a large MI and patients should be treated according to the principles outlined in section 8.<sup>385</sup> Aggressive, high-pressure balloon dilation should be used to correct underlying, stent-related, predisposing mechanical problems.<sup>386,387</sup> Liberal use of intracoronary imaging in order to detect and modify underlying mechanical factors is recommended (**Figure 7**) (see section 16.2).

Although repeat stenting in patients with stent thrombosis may be avoided when satisfactory results are obtained with balloon dilation, a new stent may be required to overcome edge-related dissections and adjacent lesions, or to optimize final results.<sup>388</sup>

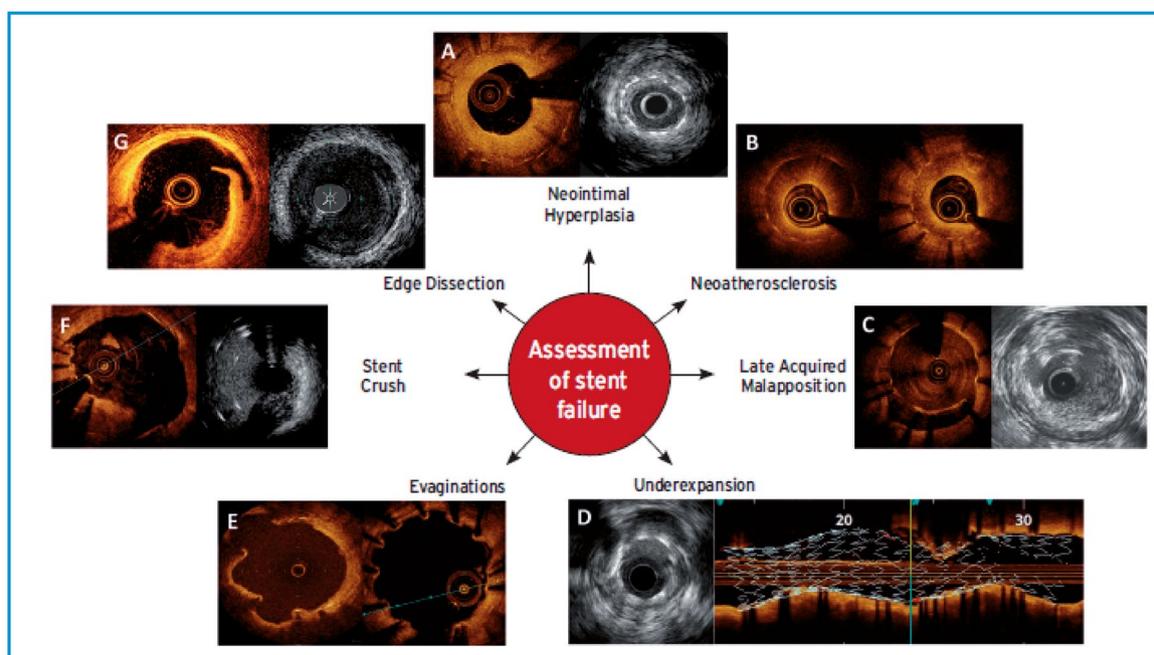
There is no evidence that the post-interventional management of patients with stent thrombosis should differ from that of patients with thrombosis of a *de novo* lesion resulting in STEMI.

## 14 Arrhythmias

### 14.1 VENTRICULAR ARRHYTHMIAS

#### 14.1.1 REVASCULARIZATION FOR THE PREVENTION OF SUDDEN CARDIAC DEATH IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE AND REDUCED LEFT VENTRICULAR FUNCTION

Revascularization plays an important role in reducing the frequency of ventricular arrhythmias in patients with normal or mildly reduced LV function,<sup>389,390</sup> as well as the risk of sudden cardiac death in patients with CAD and LVEF  $\leq 35\%$ .<sup>391</sup> Indirect evidence for a protective effect of revascularization was demonstrated in the



Examples of intracoronary imaging findings (IVUS or OCT) in patients with stent failure. **Panel A** displays OCT (left) and IVUS (right) examples of in-stent restenosis due to excessive neointimal hyperplasia. **Panel B** displays two OCT examples of in-stent restenosis due to neoatherosclerosis. **Panel C** displays OCT (left) and IVUS (right) examples of late acquired malapposition. **Panel D** displays IVUS (left) and longitudinal OCT reconstruction (right) images of stent underexpansion. **Panel E** displays two OCT examples of in-stent evaginations, a typical finding of delayed arterial healing. **Panel F** displays OCT (left) and IVUS (right) examples of stent crush. **Panel G** displays an OCT (left) and IVUS (right) case of coronary dissection at the stent edge. IVUS = intravascular ultrasound; OCT = optical coherence tomography.

Intracoronary images for this figure were kindly provided by Drs Nicolas Amabile, Fernando Alfonso, and Gennaro Sardella.

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**Figure 7.** Intracoronary imaging for the assessment of stent failure.

MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) and SCD-HEFT studies (Sudden Cardiac Death in Heart Failure Trial), where the efficacy of implantation cardioverter defibrillators (ICDs) was reduced if revascularization was performed prior to implantation.<sup>392,393</sup> CABG in patients with reduced EF reduces cardiac and overall mortality for a follow-up of 10 years.<sup>78,81</sup> In view of the protective effect of revascularization on ventricular arrhythmias, patients with ischaemic LV dysfunction (LVEF  $\leq 35\%$ ) who are considered for primary preventive ICD implantation should be evaluated for ischaemia and/or for potential revascularization targets.

#### 14.1.2 REVASCULARIZATION FOR THE TREATMENT OF ELECTRICAL STORM

Electrical storm is a life-threatening syndrome related to incessant ventricular arrhythmias, which is most frequently observed in patients with ischaemic heart disease, advanced systolic HF, valve disease, corrected congenital heart disease, and genetic disorders such as Brugada syndrome, early repolarization, and long QT syndrome.<sup>394</sup> Urgent coronary angiography and revascularization should be part of the management of patients with electrical storm, as well as antiarrhythmic drug therapy and/or ablation of ventricular tachycardia.

#### 14.1.3 REVASCULARIZATION AFTER OUT-OF-HOSPITAL CARDIAC ARREST

Approximately 70% of survivors of out-of-hospital cardiac arrest have CAD, with acute vessel occlusion observed in 50%.<sup>395</sup> Multiple non-randomized studies suggest that emergency coronary angiography and, if appropriate, PCI after out-of-hospital cardiac arrest yield a favourable survival rate of  $\leq 60\%$  at 1 year, which is considerably higher than the 25% overall survival rate in patients with aborted cardiac arrest.<sup>396,397</sup> More recent data suggest that almost one-quarter of patients, resuscitated from cardiac arrest but without ST-segment elevation, show a culprit lesion (either vessel occlusion or irregular lesion).<sup>398-401</sup> Recent large-scale observational studies have shown an impact on mortality of early angiography after out-of-hospital cardiac arrest.<sup>402,403</sup> Thus, in survivors of out-of-hospital cardiac arrest, early coronary angiography and PCI, if appropriate, should be performed irrespective of the ECG pattern if no obvious non-cardiac cause of the arrhythmia is present.<sup>404</sup>

### 14.2 ATRIAL ARRHYTHMIAS

The management of AF in patients with ischaemic heart disease is addressed by the 2016 ESC Guidelines for the management of AF developed in collaboration with EACTS.<sup>405</sup> After reviewing the subsequent literature, the current Task Force endorses the recommendations of the 2016 Guidelines and has not identified a need for any major update. Accordingly, the recommendation tables are taken from the 2016 Guidelines. For a detailed discussion, we refer to the previous Guidelines.<sup>405</sup>

#### 14.2.1 ATRIAL FIBRILLATION COMPLICATING PERCUTANEOUS CORONARY INTERVENTION

New-onset AF in patients undergoing PCI occurs in 2-6% of procedures and increases with age, pre-existing HF, AMI, and arterial

hypertension.<sup>406-409</sup> Notably, new-onset AF [defined as change from sinus rhythm (SR) at admission to AF during/after PCI] typically occurs during the first 4 days after AMI, and is associated with impaired prognosis and a more than doubling of the risk of death, congestive HF, and stroke.<sup>403</sup>

The use of oral anticoagulation (OAC) for stroke prevention in patients with AF occurring during or after PCI should follow the ESC Guidelines on Atrial Fibrillation for antithrombotic treatment of AF that occurs outside the setting of PCI,<sup>405</sup> although prospective studies are scarce. The combination and duration of anticoagulation and antiplatelet therapy should be assessed according to the clinical situation, as outlined in section 17 as well as in the ESC Guidelines on Atrial Fibrillation<sup>405</sup> and the ESC Focused Update on Dual Antiplatelet Therapy.<sup>410</sup>

#### 14.2.2 ATRIAL FIBRILLATION COMPLICATING CORONARY ARTERY BYPASS GRAFTING

Post-operative AF affects one-third of patients undergoing cardiac surgery.<sup>411-414</sup> The main risk factor for post-operative AF is age, and it is associated with an increased immediate risk of stroke, increased morbidity, and 30 day mortality.<sup>415-417</sup> In the long-term, patients with an episode of post-operative AF have a two-fold increase in cardiovascular mortality, and a substantially increased risk of future AF and ischaemic stroke compared with patients who remain in SR after surgery.<sup>416,418-422</sup>

Post-operative AF is a common complication, in which prophylactic treatment has a moderate effect. Pre-operative anti-arrhythmic drug treatment may be initiated but will have to be weighed against side effects. Beta-blockers decrease the incidence of post-operative AF after CABG.<sup>412,423-429</sup>

#### 14.2.3 POST-OPERATIVE ATRIAL FIBRILLATION AND STROKE RISK

Patients with post-operative AF have an increased stroke risk post-operatively as well as during follow-up,<sup>419,430</sup> and warfarin medication at discharge has been associated with a reduced long-term mortality.<sup>431</sup> To date, there are no studies indicating that post-operative AF is less harmful than any other form of AF, and good quality data are needed. Anticoagulation treatment with warfarin or non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in patients with post-operative AF should therefore follow the guidelines for the antithrombotic treatment of AF occurring outside the setting of CABG using the CHA<sub>2</sub>DS<sub>2</sub>-VASc [Cardiac failure, Hypertension, Age  $\geq 75$  (Doubled), Diabetes, Stroke (Doubled) - Vascular disease, Age 65-74 and Sex category (Female)] score. The duration and timing of OAC in post-operative AF patients should be assessed individually.

Whether or not surgical left atrial appendage (LAA) obliteration reduces stroke risk has been studied in smaller trials and registry studies with conflicting results,<sup>432-434</sup> and is currently under investigation in a large randomized trial.<sup>435</sup> Removal or closure of the LAA should be considered as an adjunct to anticoagulation and not as an alternative until more data are available.

### Recommendations for the prevention of ventricular arrhythmias by revascularization

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
A primary PCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG consistent with STEMI. <sup>395,397,436,437</sup>	I	B
Urgent angiography (and PCI if indicated) should be considered in patients with resuscitated cardiac arrest without diagnostic ST-segment elevation but with a high suspicion of ongoing myocardial ischaemia.	IIa	C
In patients with electrical storm, urgent coronary angiography and revascularization (as required) should be considered.	IIa	C

ECG: electrocardiogram; STEMI: ST-elevation myocardial infarction; PCI: percutaneous coronary intervention. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

### Recommendations for the prevention and treatment of atrial fibrillation in the setting of myocardial revascularization

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Perioperative oral beta-blocker therapy is recommended for the prevention of post-operative AF after CABG surgery. <sup>412,438</sup>	I	B
Restoration of sinus rhythm by electrical cardioversion or antiarrhythmic drugs is recommended in post-operative AF with haemodynamic instability.	I	C
Perioperative amiodarone should be considered as prophylactic therapy to prevent AF after CABG surgery. <sup>412,439</sup>	IIa	A
Long-term anticoagulation should be considered in patients with AF after CABG or PCI who are at risk of stroke, considering the individual stroke and bleeding risk. <sup>440,441</sup>	IIa	B
Rate control and anticoagulation should be considered as the initial management of asymptomatic post-operative AF. <sup>442</sup>	IIa	B
Antiarrhythmic drugs should be considered for symptomatic post-operative AF after CABG or PCI in an attempt to restore sinus rhythm.	IIa	C
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing CABG surgery. <sup>432-434</sup>	IIb	B

AF: atrial fibrillation; CABG: coronary artery bypass grafting; LAA: left atrial appendage; PCI: percutaneous coronary intervention. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

#### 14.3 GAPS IN THE EVIDENCE

The duration of anticoagulation and their combination with antiplatelet therapy in patients with new-onset AF after PCI or CABG has not been studied sufficiently. Likewise, the role of routine left atrial exclusion at surgery for the prevention of stroke is currently unclear.

### 15 Procedural aspects of coronary artery bypass grafting

CABG remains the most common cardiac surgical procedure, and the techniques have been refined during 50 years of evolution.<sup>443</sup> Perioperative medication and blood management are covered in separate Guidelines.<sup>410,444</sup>

#### 15.1 SURGICAL TECHNIQUES

##### 15.1.1 COMPLETENESS OF REVASCULARIZATION

Current surgical practice is largely based on an anatomical definition of complete revascularization, and aims to bypass all epicardial vessels with a diameter exceeding  $\geq 1.5$  mm and a luminal reduction of  $\geq 50\%$  in at least one angiographic view.<sup>131</sup> Depending on the definition of completeness of revascularization, the outcome after CABG in patients with incomplete revascularization was either similar<sup>445-449</sup> or inferior<sup>131,132,449-451</sup> to that of patients with complete revascularization. Certainly, in some patients with a stenosis in small vessels with little myocardium at risk, complete revascularization may not be necessary.

FFR-guided surgical revascularization has been associated with improved graft patency, but more studies are needed to investigate

whether it improves clinical outcomes.<sup>28,452</sup> Further discussion of FFR-guided revascularization is provided in sections 3.2.1.1 and 5.3.1.3.

##### 15.1.2 CONDUIT SELECTION

In addition to patient-related factors, the outcome following CABG is related to the long-term patency of grafts and therefore is maximized with the use of arterial grafts, specifically the IMA.<sup>453,454</sup> Except in rare circumstances, all patients should receive at least one arterial graft – the left IMA (LIMA) – preferentially to the LAD.<sup>453,455</sup> SVG patency rates for non-LAD targets have been reported to be suboptimal.<sup>456</sup> Bilateral IMA (BIMA) and radial artery for non-LAD targets have been shown to provide better patency rates than SVG, particularly for the left coronary artery system.<sup>457</sup> Therefore, a second arterial graft should be considered depending on the patient's life expectancy, risk factors for sternal wound complications, coronary anatomy, degree of target vessel stenosis, graft quality, and surgical expertise.

Whether or not the use of additional arterial grafts can translate into prolonged survival remains debatable. Data from non-randomized studies suggest that the use of BIMA over single IMA (SIMA) use is associated with improved long-term survival, as well as fewer non-fatal events such as MI, recurrent angina, and the need for re-operation.<sup>458-465</sup> However, observational studies are subject to selection bias, despite propensity matching, and the effect of prolonged survival with additional arterial grafts has not been confirmed in randomized trials.<sup>466</sup>

The ART trial (Arterial Revascularization Trial) has been designed to answer the question of whether BIMA can improve

10 year survival when compared with SIMA. Interim analysis showed no difference at 5 years in the rate of death or the composite of death, MI, or stroke, and 10 year results are warranted to draw final conclusions.<sup>467</sup> Limitations of the ART trial include a high crossover rate from the BIMA arm to the SIMA arm and a high rate of radial artery use in the SIMA arm that may have diluted the benefit of BIMA.<sup>468-470</sup> The use of BIMA grafting is associated with an increase in sternal dehiscence, and an increased rate of mediastinitis in obese patients and patients with diabetes.<sup>458,464,471-475</sup> In the ART trial, the use of BIMA was associated with a 1.0-1.5% absolute risk increase in the need for sternal reconstruction, and a subsequent subanalysis has found that this risk is minimized with skeletonized harvesting.<sup>476</sup> While we await the 10 year data of the ART trial, BIMA grafting should be considered in patients with a reasonable life expectancy and a low risk of sternal wound complications.

The radial artery constitutes an alternative as the second arterial graft in patients in whom BIMA grafting is not feasible, patients with a high risk of sternal wound complications, or as a third arterial graft. There is a strong, adverse influence on radial artery patency when the native coronary artery stenosis is <70%, and therefore its use should be limited to coronary artery stenosis >70% and ideally >90%.<sup>477</sup> Use of the radial artery as the second conduit of choice has been linked to improved survival in registry studies.<sup>478-480</sup> Available RCTs testing the radial artery vs. saphenous vein graft used angiographic patency as the primary endpoint, and none was powered to detect differences in clinical outcomes.<sup>481</sup> A recently published patient-level meta-analysis pooling six RCTs comparing radial artery vs. saphenous vein graft showed that the use of the radial artery was associated with a lower rate of the primary endpoint (composite of death, myocardial infarction, and repeat revascularization) at mean follow-up of 50 months, mainly driven by a significantly strong reduction of need for reintervention and a more modest reduction in subsequent MI.<sup>482</sup> Despite a significantly lower risk of occlusion at follow-up angiography, no difference in all-cause mortality was found.

### 15.1.3 MAMMARY ARTERY HARVESTING

While the skeletonized technique of harvesting the IMA has a higher theoretical potential for injury, the potential benefits include a longer conduit, more versatility (sequential anastomosis), higher blood flow, and fewer wound-healing problems.<sup>471,483-488</sup> Therefore, in patients at higher risk of sternal wound complications, skeletonization is recommended.

### 15.1.4 RADIAL ARTERY HARVESTING

Radial artery harvesting is associated with negligible morbidity if preceded by assessment of the hand's collateral circulation. Endoscopic radial harvesting is possible, but robust evidence concerning its safety and efficacy is scarce.<sup>489,490</sup> Use of the radial artery after recent coronary angiography with radial access should be discouraged due to potential endothelial damage.<sup>491</sup> Harvesting of the whole radial artery pedicle, together with the intraluminal and subadventitial injection of vasodilators, are useful steps to prevent spasm.

### 15.1.5 SAPHENOUS VEIN HARVESTING

Saphenous vein harvesting can be accomplished using open and minimally invasive techniques, which include interrupted incisions and partial or full endoscopic procedures. Endoscopic vein graft harvesting leads to a reduced rate of leg wound complications,<sup>492-495</sup> but the short- and long-term patency of endoscopically harvested vein grafts, compared with openly harvested grafts, has been challenged.<sup>456,496-498</sup> Although there is no unequivocal evidence concerning patency rates, most data from meta-analyses and randomized and non-randomized trials do not demonstrate inferior clinical outcomes with endoscopic vein harvest.<sup>492,493,499,500</sup> If an endoscopic vein graft harvest is performed, it should be undertaken by experienced surgeons or physician assistants with appropriate training and reasonable caseloads.<sup>501-503</sup> If an open technique is used, the 'no-touch' technique has shown superior patency rates in multiple randomized trials,<sup>504-507</sup> with a patency rate >80% after 16 years.<sup>507</sup>

### 15.1.6 CROSS-CLAMPING

A single cross-clamp technique may be preferred to multiple manipulations of the aorta, with the aim of reducing atheroembolic events, but a strict no-touch technique most effectively reduces embolization of atherosclerotic material.<sup>508-510</sup> In cases of off-pump surgery, devices that allow a clampless procedure may help reduce the incidence of cerebral vascular complications.<sup>511,512</sup>

### 15.1.7 INTRAOPERATIVE QUALITY CONTROL

Besides continuous ECG monitoring and transoesophageal echocardiography immediately after revascularization, intraoperative quality control may also include graft flow measurement to confirm or exclude a technical graft problem.<sup>513</sup> Transit-time flow measurement is the most frequently used technique for graft assessment and has been able to detect 2-4% of grafts that require revision.<sup>513,514</sup> In observational studies, the use of intraoperative graft assessment has been shown to reduce the rate of adverse events and graft failure, although interpretation can be challenging in sequential and T-graft configurations.<sup>513,515-517</sup>

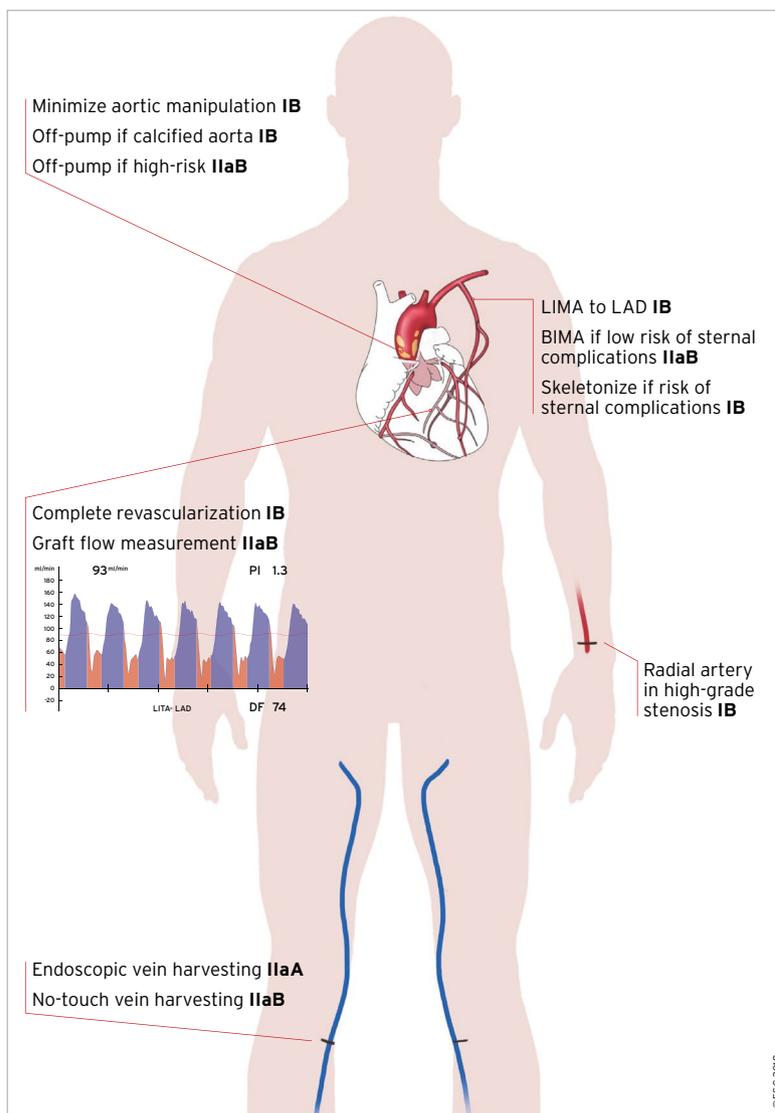
### 15.1.8 ON-PUMP AND OFF-PUMP PROCEDURES

Two large, international randomized trials have shown no difference in 30 day or 1 year clinical outcomes between on- and off-pump surgery when performed by experienced surgeons.<sup>518-520</sup> There is also evidence to conclude that, for most patients and surgeons, on-pump surgery provides excellent short- and long-term outcomes.<sup>518,520-523</sup> For some surgeons, off-pump surgery is associated with inferior early and late graft patency rates, and possibly compromised long-term survival; however, aortic no-touch/clampless off-pump procedures in the hands of highly trained teams appear to be associated with a reduced risk of early morbidity, such as stroke, and fewer transfusions.<sup>508-510,524-528</sup> In the subgroup of patients with end-stage CKD, there is some evidence that off-pump surgery is associated with lower in-hospital mortality and less need for new renal replacement therapy.<sup>529</sup>

A summary of these technical aspects can be found in **Figure 8**.

### 15.1.9 MINIMALLY INVASIVE AND HYBRID PROCEDURES

Minimally invasive coronary surgery with LIMA, harvested either directly or under video-assisted vision, may represent an attractive



**Figure 8.** Technical aspects of CABG. BIMA: bilateral internal mammary artery; CABG: coronary artery bypass grafting; IMA: internal mammary artery; LAD: left anterior descending coronary artery.

alternative to a sternotomy.<sup>530</sup> It has a similar safety and efficacy profile to conventional on-pump and off-pump procedures, with a markedly reduced post-operative length of stay and an early quality of life benefit, although spreading of the ribs is associated with increased post-operative pain.<sup>531-533</sup> It has been shown to be safe and effective in the treatment of proximal LAD stenosis or chronically occluded LAD arteries.<sup>144</sup> Moreover, when compared with PCI in a setting of single-vessel proximal LAD disease, minimally invasive coronary surgery was associated with less need for coronary reintervention.<sup>143,534,535</sup> When combined with PCI to non-LAD vessels, it provides the opportunity for hybrid coronary revascularization to be performed in selected patients with multi-vessel disease.<sup>536</sup>

Hybrid revascularization can be performed consecutively in a hybrid operating room, or sequentially on separate occasions in the conventional surgical and PCI environments.<sup>537-540</sup> In a small

randomized trial of 200 patients, 1 year and 5 year rates of death, MI, stroke, and major bleeding or repeat revascularization were not significantly different between hybrid revascularization and CABG.<sup>536,541</sup> Heart Team discussion and the prospective planning of a joint strategy are critical for the success of a hybrid revascularization strategy.<sup>542</sup>

## 15.2 REPORTING PERIOPERATIVE OUTCOMES

Perioperative reporting of outcomes after CABG procedures should be done on a risk-adjusted basis. The early risk period after CABG extends up to 3 months, is multifactorial, and depends on the interface between technical variability and patient comorbidity.<sup>543</sup>

## 15.3 GAPS IN THE EVIDENCE

The role of FFR and iwFR in guiding surgical revascularization needs further investigation into whether it improves clinical

**Recommendations on procedural aspects of coronary artery bypass grafting**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>General considerations</b>		
Complete myocardial revascularization is recommended. <sup>c 131,132</sup>	I	B
Minimization of aortic manipulation is recommended. <sup>508,509,544,545</sup>	I	B
Routine intraoperative graft flow measurement should be considered. <sup>516,517</sup>	IIa	B
CT scans of the ascending aorta should be considered in patients over 70 years of age and/or with signs of extensive generalized atherosclerosis.	IIa	C
Prior to aortic manipulation, epi-aortic ultrasound should be considered to identify atheromatous plaques and select the optimal surgical strategy.	IIa	C
<b>Conduit selection</b>		
Arterial grafting with IMA to the LAD system is recommended. <sup>453,454,546</sup>	I	B
An additional arterial graft should be considered in appropriate patients. <sup>467,482,547-551</sup>	IIa	B
The use of the radial artery is recommended over the saphenous vein in patients with high-grade coronary artery stenosis. <sup>d 482,549,550,552,553</sup>	I	B
BIMA grafting should be considered in patients who do not have a high risk of sternal wound infection. <sup>e 467,547,548,551</sup>	IIa	B
<b>Vessel harvesting</b>		
Skeletonized IMA dissection is recommended in patients with a high risk of sternal wound infection. <sup>471,484,485</sup>	I	B
Endoscopic vein harvesting, if performed by experienced surgeons, should be considered to reduce the incidence of wound complications. <sup>490,493,494,500,554</sup>	IIa	A
No-touch vein harvesting should be considered when an open technique is used. <sup>506,507,555,556</sup>	IIa	B
<b>Minimally invasive techniques</b>		
Off-pump CABG and preferably no-touch techniques on the ascending aorta, by experienced operators, are recommended in patients with significant atherosclerotic aortic disease. <sup>508,509,544,557-559</sup>	I	B
Off-pump CABG should be considered for subgroups of high-risk patients by experienced off-pump teams. <sup>525,557-560</sup>	IIa	B
Where expertise exists, minimally invasive CABG through limited thoracic access should be considered in patients with isolated LAD lesions or in the context of hybrid revascularization. <sup>143,534,535,561</sup>	IIa	B
Hybrid procedures, defined as consecutive or combined surgical and percutaneous revascularization, may be considered in specific patient subsets at experienced centres. <sup>536,561-563</sup>	IIb	B

BIMA: bilateral internal mammary artery; CABG: coronary artery bypass grafting; CT: computed tomography; IMA: internal mammary artery; LAD: left anterior descending coronary artery. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence. <sup>c</sup>Definitions of complete revascularization are provided in section 5.3.1.3. <sup>d</sup>Particularly in patients with poor vein grafts. The radial artery should not be used if previously catheterized, if the Allen test is positive or if calcific degeneration is present. <sup>e</sup>Patients with diabetes mellitus, chronic pulmonary obstructive disease, previous mediastinal radiation, and obesity, particularly when multiples of these are present.

outcomes. Likewise, there are insufficient data on the impact of intraoperative assessment of graft flow on outcomes.

In view of the limitations of observational studies comparing BIMA with SIMA and the limitations of the ART trial, the ROMA (Randomization of Single vs. Multiple Arterial Grafts) trial is recruiting to answer the question of whether the use of additional arterial conduits (either BIMA or radial artery) translates into superior clinical outcomes when compared with SIMA supplemented by SVG only.

Hybrid procedures, which combine minimally invasive arterial grafting with PCI, proved feasible and safe. However, multicentre studies are required to prove the efficacy and superiority of this approach in stable, multivessel coronary disease.

## 16 Procedural aspects of percutaneous coronary intervention

### 16.1 PERCUTANEOUS CORONARY INTERVENTION DEVICES

#### 16.1.1 BALLOON ANGIOPLASTY

Plain balloon angioplasty has been superseded in the treatment of *de novo* coronary lesions after demonstration of the superiority of stenting in terms of the requirement for repeat revascularization.<sup>564</sup> Balloon angioplasty might be considered for the treatment

of selected patients in whom implantation of stents is not technically feasible, or in a vessel that is considered to be too small to be stented. Balloon angioplasty is no longer preferred to stenting with DES for patients who require urgent non-cardiac surgery as short-duration DAPT may be reasonable with both strategies.<sup>565,566</sup>

#### 16.1.2 CHOICE OF CORONARY STENTS

Stenting with BMS results in an approximately 30% lower rate of restenosis in comparison with plain balloon angioplasty.<sup>564</sup> Although many efforts have been made to further reduce restenosis by the modification of stent designs and materials, reducing the thickness of stent struts has been the only proven modification capable of reducing restenosis of BMS.<sup>567,568</sup>

A major reduction in the risk of restenosis has been achieved with DES technology. Early-generation DES released sirolimus<sup>569</sup> or paclitaxel<sup>570</sup> from a permanent polymer matrix coating on a relatively thick-strut (120-140 μm) stainless steel backbone. These devices reduced angiographic and clinical restenosis by approximately 50-70%, but increased the risk of very late stent thrombosis compared with BMS.<sup>336,571</sup>

Early-generation DES have now been supplanted by new-generation DES. These stents represented an iterative development of early generation technology, including polymers with enhanced

biocompatibility (permanent or biodegradable), exclusively sirolimus-analogue active drugs, and stent backbones with thin struts (50-100  $\mu\text{m}$ ) composed of stainless steel, cobalt chromium, or platinum chromium.<sup>572-577</sup> New-generation DES have higher efficacy and safety in comparison with both early-generation DES and BMS.<sup>336,571,578</sup> Although stenting with new-generation DES confers a similar risk of death or MI at mid- to long-term follow-up in comparison with BMS,<sup>579</sup> the risk of subacute and late stent thrombosis is significantly lower.<sup>579,580</sup> Moreover, the risk of very late stent thrombosis is at least comparable to that of BMS and lower than that of early-generation DES.<sup>336,571,579,580</sup> These observations were confirmed in a recent trial enrolling patients aged 75 years or older and demonstrating superior outcomes (composite of all-cause mortality, MI, stroke, or ischaemia-driven target lesion revascularization) with DES as compared with BMS with similar duration of intended DAPT (1 month or 6 months) in both treatment arms.<sup>581</sup> Similarly, there is no clear evidence of a difference between DES and BMS on the risk of stent thrombosis following unplanned disruption of DAPT.<sup>565</sup> Accordingly, new-generation DES should be preferred to BMS for routine use.

A large number of new-generation DES have received approval for use and CE mark in Europe.<sup>578</sup> **Supplementary Table 6** displays a list of new-generation DES with the CE mark and evidence from large-scale clinical trials powered for clinical primary endpoints.

Biodegradable polymer and polymer-free DES offer the potential to reduce late adverse events after PCI by eliminating inflammatory reactions to permanent polymer coatings. A number of large-scale trials showed comparable efficacy and safety compared with permanent polymer stents.<sup>575,576,582-590</sup> However, at the moment, there is no evidence of differential efficacy with new-generation biodegradable polymer DES in comparison with new-generation permanent polymer DES in large-scale randomized trials with follow-up out to 5 years.<sup>591-594</sup>

Regarding polymer-free DES, two large-scale trials with different devices showed comparable results with new-generation DES and superior results to BMS.<sup>173,577</sup> Long-term follow-up from randomized trials vs. new-generation permanent polymer DES is only available for a single device and shows comparable outcomes between the devices.<sup>591</sup>

The high clinical efficacy and safety of new-generation DES support their preferred use in patients with an indication for PCI, including patients with diabetes, CKD, multivessel and LMS disease, AMI, vein grafts, restenotic lesions, and chronic total occlusions. New-generation DES should therefore be considered as the default stent type for PCI regardless of clinical presentation, lesion subtype, concomitant therapies, or comorbidities.

### 16.1.3 BIORESORBABLE SCAFFOLDS

Completely bioresorbable scaffolds (BRS), which degrade to predominantly inert end products after fulfilling their scaffold function in the lesion site of the coronary vessel, have been developed with the goal of reducing or eliminating stent-related adverse events at long-term follow-up. Current scaffold platforms to have reached clinical testing are based on two different technologies:

bioresorbable, polymer-based scaffolds (resorption up to 3-4 years) and resorbable, metallic (magnesium) scaffolds (resorption up to 1 year).<sup>595</sup> Although a number of devices have received approval for use in Europe (see **Supplementary Table 7**), randomized trial data are available only with the Absorb bioresorbable vascular scaffold (BVS) (Abbott Vascular).

The safety and efficacy profile of the Absorb BVS has been compared with contemporary DES in several trials. Findings of these trials as well as meta-analyses consistently indicate the inferior efficacy and safety of Absorb BVS compared with contemporary DES during long-term follow-up. Specifically, the Absorb BVS is associated with a significantly increased risk of target lesion revascularization and device thrombosis, with numbers needed to harm of 40-60.<sup>596,597</sup> Of note, commercial use of the Absorb BVS was stopped in 2017 (for additional details see the Supplementary Data).

Available evidence on the magnesium scaffold is limited to small observational studies. Initial results appear encouraging, but further evaluation is needed. Therefore, the Task Force endorses the recommendation of the recent ESC/European Association for Percutaneous Cardiovascular Interventions (EAPCI) document on bioresorbable scaffolds that any BRS should not be used outside well-controlled clinical studies. In patients who have been treated with BRS, prolonged-duration DAPT for 3 years or longer may be considered.

### 16.1.4 DRUG-COATED BALLOONS

The rationale for using DCBs is based on the concept that with highly lipophilic drugs, even short contact times between the balloon surface and the vessel wall are sufficient for effective drug delivery. There are various types of DCB that are approved for use in Europe and their main characteristics are listed in **Supplementary Table 8**. Although specifically designed comparative randomized trials are lacking, a class effect for all DCBs cannot be assumed.<sup>598</sup> Randomized trial data supporting the use of DCB angioplasty are limited to the treatment of in-stent restenosis (see section 13.4). In terms of the use of DCB angioplasty for *de novo* disease, a number of small randomized trials have been reported with somewhat conflicting results.<sup>599-601</sup> At present, there are no convincing data to support the use of DCB angioplasty for this indication.

### 16.1.5 DEVICES FOR LESION PREPARATION

Lesion preparation is critical for successful PCI. In addition to plain balloon angioplasty (with standard or non-compliant balloons), cutting or scoring balloon angioplasty or rotational atherectomy may be required in selected lesions – particularly those with heavy calcification – in order to adequately dilate lesions prior to stent implantation. However, studies investigating the systematic use of these adjunctive technologies, such as rotational atherectomy, have failed to show clear clinical benefit.<sup>602</sup>

## 16.2 INVASIVE IMAGING TOOLS FOR PROCEDURAL GUIDANCE

### 16.2.1 INTRAVASCULAR ULTRASOUND

The majority of the existing clinical trial data relate to the use of IVUS guidance during PCI. In the BMS era, several RCTs

addressed the potential of IVUS in reducing restenosis and adverse events after stenting, with somewhat conflicting results. Findings from one meta-analysis of randomized trials suggested better outcomes with IVUS guidance in terms of acute procedural results and reduced angiographic restenosis, repeat revascularization, and MACE, with no effect on death and MI.<sup>603,604</sup> In the DES era, meta-analysis of randomized and observational studies also suggests better clinical outcomes with IVUS-guided vs. angiography-guided PCI.<sup>605,606</sup> However, the contribution of findings from observational studies must be weighed against the likelihood of considerable residual confounding due to treatment selection bias. Similarly, findings of improved outcome in patients undergoing LM stem PCI with IVUS-guided PCI vs. angiography-guided PCI from a propensity score matched analysis must be interpreted with caution.<sup>35</sup>

In cases of stent failure, including restenosis and stent thrombosis, the use of IVUS should be considered in order to identify and correct underlying mechanical factors (see section 13).<sup>386</sup>

### 16.2.2 OPTICAL COHERENCE TOMOGRAPHY

A number of studies have assessed OCT imaging for PCI guidance. Two observational studies show that while OCT imaging changes operator behaviour, its impact on clinical outcomes is unclear.<sup>607,608</sup> Indeed, OCT is more accurate than angiography or IVUS in detecting subtle morphological details including malapposition, residual thrombus, plaque prolapse, and residual dissections, although many of these additional findings may have a benign course.<sup>609,610</sup> A single randomized trial compared OCT with IVUS and coronary angiography, and showed that OCT-guided PCI was safe and resulted in a similar minimum stent area to that of IVUS-guided PCI.<sup>611</sup> However, OCT guidance was not superior to either IVUS or angiography alone. An additional randomized trial that enrolled patients with NSTEMI-ACS compared OCT-guided PCI with angiography-guided PCI and found no signal of impact on clinical outcomes.<sup>612</sup>

A number of observational studies have shown that OCT is feasible and safe in the assessment of stent failure due to thrombosis, and may yield information that may be clinically useful.<sup>386,387,613,614</sup> Likewise, in cases of in-stent restenosis, intrastent neointimal tissue may be characterized by OCT, enabling for example the detection of neoatherosclerosis.<sup>386,615,616</sup> In cases of stent failure, the use of OCT should be considered in order to identify and correct underlying mechanical factors (see section 13).

## 16.3 SPECIFIC LESION SUBSETS

### 16.3.1 BIFURCATION STENOSIS

A number of RCTs have investigated the optimal intervention strategy in patients with bifurcation lesions and showed no benefit for the systematic two-stent approach vs. main branch-only stenting with provisional stenting of the side branch in terms of clinical outcomes.<sup>617</sup> A recent pooled analysis of two RCTs showed lower 5 year survival in patients randomized to a systematic two-stent approach.<sup>618</sup> In addition, procedure time, contrast volume, radiation exposure, and cost are higher with a two-stent approach.<sup>618</sup>

The EBC TWO (European Bifurcation Coronary TWO) trial found no difference between a provisional T-stent strategy and a systematic two-stent strategy (culotte technique) in terms of the composite endpoint of death, MI, and TVR at 12 months among 200 patients with large-calibre true bifurcation lesions (side branch diameter  $\geq 2.5$  mm) and significant ostial disease length ( $\geq 5$  mm).<sup>619</sup> Thus, main branch-only stenting with provisional stenting of the side branch should be the preferred approach for most bifurcation lesions. Exceptions to this rule, where upfront side branch stenting may be preferable, include the presence of a large side branch ( $\geq 2.75$  mm) with a long ostial side branch lesion ( $> 5$  mm) or anticipated difficulty in accessing an important side branch after main branch stenting, and true distal LM bifurcations. Recently, a multicentre trial conducted in China directly compared a double-kissing crush two-stent strategy with provisional stenting of the main branch in 482 patients with distal LM bifurcation disease. Double-kissing crush resulted in a lower risk of the primary endpoint target lesion failure at 1 year compared with provisional stenting.<sup>620</sup>

When a two-stent strategy is necessary, which two-stent technique should be preferred is debated. The three most widely used contemporary two-stent techniques are culotte, crush (classic or double-kissing crush), and T and protrusion (TAP).<sup>621,622</sup> Several RCTs have compared these techniques. In non-LM bifurcation lesions, there is no compelling evidence that one technique is superior to the others in terms of major clinical endpoints.<sup>621,622</sup> In LM true bifurcation lesions, double-kissing crush has the most favourable outcome data.<sup>623</sup>

Final 'kissing' balloon dilation is generally recommended when two stents are eventually required, with no advantage from final kissing with the one-stent technique.<sup>624,625</sup> Several stents, designed specifically for the treatment of bifurcation lesions, have undergone extensive evaluation with promising angiographic and clinical results, though RCTs against current recommended therapy are limited.<sup>626</sup> Further technical details relating to bifurcation PCI are described in the consensus document of the European Bifurcation Club.<sup>627</sup>

### 16.3.2 CHRONIC TOTAL CORONARY OCCLUSION

Dedicated RCTs examining the outcomes of patients with chronic total occlusion (CTO) allocated to revascularization or conservative therapy are scarce. One trial randomized patients with STEMI and CTO in a non-culprit vessel to CTO-PCI vs. conservative therapy, and found no difference in the primary endpoint of LVEF and LV end-diastolic volume at 4 months.<sup>628</sup> More recently, the prospective randomized EUROCTO (Randomized Multicentre Trial to Compare Revascularization With Optimal Medical Therapy for the Treatment of Chronic Total Occlusions) trial showed symptomatic improvement by PCI of CTO.<sup>629</sup> This trial included 396 patients who were randomly assigned to PCI of CTO with optimal medical therapy, or optimal medical therapy alone. During the 12 month follow-up, the primary endpoint—the change in health status assessed by the Seattle angina questionnaire—showed significantly greater improvement of angina frequency and quality of life with CTO PCI as compared

with optimal medical therapy alone. Yet, MACE were comparable between the two groups. A systematic review of 25 observational studies showed that at median follow-up of 3 years, successful CTO-PCI was associated with improved clinical outcomes in comparison with failed revascularization, including overall survival, angina burden, and the requirement for bypass surgery.<sup>630</sup> Broadly speaking, the treatment of CTOs may be considered analogous to the treatment of non-CTO lesions (see recommendations in section 5). In cases of regional wall motion abnormalities in the territory of the CTO, objective evidence of viability should be sought. The decision to attempt CTO-PCI should be considered against the risk of greater contrast volume, longer fluoroscopy time, and higher MACE rates in comparison with non-CTO PCI patients.<sup>631</sup> *Ad hoc* PCI is generally not recommended for CTOs, although it may be necessary in selected cases (e.g. acute bypass graft failure not amenable to recanalization of the bypass graft).

Recent developments in catheter and wire technology, and increasing operator expertise with both antegrade and retrograde approaches as well as wire escalation and dissection/re-entry techniques, have translated into increasing success rates of CTO-PCI with low rates of MACE.<sup>631-633</sup> Success rates are strongly dependent on operator skills, depending on experience with specific procedural techniques, and the availability of dedicated equipment, and vary from 60-70% to >90%.<sup>631-633</sup>

### 16.3.3 OSTIAL LESIONS

In ostial coronary lesions, additional judgement and caution is essential before proceeding to PCI. In particular, a catheter-induced coronary spasm must be rigorously excluded. Lesion assessment with IVUS may be helpful, particularly in LM ostial stenosis. FFR measurement may also be valuable in the assessment of ostial lesions of borderline significance,<sup>634</sup> taking special care to avoid a wedge position of the guiding catheter and using i.v., rather than intracoronary, adenosine. When performing an intervention, due to interaction between the guide catheter and the proximal stent edge, the risk of longitudinal stent deformation must be considered<sup>635</sup> and avoided with careful catheter manipulation. The accurate positioning of the stent, precisely in the coronary ostium, may be technically challenging and some specialized techniques that may help to achieve optimal stent placement have been described.<sup>636,637</sup>

### 16.4 VASCULAR ACCESS

A number of RCTs have compared radial access with femoral access for diagnostic angiography and PCI. The two largest were RIVAL (Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes) and MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial access Site and Systemic Implementation of AngioX).<sup>172,638</sup> In the RIVAL trial, which enrolled 7021 patients, the primary outcome of death, MI, stroke, or non-CABG-related major bleeding at 30 days occurred at a similar rate in radial vs. femoral access (HR 0.92, 95% CI 0.72-1.17, P=0.50).<sup>638</sup> In the MATRIX trial, 8404 ACS patients were randomly allocated to radial or femoral access.<sup>172</sup>

#### Recommendations on choice of stent and access site

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
DES are recommended over BMS for any PCI irrespective of: – clinical presentation – lesion type – planned non-cardiac surgery – anticipated duration of DAPT – concomitant anticoagulant therapy. <sup>100,578,579,640</sup>	I	A
Radial access is recommended as the standard approach, unless there are overriding procedural considerations. <sup>172,638,641</sup>	I	A
BRS are currently not recommended for clinical use outside of clinical studies. <sup>642-650</sup>	III	C

BMS: bare-metal stents; BRS: bioresorbable scaffolds; DAPT: dual antiplatelet therapy; DES: drug-eluting stents; PCI: percutaneous coronary intervention. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

In terms of the first co-primary endpoint of 30 day MACE, there was no significant difference between radial access and femoral access (RR 0.85, 95% CI 0.74-0.99, two-sided P=0.031; non-significant at a pre-specified  $\alpha$  of 0.025). The second co-primary outcome of 30 day net adverse clinical events [MACE or non-CABG BARC (Bleeding Academic Research Consortium (major bleeding)] was significantly lower with radial access (RR 0.83, 95% CI 0.73-0.96; P=0.009). Major BARC 3 or 5 bleeding was significantly reduced in the radial group (1.6 vs. 2.3%; RR 0.67, 95% CI 0.49-0.92; P=0.013), and radial access was associated with a lower risk of all-cause mortality (1.6 vs. 2.2%; RR 0.72, 95% CI 0.53-0.99,

#### Recommendations on intravascular imaging for procedural optimization

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
IVUS or OCT should be considered in selected patients to optimize stent implantation. <sup>603,612,651-653</sup>	Ila	B
IVUS should be considered to optimize treatment of unprotected left main lesions. <sup>35</sup>	Ila	B

IVUS: intravascular ultrasound; OCT: optical coherence tomography. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

#### Recommendations on specific lesion subsets

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Stent implantation in the main vessel only, followed by provisional balloon angioplasty with or without stenting of the side branch, is recommended for PCI of bifurcation lesions. <sup>654-658</sup>	I	A
Percutaneous revascularization of CTOs should be considered in patients with angina resistant to medical therapy or with a large area of documented ischaemia in the territory of the occluded vessel. <sup>629,659-663</sup>	Ila	B
In true bifurcation lesions of the left main, the double-kissing crush technique may be preferred over provisional T-stenting. <sup>620</sup>	Ilb	B

CTO: chronic total occlusion; PCI: percutaneous coronary intervention. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

P=0.045). However, the benefit of radial over femoral access depends upon the operator's expertise in the radial technique.<sup>639</sup>

Treatment of restenotic and saphenous vein graft lesions are discussed in section 13.3.

## 17 Antithrombotic treatments

Antithrombotic treatment is mandatory in CAD patients undergoing myocardial revascularization. The choice of treatment, the combination, the time point of initiation, and the duration depend on the patient's characteristics, comorbidities, the clinical setting (elective revascularization vs. ACS), and the mode (PCI vs. CABG) of revascularization. Both ischaemic and bleeding events significantly influence the outcome of CAD patients and their overall mortality risk during and after myocardial revascularization.<sup>664</sup> Thus, the choice of treatment should reflect the ischaemic and bleeding risk. The recommended drugs (**Figure 9**) and doses (**Table 7**) for anticoagulant and antiplatelet drugs used in conjunction with myocardial revascularization are summarized below.

### 17.1 PERCUTANEOUS CORONARY INTERVENTION IN STABLE CORONARY ARTERY DISEASE

#### 17.1.1 CHOICE OF TREATMENT AND PRE-TREATMENT

DAPT consisting of aspirin and a P2Y<sub>12</sub> receptor inhibitor represents the cornerstone of treatment in patients undergoing elective

PCI.<sup>665</sup> The P2Y<sub>12</sub> receptor inhibitor clopidogrel is recommended for elective stenting procedures. For routine clopidogrel pre-treatment (administration of the drug when the coronary anatomy is unknown), there is no compelling evidence for a significant clinical benefit in SCAD patients.<sup>666-668</sup> Thus, pre-treatment may only be an option in selected patients with high probability of PCI or before staged PCI procedures. **Figures 9 and 10** summarize the commonly used antiplatelet and anticoagulant drugs in SCAD patients undergoing PCI.

#### 17.1.2 PERI-INTERVENTIONAL TREATMENT

While aspirin and clopidogrel are indicated for elective stenting procedures, prasugrel or ticagrelor may only be considered in selected patients for specific high-risk situations of elective stenting (e.g. complex PCI procedures such as LM stenting and CTO procedures) or in patients with a history of stent thrombosis on clopidogrel treatment.

In parallel with antiplatelet treatment, the use of anticoagulants is standard of care during elective PCI to inhibit thrombin generation and activity. Different agents, including unfractionated heparin (UFH) and bivalirudin, have been evaluated for their use in clinical practice. The REPLACE-2 (Randomised Evaluation in PCI Linking Angiomax to Reduced Clinical Events 2) trial demonstrated that the outcome with bivalirudin and provisional glycoprotein (GP) IIb/IIIa blockade is similar to that of

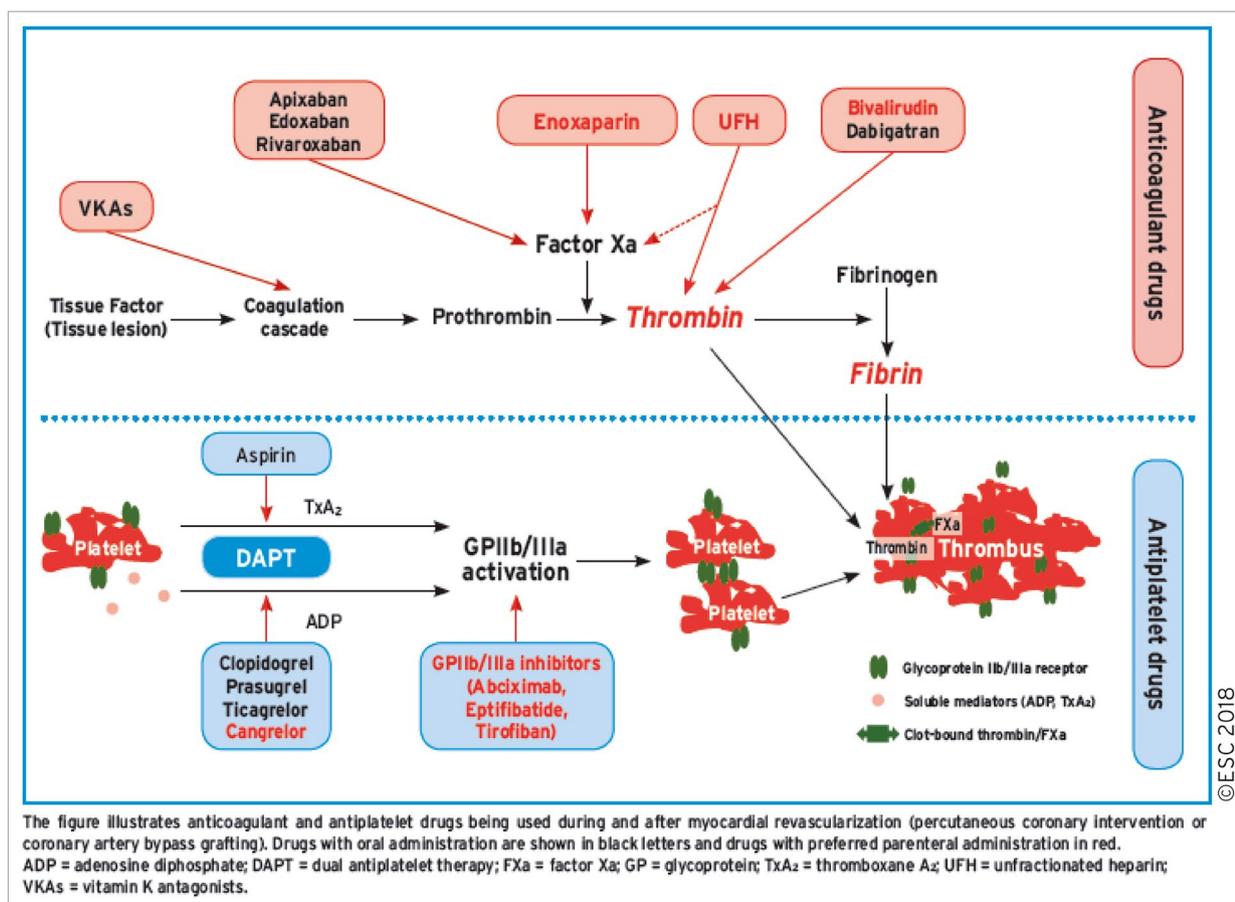


Figure 9. Antithrombotic treatment for myocardial revascularization and its pharmacological targets.

**Table 7. Doses of antiplatelet and anticoagulant drugs used during and after myocardial revascularization.**

Antiplatelet drugs	
Aspirin	Loading dose of 150-300 mg orally or 75-150 mg i.v. if oral ingestion is not possible, followed by a maintenance dose of 75-100 mg/day.
Clopidogrel	Loading dose of 600 mg orally, followed by a maintenance dose of 75 mg/day.
Prasugrel	Loading dose of 60 mg orally, followed by a maintenance dose of 10 mg/day.
	In patients with body weight <60 kg, a maintenance dose of 5 mg is recommended.
	In patients aged >75 years, prasugrel is generally not recommended, but a dose of 5 mg should be used if treatment is deemed necessary.
Ticagrelor	Loading dose of 180 mg orally, followed by a maintenance dose of 90 mg b.i.d.
Abciximab	Bolus of 0.25 mg/kg i.v. and 0.125 lg/kg/min infusion (maximum 10 lg/min) for 12 h.
Eptifibatide	Double bolus of 180 lg/kg i.v. (given at a 10 min interval) followed by an infusion of 2.0 lg/kg/min for up to 18 h.
Tirofiban	Bolus of 25 lg/kg over 3 min i.v., followed by an infusion of 0.15 lg/kg/min for up to 18 h.
Cangrelor	Bolus of 30 mg/kg i.v. followed by 4 mg/kg/min infusion for at least 2 h or duration of procedure, whichever is longer.
Anticoagulant drugs for PCI	
Unfractionated heparin	– 70-100 U/kg i.v. bolus when no GP IIb/IIIa inhibitor is planned. – 50-70 U/kg i.v. bolus with GP IIb/IIIa inhibitors.
Enoxaparin	0.5 mg/kg i.v. bolus.
Bivalirudin	0.75 mg/kg i.v. bolus followed by i.v. infusion of 1.75 mg/kg/h for up to 4 h after the procedure as clinically warranted.
Oral anticoagulant drugs (concomitant treatment after PCI)	
Vitamin K antagonists (e.g. warfarin, phenprocoumon)	Dosing is based on INR value and the respective clinical indication.
Apixaban	Maintenance doses of 5 and 2.5 <sup>a</sup> mg b.i.d.
Dabigatran	Maintenance doses of 150 and 110 mg b.i.d.
Edoxaban	Maintenance doses of 60 and 30 <sup>a</sup> mg/day
Rivaroxaban	Maintenance doses of 20 and 15 <sup>a</sup> mg/day, and 2.5 mg b.i.d. (vascular dose).
<sup>a</sup> Specific criteria for reduced dose apply (see recommendation table in section 17.5.1). b.i.d.: twice daily; GP: glycoprotein; INR: international normalized ratio; i.v.: intravenous; PCI: percutaneous coronary intervention.	

UFH plus planned GP IIb/IIIa inhibition during elective PCI.<sup>669</sup> The ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen Rapid Early Action for Coronary Treatment) 3 trial also showed a similar outcome for bivalirudin vs. UFH treatment.<sup>670</sup> In ISAR REACT 3A,<sup>671</sup> evaluating a lower dose of 100 U/kg UFH, this lower dose showed net clinical benefit compared with

the historical control cohort and this benefit was mostly driven by a reduction in bleeding events. In view of the primary endpoint results of the RCTs and in view of a trend towards a lower risk of MI, UFH remains the standard anticoagulant for elective PCI. Based on the results of the STEEPLE (Safety and Efficacy of Intravenous Enoxaparin in Elective Percutaneous Coronary Intervention Randomised Evaluation) trial, enoxaparin should be considered as an alternative anticoagulant drug.<sup>672</sup>

Drugs for parenteral antiplatelet treatment include cangrelor and GP IIb/IIIa inhibitors. Cangrelor is a direct reversible, short-acting P2Y<sub>12</sub>-inhibitor that has been evaluated during PCI for SCAD and ACS in clinical trials comparing cangrelor with clopidogrel, administered before PCI [CHAMPION (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) PCI] or after PCI (CHAMPION PLATFORM and CHAMPION PHOENIX).<sup>673</sup> A meta-analysis showed a benefit with respect to major ischaemic endpoints that is counterbalanced by an increase in relevant bleeding.<sup>673</sup> Moreover, the benefit of cangrelor with respect to ischaemic endpoints was attenuated in CHAMPION PCI with upfront administration of clopidogrel. Nevertheless, due to its proven efficacy in preventing intraprocedural and post-procedural stent thrombosis in P2Y<sub>12</sub>-inhibitor naïve patients, cangrelor may be considered in P2Y<sub>12</sub>-inhibitor naïve patients undergoing PCI (for more detailed discussion see the Supplementary Data).

Available GP IIb/IIIa inhibitors include abciximab, eptifibatide, and tirofiban. In a setting of elective PCI, clinical trials did not demonstrate an additional benefit of GP IIb/IIIa inhibitor administration in SCAD patients in a setting of DAPT treatment that includes loading with clopidogrel.<sup>674,675</sup> A meta-analysis on this topic revealed no mortality benefit of GP IIb/IIIa treatment and while non-fatal MIs were reduced, (minor) bleeding events were significantly higher when utilizing these agents.<sup>676</sup> Thus, GP IIb/IIIa inhibitors may only be considered in specific 'bail-out' situations including high intraprocedural thrombus burden, slow flow, or no-flow with closure of the stented coronary vessel.

An algorithm for the use of antithrombotic drugs in patients undergoing PCI is shown in **Figure 10**.

### 17.1.3 POST-INTERVENTIONAL AND MAINTENANCE TREATMENT

Following elective stenting, DAPT consisting of clopidogrel in addition to aspirin is generally recommended for 6 months, irrespective of the stent type. In specific clinical scenarios, this standard DAPT duration can be shortened (<6 months) or extended (>6-12 months). For a more detailed description of the pertinent clinical trials in the field of DAPT duration, we refer the reader to the 2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease.<sup>410</sup> Following DAPT, a life-long single antiplatelet therapy (usually with aspirin) is recommended, and patients should be advised not to prematurely discontinue oral antiplatelet therapy after stenting due to the risks of stent thrombosis and recurrent MI.<sup>677</sup> Recently, the value of a vascular dose of rivaroxaban (2.5 mg b.i.d.) in conjunction with aspirin

**Recommendations for antithrombotic treatment in stable coronary artery disease patients undergoing percutaneous coronary intervention**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Pre-treatment and antiplatelet therapy</b>		
Treatment with 600 mg clopidogrel is recommended in elective PCI patients once the coronary anatomy is known and a decision is made to proceed with PCI. <sup>667,679,680</sup>	I	A
Pre-treatment with clopidogrel may be considered if the probability of PCI is high.	IIb	C
In patients on a maintenance dose of 75 mg clopidogrel, a new loading dose of 600 mg may be considered once the indication for PCI is confirmed.	IIb	C
<b>Peri-interventional treatment</b>		
Aspirin is indicated before elective stenting. <sup>681-683</sup>	I	A
An oral loading dose of aspirin (150-300 mg p.o. or 75-250 mg i.v.) is recommended if the patient is not pre-treated.	I	C
Clopidogrel (600 mg loading dose, 75 mg daily maintenance dose) is recommended for elective stenting. <sup>684-688</sup>	I	A
Glycoprotein IIb/IIIa antagonists should be considered only for bail-out.	IIa	C
Prasugrel or ticagrelor may be considered in specific high-risk situations of elective stenting (e.g. history of stent thrombosis or left main stenting).	IIb	C
Unfractionated heparin is indicated as the standard anticoagulant (70-100 U/kg). <sup>670,671</sup>	I	B
Bivalirudin (0.75 mg/kg bolus, followed by 1.75 mg/kg/h for up to 4 h after the procedure) is indicated in the case of heparin-induced thrombocytopenia.	I	C
Enoxaparin (i.v. 0.5 mg/kg) should be considered as an alternative agent. <sup>672,689</sup>	IIa	B
Cangrelor may be considered in P2Y <sub>12</sub> -inhibitor naïve patients undergoing PCI. <sup>673</sup>	IIb	A
<b>Post-interventional and maintenance treatment</b>		
Life-long single antiplatelet therapy, usually aspirin, is recommended. <sup>681,683</sup>	I	A
Instruction of patients about the importance of complying with antiplatelet therapy is recommended.	I	C
In patients with SCAD treated with coronary stent implantation, DAPT consisting of clopidogrel in addition to aspirin is generally recommended for 6 months, irrespective of the stent type. <sup>c 690-694</sup>	I	A
In patients with SCAD treated with BRS, DAPT should be considered for at least 12 months and up to the presumed full absorption of the BRS, based on an individual assessment of bleeding and ischaemic risk.	IIa	C
In patients with SCAD treated with DCB, DAPT should be considered for 6 months. <sup>369,371</sup>	IIa	B
In patients with SCAD considered at high bleeding risk (e.g. PRECISE-DAPT $\geq 25$ ), DAPT should be considered for 3 months. <sup>d 695,696</sup>	IIa	A
In patients with SCAD who have tolerated DAPT without a bleeding complication and who are at low bleeding risk but high thrombotic risk, continuation of DAPT with clopidogrel for >6 months and up to 30 months may be considered. <sup>697-700</sup>	IIb	A
In patients with SCAD in whom 3 month DAPT poses safety concerns, DAPT may be considered for 1 month.	IIb	C

BRS: bioresorbable scaffold; CAD: coronary artery disease; DAPT: dual antiplatelet therapy; DCB: drug-coated balloon; i.v.: intravenous; MI: myocardial infarction; PCI: percutaneous coronary intervention; p.o.: orally; PRECISE-DAPT: PREdicting bleeding Complications In patients undergoing Stent implantation and subSequent Dual Anti Platelet Therapy; SCAD: stable coronary artery disease. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence. <sup>c</sup>These recommendations refer to stents that are supported by large-scale randomized trials with clinical endpoint evaluation leading to an unconditional CE mark. <sup>d</sup>The evidence supporting this recommendation comes from two studies where the zotarolimus-eluting Endeavour stent was investigated in conjunction with a 3 month DAPT regimen.

was demonstrated in the large-scale COMPASS (Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease) trial.<sup>678</sup> However, its utilization in SCAD patients is a matter of secondary prevention and is not linked to myocardial revascularization procedures.

## 17.2 NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

The activation of blood platelets and the coagulation cascade plays a key role in the initial phase and evolution of an ACS. Hence, sufficient platelet inhibition and anticoagulation is essential during ACS, and especially in ACS patients undergoing PCI.

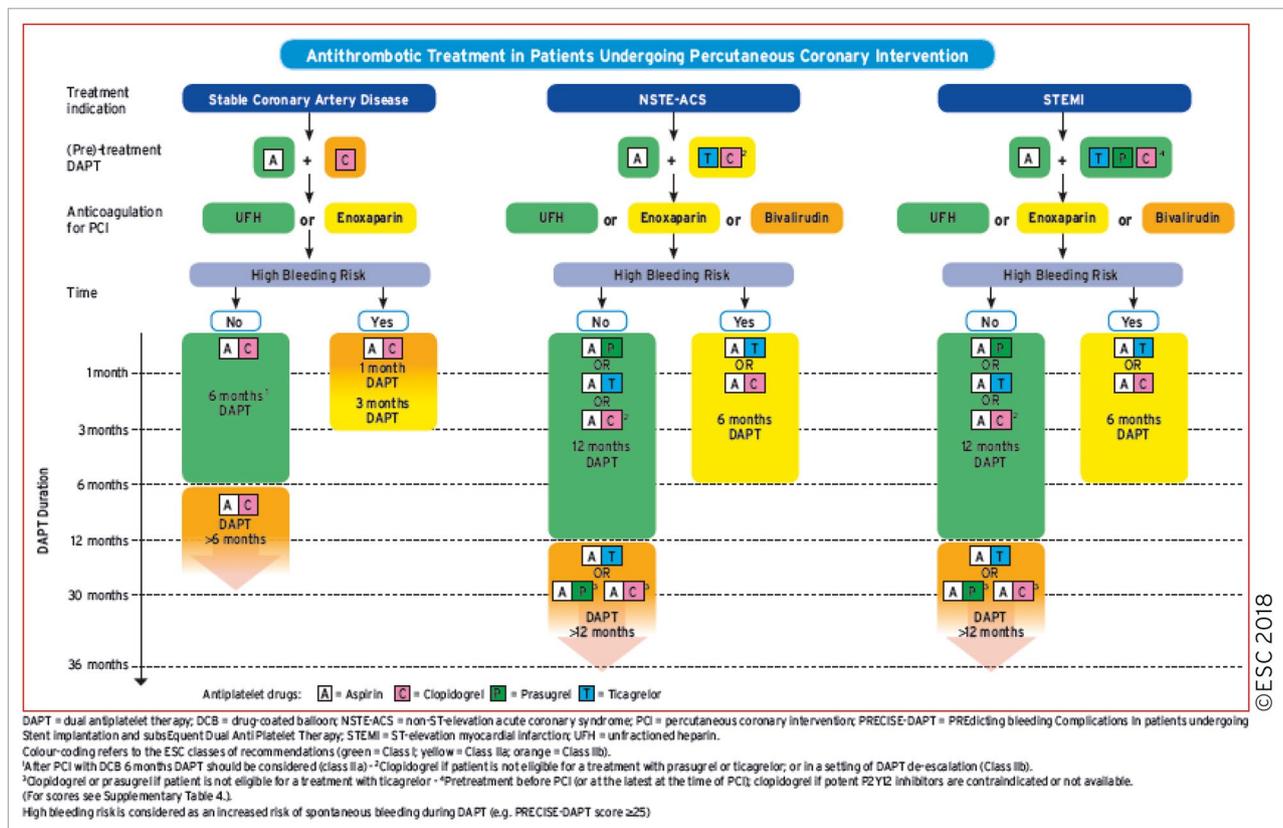
### 17.2.1 CHOICE OF TREATMENT AND PRE-TREATMENT

For NSTEMI-ACS patients, DAPT including aspirin and a potent P2Y<sub>12</sub> receptor inhibitor (prasugrel or ticagrelor) is recommended (see the Supplementary Data).<sup>701,702</sup> Clopidogrel should only be used when prasugrel or ticagrelor are not available or are contraindicated. Based on the results of the ACCOAST

(Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction) trial,<sup>165</sup> it is not recommended that prasugrel is administered in patients in whom coronary anatomy is not known. Nevertheless, pre-treatment with ticagrelor was part of the PLATO trial (Study of Platelet Inhibition and Patient Outcomes) and was associated with an early benefit over clopidogrel.<sup>702</sup> For these reasons, pre-treatment with ticagrelor can be used, although there is no direct evidence from head-to-head comparisons between pre-treatment strategies.

### 17.2.2 PERI-INTERVENTIONAL TREATMENT

Anticoagulation is recommended for all patients in addition to antiplatelet therapy during PCI for NSTEMI-ACS.<sup>703</sup> In general, a crossover between anticoagulants should be avoided [especially between UFH and low-molecular-weight heparin (LMWH)], with the exception of adding UFH to fondaparinux when a patient proceeds to PCI.<sup>704,705</sup> The respective agents should be discontinued



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**Figure 10.** Algorithm for the use of antithrombotic drugs in patients undergoing percutaneous coronary intervention. High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score  $\geq 25$ ). Colour-coding refers to the ESC classes of recommendations (green: class I; yellow: class IIa; and orange: class IIb).

after PCI except for specific clinical settings, such as the presence of an LV aneurysm with thrombus or AF requiring anticoagulation.

A number of trials have compared bivalirudin with UFH in ACS patients undergoing PCI (see the Supplementary Data). Some of these trials pursued a balanced use of adjunctive GP IIb/IIIa inhibitors with both bivalirudin and heparin, whereas others, predominantly the older ones, had selective use of GP IIb/IIIa inhibitors in the heparin arm. These trials have been reviewed extensively in a number of meta-analyses.<sup>706-708</sup> A meta-analysis that included the MATRIX trial but not VALIDATE-SWEDEHEART (Bivalirudin versus Heparin in ST-Segment and Non-ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy on the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) showed no significant benefit of bivalirudin compared with UFH with respect to death, MACE, and MI.<sup>708</sup> Nevertheless, bivalirudin was associated with a significant increase in the risk of stent thrombosis and a significant decrease in the risk of bleeding. However, the reduction of bleeding risk was linked to unbalanced use of GP IIb/IIIa inhibitors predominantly with UFH. Recently, the VALIDATE-SWEDEHEART study<sup>709</sup> compared UFH vs. bivalirudin in a background of radial access and limited use of GP IIb/IIIa inhibitors. The study demonstrated similar

risk patterns for both ischaemia and bleeding when comparing the two drugs. Of note, while prior studies reported a reduced bleeding risk with bivalirudin vs. UFH, this was not confirmed in VALIDATE-SWEDEHEART and in a contemporary setting of preferred radial access and selective use of GP IIb/IIIa inhibitors. More recently, a meta-analysis updated for the results of VALIDATE-SWEDEHEART confirmed that bivalirudin compared with heparin was associated with a similar incidence of all-cause death and ischaemic events after PCI for ACS.<sup>710</sup> A significant association of bivalirudin with decreased risk of bleeding was only found with unbalanced use of GP IIb/IIIa inhibitors in conjunction with heparin. In summary and based on the above-mentioned trials, UFH is primarily recommended as an anticoagulant for PCI. Due to its short half-life and favourable results in some of the studies, bivalirudin may be considered as an alternative to UFH in selected cases.

Patients may undergo cardiac catheterization after a conservative treatment phase and these patients are commonly treated with fondaparinux during the conservative treatment phase. This regimen is based on the OASIS-5 (Optimal Antiplatelet Strategy for Interventions 5) trial.<sup>711</sup> Of note, catheter thrombus formation was an issue with fondaparinux and therefore full-dose UFH must be added to prevent thrombus formation when the patient proceeds to PCI. Enoxaparin should be considered as anticoagulant for PCI

in patients pre-treated with subcutaneous enoxaparin. A benefit of enoxaparin over UFH in reducing mortality and bleeding complications was recently reported in a meta-analysis including NSTEMI-ACS patients.<sup>689</sup> Yet, this meta-analysis did not include a dedicated randomized study in NSTEMI-ACS and was largely based on non-randomized comparisons.

Most of the trials evaluating GP IIb/IIIa inhibitors in PCI-treated patients pre-date the era of routine oral DAPT treatment. These early trials demonstrated a reduction in the incidence of ischaemic events in favour of GP IIb/IIIa treatment in combination with UFH compared with UFH alone, primarily through a reduction in MI.<sup>712</sup> However, coronary angiography and PCI were delayed compared with what is recommended now, and a consistent major bleeding risk was observed. Overall, there is no compelling evidence for an additional benefit of routine upstream use of GP IIb/IIIa inhibitors in NSTEMI-ACS patients scheduled for coronary angiography and receiving DAPT treatment.<sup>713,714</sup> In a setting of potent platelet inhibition with ticagrelor or prasugrel, where randomized data on GP IIb/IIIa inhibitor use is limited, routine use of these agents cannot be recommended. Nevertheless, it should be considered for bail-out situations or thrombotic complications, and may be used for high-risk PCI in patients without pre-treatment with

P2Y<sub>12</sub>-inhibitors. The available evidence on cangrelor suggests that the potential benefit is independent of the clinical presentation. Thus, similar to SCAD patients, cangrelor may be considered in specific settings in P2Y<sub>12</sub>-naïve patients undergoing PCI.

### 17.2.3 POST-INTERVENTIONAL AND MAINTENANCE TREATMENT

Following PCI for NSTEMI-ACS, DAPT consisting of a P2Y<sub>12</sub> receptor inhibitor in addition to aspirin is generally recommended for 12 months, irrespective of the stent type. Recently, the SMART-DATE (Smart Angioplasty Research Team-safety of 6-month duration of Dual Antiplatelet Therapy after percutaneous coronary intervention in patients with acute coronary syndromes) prospective multicentre randomized trial supported this notion in the setting of contemporary interventional practice. The study randomly assigned 2712 patients undergoing PCI for NSTEMI-ACS or STEMI to either 6 month DAPT or 12 month or longer DAPT. Although the primary endpoint – a composite of all-cause death, MI, or stroke – did not confirm the benefit of prolonged DAPT over 6 month DAPT (cumulative event rate 4.7 vs. 4.2%; absolute risk difference 0.5%; upper limit of one-sided 95% CI 1.8%; Pnon-inferiority=0.03 with a predefined non-inferiority margin of 2.0%), MI occurred more frequently in the 6 month DAPT group

#### Recommendations for antithrombotic treatment in patients with non-ST-elevation acute coronary syndromes undergoing percutaneous coronary intervention

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Pre-treatment and antiplatelet therapy</b>		
Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150-300 mg (or 75-250 mg i.v.), and at a maintenance dose of 75-100 mg daily long-term. <sup>681,683,721</sup>	I	A
A P2Y <sub>12</sub> inhibitor is recommended in addition to aspirin, maintained over 12 months unless there are contraindications such as an excessive risk of bleeding. <sup>701,702,722,723</sup> Options are:	I	A
Prasugrel in P2Y <sub>12</sub> -inhibitor naïve patients who proceed to PCI (60 mg loading dose, 10 mg daily dose). <sup>701</sup>	I	B
Ticagrelor irrespective of the preceding P2Y <sub>12</sub> inhibitor regimen (180 mg loading dose, 90 mg b.i.d.). <sup>702</sup>	I	B
Clopidogrel (600 mg loading dose, 75 mg daily dose) only when prasugrel or ticagrelor are not available or are contraindicated. <sup>722-724</sup>	I	B
GP IIb/IIIa antagonists should be considered for bail-out if there is evidence of no-reflow or a thrombotic complication.	IIa	C
For pre-treatment in patients with NSTEMI-ACS undergoing invasive management, ticagrelor administration (180 mg loading dose, 90 mg b.i.d.), or clopidogrel (600 mg loading dose, 75 mg daily dose) if ticagrelor is not an option, should be considered as soon as the diagnosis is established.	IIa	C
Cangrelor may be considered in P2Y <sub>12</sub> -inhibitor naïve patients undergoing PCI. <sup>673</sup>	IIb	A
GP IIb/IIIa antagonists may be considered in P2Y <sub>12</sub> -inhibitor naïve patients undergoing PCI.	IIb	C
Pre-treatment with GP IIb/IIIa antagonists in patients in whom coronary anatomy is not known is not recommended. <sup>713,714,725</sup>	III	A
Administration of prasugrel in patients in whom coronary anatomy is not known is not recommended. <sup>165</sup>	III	B
<b>Peri-interventional therapy</b>		
Anticoagulation is recommended for all patients in addition to antiplatelet therapy. <sup>703,726</sup>	I	A
It is recommended that anticoagulation is selected according to both ischaemic and bleeding risks, and according to the efficacy-safety profile of the chosen agent.	I	C
UFH is recommended.	I	C
In patients on fondaparinux, a single bolus UFH (85 IU/kg, or 60 IU in the case of concomitant use of GP IIb/IIIa receptor inhibitors) is indicated. <sup>727</sup>	I	B
Enoxaparin should be considered in patients pre-treated with subcutaneous enoxaparin. <sup>689</sup>	IIa	B
Discontinuation of parenteral anticoagulation should be considered immediately after an invasive procedure.	IIa	C
Bivalirudin (0.75 mg/kg bolus, followed by 1.75 mg/kg/h for up to 4 h after the procedure) may be considered as an alternative to UFH. <sup>163,708,710,714,728</sup>	IIb	A
Crossover of UFH and LMWH is not recommended. <sup>705</sup>	III	B

b.i.d.: twice daily; GP: glycoprotein; i.v.: intravenous; LMWH: low-molecular-weight heparin; NSTEMI-ACS: non-ST-segment elevation acute coronary syndromes; PCI: percutaneous coronary intervention; UFH: unfractionated heparin. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

**Recommendations for post-interventional and maintenance treatment in patients with non-ST-elevation acute coronary syndromes and ST-elevation myocardial infarction undergoing percutaneous coronary intervention**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
In patients with ACS treated with coronary stent implantation, DAPT with a P2Y <sub>12</sub> inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as an excessive risk of bleeding (e.g. PRECISE-DAPT ≥25). <sup>701,702,722,723</sup>	I	A
In patients with ACS and stent implantation who are at high risk of bleeding (e.g. PRECISE-DAPT ≥25), discontinuation of P2Y <sub>12</sub> inhibitor therapy after 6 months should be considered. <sup>729,730</sup>	IIa	B
In patients with ACS treated with BRS, DAPT should be considered for at least 12 months and up to the presumed full absorption of the BRS, based on an individual assessment of bleeding and ischaemic risk.	IIa	C
De-escalation of P2Y <sub>12</sub> inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) guided by platelet function testing may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for 12-month potent platelet inhibition. <sup>717</sup>	IIb	B
In patients with ACS who have tolerated DAPT without a bleeding complication, continuation of DAPT for longer than 12 months may be considered. <sup>700,731</sup>	IIb	A
In patients with MI and high ischaemic risk who have tolerated DAPT without a bleeding complication, ticagrelor 60 mg b.i.d. for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel. <sup>732-734</sup>	IIb	B
In ACS patients with no prior stroke/TIA, and at high ischaemic risk as well as low bleeding risk, receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg b.i.d. for approximately 1 year) may be considered after discontinuation of parenteral anticoagulation. <sup>720</sup>	IIb	B

ACS: acute coronary syndrome; b.i.d.: twice daily; BRS: bioresorbable scaffold; DAPT: dual antiplatelet therapy; MI: myocardial infarction; PCI: percutaneous coronary intervention; PRECISE-DAPT: PREDicting bleeding Complications In patients undergoing Stent implantation and subSEquent Dual Anti Platelet Therapy; TIA: transient ischaemic attack. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence. <sup>c</sup>Defined as ≥50 years of age and having one of the following additional high-risk features: age ≥65 years or older, diabetes mellitus requiring medication, a second prior spontaneous MI, multivessel coronary artery disease, or chronic renal dysfunction, defined as an estimated creatinine clearance <60 mL/min.

than in the prolonged DAPT group (1.8 vs. 0.8%; P=0.02). The rate of BARC type 2-5 bleeding was not significantly affected by prolonged DAPT (HR 0.69, 95% CI 0.45-1.05, P=0.09). The authors stated that the increased risk of MI with 6 month DAPT and the wide non-inferiority margin prevented them from concluding that short-term DAPT was safe in this setting, and suggested that prolonged DAPT should remain the standard of care in patients with ACS without excessive risk of bleeding.<sup>715</sup>

In specific clinical scenarios, this standard DAPT duration can be shortened (<12 months) or extended (>12 months). Further on, switching and especially a de-escalation of DAPT (switching from potent P2Y<sub>12</sub>-inhibitors to clopidogrel) was subject to a number of randomized clinical trials.<sup>716,717</sup> Triggers for DAPT de-escalation include clinical (bleeding events or presumed high bleeding risk) and socio-economic factors.<sup>716</sup> Based on recent results from the randomized TROPICAL-ACS (Testing responsiveness to platelet inhibition on chronic antiplatelet treatment for acute coronary syndromes) trial<sup>717</sup>, an approach of DAPT de-escalation guided by platelet function testing may be considered in ACS patients (NSTE-ACS and STEMI) as an alternative to 12 months potent platelet inhibition, especially for patients deemed unsuitable for maintained potent platelet inhibition. For a more detailed description of the pertinent clinical trials in the field of DAPT duration and switching antiplatelet drugs, we refer the reader to the International Expert Consensus document on Switching Platelet P2Y<sub>12</sub> Receptor-Inhibiting Therapies<sup>718</sup> and the 2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease.<sup>410</sup> Following DAPT, lifelong single antiplatelet therapy (usually with aspirin) is recommended and patients should be advised not to prematurely discontinue oral antiplatelet therapy after stenting.<sup>677,719</sup>

Based on the results of the ATLAS-ACS 2-TIMI 51 (Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard therapy in subjects with Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction 51) trial in NSTE-ACS and STEMI patients,<sup>720</sup> low-dose rivaroxaban may be considered after discontinuation of parenteral anticoagulation for patients with no prior stroke/TIA, and at high ischaemic risk as well as low bleeding risk, receiving aspirin and clopidogrel. Of note, rivaroxaban has not been investigated in a background of potent P2Y<sub>12</sub>-inhibitors.

**17.3 ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION**  
**17.3.1 CHOICE OF TREATMENT AND PRE-TREATMENT**

STEMI patients undergoing primary PCI should receive aspirin and a P2Y<sub>12</sub> receptor inhibitor as soon as the diagnosis of STEMI is established. In line with the treatment recommendations for NSTE-ACS patients, DAPT is the cornerstone of treatment for STEMI patients and includes aspirin and a potent P2Y<sub>12</sub> receptor inhibitor (prasugrel or ticagrelor).<sup>701,702</sup> For both antiplatelet drugs, published subgroup analyses on STEMI patients are available (see the Supplementary Data). Randomized data on a comparison of ticagrelor vs. prasugrel in STEMI patients are limited, but the recently published randomized PRAGUE-18 (Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction) trial<sup>735</sup> with limited statistical power found similar safety and efficacy profiles of ticagrelor and prasugrel in a setting of primary PCI. When potent P2Y<sub>12</sub> receptor inhibitors are contraindicated or are not available, clopidogrel should be given for primary PCI instead.<sup>724</sup> The value of pre-treatment with ticagrelor was addressed in the ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST-Elevation Myocardial Infarction to

Open the Coronary Artery) trial.<sup>736</sup> No significant differences were observed in the levels of the two co-primary surrogate endpoints measured before PCI (thrombolysis in Myocardial Infarction flow and ST-segment resolution). Likewise, the incidence of a combined ischaemic endpoint (death, MI, stroke, stent thrombosis, and urgent revascularization) did not differ between the two treatment arms. Nevertheless, in both the TRITON (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction) and PLATO trials, pre-treatment was part of the therapeutic regimen in STEMI.

### 17.3.2 PERI-INTERVENTIONAL TREATMENT

Immediate and sufficient anticoagulation is mandatory in the setting of primary PCI for STEMI and available options include UFH, bivalirudin, and enoxaparin. A number of RCTs compared bivalirudin vs. UFH in different settings and with different utilization of GP IIb/IIIa inhibitors (see the Supplementary Data). The primary recommendation of UFH, reserving bivalirudin for selected cases, is essentially the same for primary PCI as for PCI in NSTEMI-ACS, and is mostly based on the same clinical trials<sup>706,709</sup> (see section 17.2.2).

Enoxaparin was compared with UFH in the randomized open-label ATOLL (Acute STEMI Treated with primary PCI and intravenous enoxaparin Or UFH to Lower ischaemic and bleeding events at short- and Long-term follow-up) trial,<sup>737</sup> and based on the trial results, enoxaparin should be considered as an alternative to UFH treatment in STEMI patients.

A number of clinical trials, performed at a time when pre-treatment and potent platelet inhibition was not part of routine clinical practice, have documented clinical benefits of GP IIb/IIIa inhibitors as an adjunct to primary PCI performed with UFH.<sup>738,739</sup> A meta-analysis showed a significant survival benefit, especially in high-risk STEMI patients, but also a higher risk of bleeding with GP IIb/IIIa administration.<sup>740</sup> Dedicated trials have investigated the value of upstream treatment in the past.<sup>741,742</sup> Based upon the available evidence, the routine use of i.v. or intracoronary GP IIb/IIIa inhibitor administration – regardless of whether treatment starts upstream or in the catheterization laboratory – cannot be recommended. Especially in a setting where potent P2Y<sub>12</sub>-inhibitors like prasugrel or ticagrelor are used, the value of GP IIb/IIIa inhibitors remains uncertain as these agents exhibit a fast onset of action (usually <1 h). GP IIb/IIIa inhibitors remain an option as bail-out therapy or in high-risk PCI without pre-treatment with P2Y<sub>12</sub>-inhibitors. Of note, the bail-out scenarios have never been addressed in randomized controlled trials. For reasons discussed above (see sections 17.1 and 17.2), cangrelor may be considered in specific settings in P2Y<sub>12</sub>-naïve patients undergoing PCI.

### 17.3.3 POST-INTERVENTIONAL AND MAINTENANCE TREATMENT

Following PCI for STEMI, DAPT consisting of a P2Y<sub>12</sub> receptor inhibitor in addition to aspirin is generally recommended for 12 months. Recommendations for maintenance DAPT treatment are generally consistent with those for NSTEMI-ACS patients and are detailed in section 17.2.3.

## Recommendations for antithrombotic treatment in ST-elevation myocardial infarction patients undergoing percutaneous coronary intervention

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Pre-treatment and antiplatelet therapy</b>		
Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150-300 mg (or 75-250 mg i.v.), and at a maintenance dose of 75-100 mg daily long-term regardless of treatment strategy. <sup>681,683,721</sup>	I	A
A potent P2Y <sub>12</sub> inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding. <sup>701,702,724,743</sup>	I	A
GP IIb/IIIa inhibitors should be considered for bail-out if there is evidence of no-reflow or a thrombotic complication.	IIa	C
Cangrelor may be considered in P2Y <sub>12</sub> -inhibitor naïve patients undergoing PCI. <sup>673</sup>	IIb	A
GP IIb/IIIa antagonists may be considered in P2Y <sub>12</sub> -inhibitor naïve patients undergoing PCI.	IIb	C
<b>Peri-interventional therapy</b>		
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during PCI. <sup>703,726</sup>	I	A
Routine use of UFH is recommended.	I	C
Routine use of enoxaparin should be considered. <sup>737</sup>	IIa	B
Routine use of bivalirudin may be considered. <sup>708,710,728,744-746</sup>	IIb	A

GP: glycoprotein; i.v.: intravenous; PCI: percutaneous coronary intervention; UFH: unfractionated heparin. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

## 17.4 CORONARY ARTERY BYPASS GRAFTING

Antithrombotic treatment before and after CABG is addressed in the 2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease.<sup>410</sup> After reviewing the subsequent literature, the current Task Force endorses the recommendations of the update on DAPT and does not identify a need for any major update. Accordingly, the recommendation tables in this section are taken from the Focused Update. For a detailed discussion, we refer the reader to the Focused Update.

## 17.5 SPECIAL CONDITIONS

### 17.5.1 ANTITHROMBOTIC THERAPY AFTER PERCUTANEOUS CORONARY INTERVENTION IN PATIENTS REQUIRING ORAL ANTICOAGULATION

Compared with OAC therapy alone, the addition of DAPT to OAC therapy results in a two- to three-fold increase in bleeding complications, suggesting that every effort should be undertaken to avoid bleeding (Table 8).<sup>753</sup> Assessing the balance of ischaemic and bleeding risks of relatively short (i.e. ≤6 months) triple therapy duration compared with double therapy consisting of clopidogrel and an OAC requires patient-by-patient decisions. Of note, previous randomized studies evaluating the duration of triple therapy or the benefit of NOACs vs. vitamin K antagonists (VKAs) were not adequately powered to assess ischaemic events,

**Dual antiplatelet therapy in patients undergoing cardiac surgery**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that the Heart Team estimates the individual bleeding and ischaemic risks, and guides the timing of CABG as well as the anti-thrombotic management.	I	C
In patients on aspirin who need to undergo non-emergent cardiac surgery, it is recommended to continue aspirin at a low daily regimen throughout the peri-operative period.	I	C
In patients treated with DAPT after coronary stent implantation who subsequently undergo cardiac surgery, it is recommended to resume P2Y <sub>12</sub> inhibitor therapy post-operatively as soon as it is deemed safe, so that DAPT continues until the recommended duration of therapy is completed.	I	C
In patients with ACS (NSTEMI-ACS or STEMI) treated with DAPT who are undergoing CABG and do not require long-term OAC therapy, resumption of P2Y <sub>12</sub> inhibitor therapy as soon as deemed safe after surgery and its continuation up to 12 months is recommended.	I	C
In patients on P2Y <sub>12</sub> inhibitors who need to undergo non-emergent cardiac surgery, postponing surgery for at least 3 days after discontinuation of ticagrelor, at least 5 days after clopidogrel, and at least 7 days after prasugrel should be considered. <sup>747-749</sup>	IIa	B
In CABG patients with prior MI who are at high risk of severe bleeding (e.g. PRECISE-DAPT ≥25), discontinuation of P2Y <sub>12</sub> inhibitor therapy after 6 months should be considered.	IIa	C
Platelet function testing may be considered to guide the decision on the timing of cardiac surgery in patients who have recently received P2Y <sub>12</sub> inhibitors. <sup>193,750-752</sup>	IIb	B
In patients perceived to be at high ischaemic risk with prior MI and CABG, who have tolerated DAPT without a bleeding complication, treatment with DAPT for longer than 12 months and up to 36 months may be considered.	IIb	C

ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; DAPT: dual antiplatelet therapy; MI: myocardial infarction; NSTEMI-ACS: non-ST-elevation acute coronary syndrome; OAC: oral anticoagulant; STEMI: ST-elevation myocardial infarction. PRECISE-DAPT: PREdicting bleeding Complications In patients undergoing Stent implantation and subseqEnt Dual Anti Platelet Therapy. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

and data are lacking on the efficacy of dual therapy in patients at high risk of stroke or recurrent ACS.<sup>754-757</sup> In the major trials, there was no interaction between the duration of triple therapy and clinical presentation (ACS vs. no ACS). The rate of bleeding events peaked within the first 30 days of initiation of triple therapy, and was twice as high when compared with the rate of acute coronary events including recurrent MI and stent thrombosis. For these reasons, the duration of triple therapy should be minimized depending on bleeding and ischaemic risks (see **Tables 8 to 10** for guidance in decision-making). In stabilized event-free patients, discontinuation of any antiplatelet agent at 1 year after stenting is encouraged, while dual therapy may be continued beyond 1 year according to the stent-driven risk shown in **Table 9**.

Based on the favourable bleeding risk in the large phase 3 studies, a NOAC should be preferred over a VKA. The PIONEER<sup>756</sup>

**Table 8. Strategies to avoid bleeding complications in oral anticoagulation patients.**

Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA <sub>2</sub> DS <sub>2</sub> -VASc, ABC, and HAS-BLED) with a focus on modifiable risk factors.
Keep triple therapy duration as short as possible; dual therapy after PCI (OAC and clopidogrel) to be considered instead of triple therapy.
One should consider the use of a NOAC instead of a VKA when NOACs are not contraindicated.
Consider a target INR in the lower part of the recommended target range and maximize time in the therapeutic range (i.e. >65%) when a VKA is used.
Clopidogrel is the P2Y <sub>12</sub> inhibitor of choice.
Use low-dose (≤100 mg daily) aspirin.
Routine use of PPIs.
ABC: Age, Biomarkers, Clinical history; CHA <sub>2</sub> DS <sub>2</sub> -VASc: Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, prior Stroke or transient ischaemic attack or thromboembolism (doubled), Vascular disease, Age 65-74 years, Sex category (female); HAS-BLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly; INR: international normalized ratio; NOAC: non-vitamin K antagonist OAC; OAC: oral anticoagulant; PPIs: proton pump inhibitors; VKA: vitamin K antagonist. Adapted from Valgimigli et al. <sup>410</sup>

**Table 9. High-risk features for ischaemic events.**

Prior stent thrombosis on adequate antiplatelet therapy
Stenting of the last remaining patent coronary artery
Diffuse multivessel disease, especially in diabetic patients
Chronic kidney disease (i.e. creatinine clearance <60 mL/min)
At least three stents implanted
At least three lesions treated
Bifurcation with two stents implanted
Total stented length >60 mm
Treatment of a chronic total occlusion
History of STEMI
STEMI: ST-elevation myocardial infarction.

**Table 10. Unfavourable patient profile for a combination of oral anticoagulant and antiplatelet therapy.**

Short life expectancy
Ongoing malignancy
Poor expected adherence
Poor mental status
End-stage renal failure
Advanced age
Prior major bleeding/prior haemorrhagic stroke
Chronic alcohol abuse
Anaemia
Clinically significant bleeding on dual antithrombotic therapy

**Dual antiplatelet therapy duration in patients with indication for oral anticoagulation**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that periprocedural aspirin and clopidogrel are administered to patients undergoing coronary stent implantation.	I	C
In patients treated with coronary stent implantation, triple therapy with aspirin, clopidogrel, and an OAC should be considered for 1 month, irrespective of the type of stent used. <sup>755</sup>	IIa	B
Triple therapy with aspirin, clopidogrel, and an OAC for longer than 1 month and up to 6 months should be considered in patients with high ischaemic risk due to ACS or other anatomical/procedural characteristics, which outweigh the bleeding risk. <sup>755</sup>	IIa	B
Dual therapy with clopidogrel 75 mg/day and an OAC should be considered as an alternative to 1-month triple antithrombotic therapy in patients in whom the bleeding risk outweighs the ischaemic risk. <sup>754,756,757</sup>	IIa	A
In patients with non-valvular AF requiring anti-coagulation and antiplatelet treatment, a NOAC should be preferred over VKAs. <sup>758-760</sup>	IIa	A
In patients with an indication for a VKA in combination with aspirin and/or clopidogrel, the dose intensity of the VKA should be carefully regulated with a target INR in the lower part of the recommended target range and time in the therapeutic range >65%. <sup>754,755</sup>	IIa	B
Discontinuation of antiplatelet treatment in patients treated with OAC should be considered at 12 months. <sup>753</sup>	IIa	B
When a NOAC is used in combination with aspirin and/or clopidogrel, the lowest approved dose effective for stroke prevention tested in AF trials should be considered. <sup>c</sup>	IIa	C
When rivaroxaban is used in combination with aspirin and/or clopidogrel, rivaroxaban 15 mg q.d. may be used instead of rivaroxaban 20 mg q.d. <sup>756</sup>	IIb	B
When dabigatran is used in combination with aspirin or clopidogrel, a dose of 150 mg b.i.d. may be preferred over a dose of 110 mg b.i.d. <sup>757</sup>	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and an OAC.	III	C

ACS: acute coronary syndrome; AF: atrial fibrillation; b.i.d.: twice daily; INR: international normalized ratio; OAC: oral anticoagulant; NOAC: non-vitamin K oral anticoagulant; q.d.: once daily; VKA: vitamin K antagonist. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence. <sup>c</sup>Apixaban 5 mg b.i.d. or apixaban 2.5 mg b.i.d. if at least two of the following: age ≥80 years, body weight ≤60 kg, or serum creatinine level ≥1.5 mg/dL (133 mmol/L); dabigatran 110 mg or 150 mg b.i.d.; and edoxaban 60 mg q.d. or edoxaban 30 mg q.d. if any of the following: creatinine clearance of 30-50 mL/min; body weight ≤60 kg; concomitant use of verapamil, quinidine, or dronedarone; and rivaroxaban 20 mg q.d. or rivaroxaban 15 mg q.d. if creatinine clearance 30-49 mL/min.

(Prevention of bleeding in patients with AF undergoing PCI) trial and the more recent RE-DUAL (Randomised Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention)<sup>757</sup> trial compared a NOAC plus single antiplatelet therapy with triple therapy with a VKA plus DAPT and consistently showed significantly lower bleeding risks with the dual antithrombotic regimen. In RE-DUAL, both dosing regimens for dabigatran (150 mg and 110 mg b.i.d.) vs. warfarin triple therapy were associated with a significant reduction of major or clinically relevant bleeding events. However, as compared with triple therapy, an increase in both MI (4.5 vs. 3.0%, P=0.09) and stent thrombosis risk (1.5 vs. 0.8%, P=0.15) was reported for the lower dabigatran dose (110 mg b.i.d.), but not for the higher dabigatran dose (150 mg b.i.d.). Although statistical significance was missed, these findings raise concern about the efficacy of the lower dabigatran dose in combination with single antiplatelet therapy in preventing coronary events. Thus, the 150 mg b.i.d. dose of dabigatran is preferred. At present, evidence for a dual treatment approach is available for VKA,<sup>755</sup> rivaroxaban,<sup>756</sup> and dabigatran,<sup>757</sup> but none of these studies were powered to assess the efficacy of preventing stent thrombosis or thrombo-embolic events and only RE-DUAL used a NOAC dose that was previously shown to be effective in the prevention of thrombo-embolic events. The ongoing AUGUSTUS trial (ClinicalTrials.gov Identifier: NCT02415400) will address the value of apixaban in a similar

setting, and with and without aspirin. Edoxaban is currently being investigated in a setting of triple treatment in the ENTRUST-AF-PCI (Evaluation of the safety and efficacy of an edoxaban-based antithrombotic regimen in patients with atrial fibrillation following successful percutaneous coronary intervention) trial (ClinicalTrials.gov Identifier: NCT02866175).

**Figure 11** illustrates applicable DAPT algorithms in patients with an indication for OAC undergoing PCI with the respective classes of recommendations for the different treatment regimens. For more details on the pertinent studies in the field of triple treatment (DAPT plus OAC) and the associated issues, we refer the reader to the 2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease.<sup>410</sup>

### 17.5.2 REVASCULARIZATION IN PATIENTS WITH RENAL FAILURE

See the **Supplementary Data**.

### 17.5.3 MONITORING OF ANTIPLATELET DRUGS (PLATELET FUNCTION TESTING AND GENOTYPING)

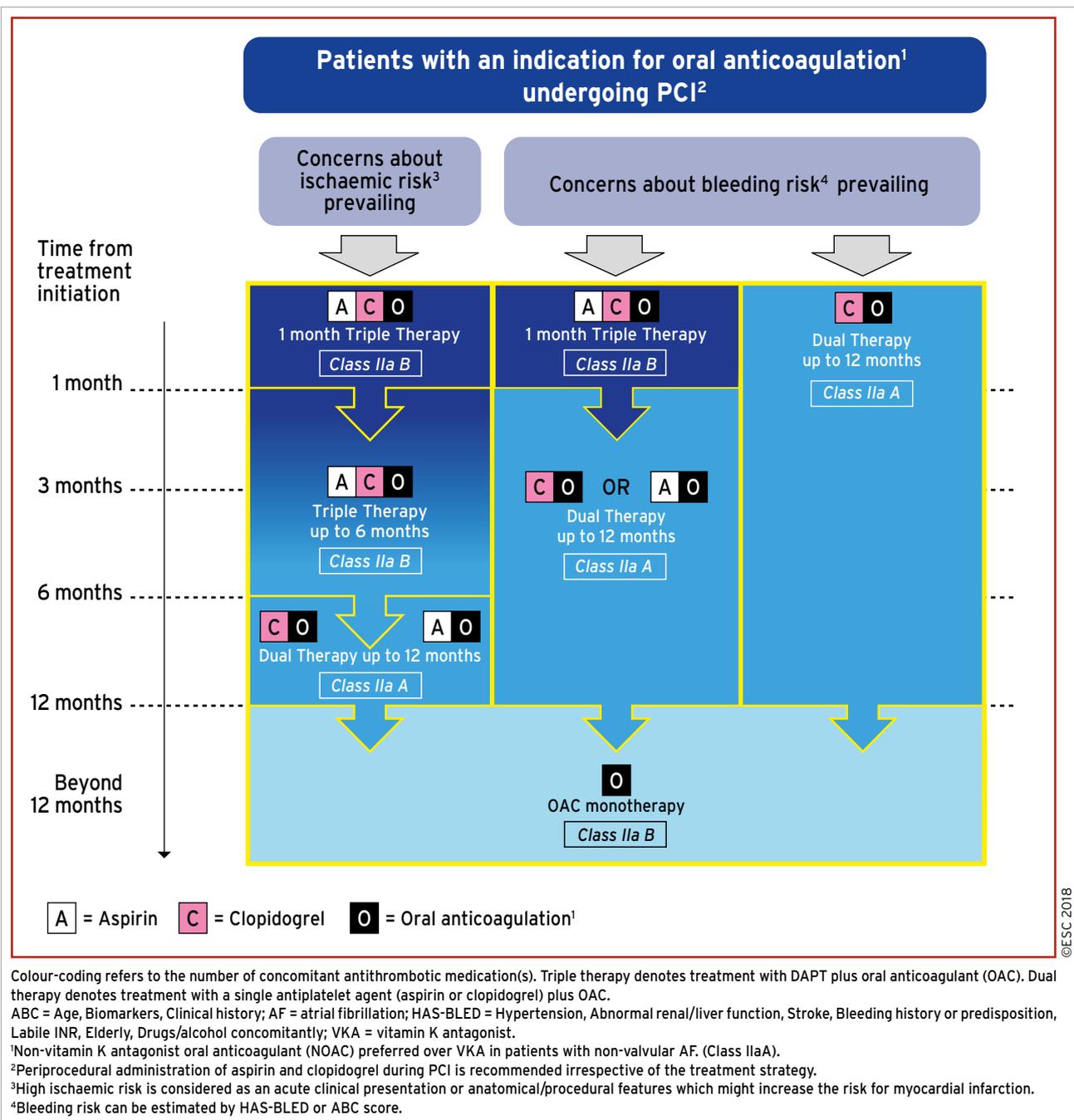
See the **Supplementary Data**.

### 17.5.4 SURGERY IN PATIENTS ON DUAL ANTIPLATELET THERAPY

See 2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease.<sup>410</sup>

## 17.6 GAPS IN THE EVIDENCE

The value of pre-hospital pre-treatment with prasugrel in STEMI patients, as well as the safety and efficacy of ticagrelor given at



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**Figure 11.** Algorithm for dual antiplatelet therapy in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention.

hospital admission in NSTEMI-ACS patients, has not been addressed in dedicated randomized studies.

The safety and efficacy of short-term potent antiplatelet treatment with either prasugrel or ticagrelor in SCAD patients is unknown, and is subject to ongoing clinical trials [the ALPHEUS (Assessment of Loading With the P2Y<sub>12</sub> Inhibitor Ticagrelor or Clopidogrel to Halt Ischemic Events in Patients Undergoing Elective Coronary Stenting) trial: NCT02617290 and the SASSICAIA (Comparison of Loading Strategies With Antiplatelet Drugs in Patients Undergoing Elective Coronary Intervention) trial: NCT02548611].

The clinical benefit of a short-term DAPT duration followed by long-term ticagrelor monotherapy (and stopping aspirin) remains unknown. The ongoing GLOBAL LEADERS (Long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing biolimus-eluting stent implantation) and TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trials aim to close this gap in our current knowledge (NCT01813435 and NCT02270242, respectively).

## 18 Volume outcome relationship for revascularization procedures

Operator experience influences outcomes, particularly in critical, complex situations. Greater total experience of an entire hospital team – consisting of the supporting members in the operating room or catheterization laboratory and those responsible for post-operative care – results in more favourable outcomes.

### 18.1 CORONARY ARTERY BYPASS GRAFTING

Studies have suggested that the volume of CABG surgery in a hospital significantly impacts in-hospital mortality, although no consistent cut-offs for volume were used in these studies.<sup>761-762</sup> This increase in mortality observed in lower volume centres seems to be attributable to so-called 'failure to rescue': although patients operated on at low-volume centres are not at particularly higher risk of suffering a major complication, they are more likely to die from such a complication should it occur.<sup>763</sup> Therefore, consideration should be given to the performance of CABG in centres with an annual volume of at least 200 CABG cases. Apart from hospital volume, higher surgeon volume also appears to be inversely related to operative mortality. Birkmeyer et al. provided evidence suggesting that both hospitals and surgeons have some impact on outcomes.<sup>764</sup>

Several studies suggest that quality measures are more important than volume *per se*.<sup>765,766</sup> Missing quality indicators in hospitals strongly predicted mortality, irrespective of surgeon or hospital case volumes.<sup>767</sup> Therefore, it is recommended that such quality measures (as an example see **Supplementary Table 9**) are adopted and reported to facilitate focused quality improvement.<sup>768</sup>

### 18.2 PERCUTANEOUS CORONARY INTERVENTION

Numerous studies have investigated the relationship between the volume of procedures and outcomes of PCI, suggesting a volume-outcome relationship at the operator level, as well as at the institutional level.<sup>761,769-773</sup> A population-based study from the PCI reporting system of New York indicated that hospital case volumes

<400 PCIs per year and operator case volumes <75 PCIs per year were associated with impaired outcomes.<sup>769</sup>

Among patients with ACS, particularly STEMI, operator and hospital volumes play important roles. A large study in the USA reported that, in a cohort of 36 535 patients undergoing primary PCI, in-hospital mortality was significantly lower in institutions with higher primary PCI volumes (5.7% in hospitals performing >33 primary PCIs/year vs. 7.7% in hospitals performing <12 primary PCIs/year).<sup>774</sup>

Operator volume has also been shown to impact outcomes in LM PCI. A single-centre study of 1948 patients who underwent unprotected LM PCI, performed by 25 operators over a 7 year period, showed reduced 30 day and 3 year mortality for patients who had their PCI performed by a high-volume operator (defined as  $\geq 15$  LM PCI/year; mean 25/year) vs. a low-volume operator (<15 LM PCI/year).<sup>775</sup>

An example of quality measures for PCI is provided in **Supplementary Table 10**.

### 18.3 TRAINING IN CARDIAC SURGERY AND INTERVENTIONAL CARDIOLOGY FOR MYOCARDIAL REVASCULARIZATION

A European training programme in interventional cardiology has been proposed by the EAPCI in order to ensure the high quality of patient care and clinical excellence.<sup>776</sup> The programme should last 1-2 years at high-volume institutions that handle  $\geq 800$  PCIs per year and that have an established 24 h/7 day service for the treatment of patients with ACS.

For CABG, no standardized European programme exists at this time. However, the pace at which proficiency reaches certain acceptable standards differs from trainee to trainee. Therefore, although it is recommended that trainees perform  $\geq 200$  CABG procedures under supervision before becoming completely independent, a competency-driven residency programme with regular evaluation of progress is recommended over a volume-driven programme.

#### Recommendations for operator/institutional volume in myocardial revascularization

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>CABG</b>		
It should be considered that CABG be performed at institutions with annual institutional volumes of $\geq 200$ CABG cases.	IIa	C
<b>PCI</b>		
It should be considered that PCI for ACS be performed by trained operators with annual volumes of $\geq 75$ procedures at institutions performing $\geq 400$ PCIs per year with an established 24 h/7 day service for the treatment of patients with ACS.	IIa	C
It should be considered that PCI for SCAD be performed by trained operators with annual volumes of $\geq 75$ procedures at institutions performing $\geq 200$ PCIs per year.	IIa	C
It should be considered that institutions with annual volumes of <400 PCIs collaborate in networks with higher-volume institutions (>400 PCIs per year), with shared written protocols and exchange of operators and support staff.	IIa	C
It should be considered that PCI for LM be performed by trained operators with an annual volume of $\geq 25$ LM PCI cases per year.	IIa	C
It should be considered that non-emergency high-risk PCI procedures – such as for LM disease, single remaining patent coronary artery, and complex chronic total occlusions – are only performed by adequately experienced operators at centres that have access to circulatory support and intensive care treatment.	IIa	C

ACS: acute coronary syndromes; CABG: coronary artery bypass grafting; LM: left main; PCI: percutaneous coronary intervention; SCAD: stable coronary artery disease. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

### Recommendations for training in myocardial revascularization

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Training in CABG</b>		
It is recommended that trainees in cardiac surgery and interventional cardiology follow a competency-driven residency programme with regular evaluation of progression.	I	C
It should be considered that trainees in cardiac surgery perform ≥200 CABG procedures under supervision before being independent.	Ila	C
<b>Training in PCI</b>		
It should be considered that trainees in interventional cardiology perform ≥200 PCI procedures as first operator, with one-third of PCI procedures in emergency or ACS patients under supervision, before being independent.	Ila	C
It should be considered that trainees in interventional cardiology complete formal training according to a 1-2 year curriculum at institutions with ≥800 PCIs per year and an established 24 h/7 day service for the treatment of patients with ACS.	Ila	C

ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

### Recommendations for outcome registration, monitoring, and benchmarking

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that specific quality performance measures for CABG are adopted at a national level to allow outcome monitoring and benchmarking.	I	C
It is recommended that national societies establish national databases on CABG practice and outcomes.	I	C
It is recommended that CABG outcome data are reported by hospitals to national databases.	I	C

CABG: coronary artery bypass grafting. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence.

## 19 Medical therapy, secondary prevention, and strategies for follow-up

Myocardial revascularization must be accompanied by medical therapy and other secondary prevention strategies for risk factor modification and permanent lifestyle changes.<sup>42</sup> Secondary prevention and cardiac rehabilitation are an integral part of management after revascularization because such measures reduce future morbidity and mortality in a cost-effective way, and can further improve symptoms. These measures are discussed in detail in the European Guidelines on Cardiovascular Disease Prevention that were published in 2016.<sup>42</sup>

The need to detect restenosis has reduced in the DES era. Likewise, the durability of CABG results have increased with the use of arterial grafts, and ischaemia stems mainly from SVG attrition and/or progression of CAD in native vessels. Nevertheless, the recurrence of symptoms or ischaemia due to disease progression or restenosis deserves attention.

### 19.1 GAPS IN THE EVIDENCE

In all studies to date on the optimal follow-up after PCI, the gain from discovering patients with restenosis is obscured by the high rate of false positive exercise ECG tests indicating ischaemia. Therefore, simple exercise ECG testing is not recommended for follow-up and a non-invasive imaging approach is preferred.

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

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
After CABG or PCI for AMI, participation in a cardiac rehabilitation programme is recommended to improve patient outcomes. <sup>777</sup>	I	A
It is recommended that secondary prevention measures, including medical therapy and lifestyle changes, are started and reinforced after myocardial revascularization. <sup>683,778-785</sup>	I	A
It is recommended that patients are re-evaluated after myocardial revascularization (e.g. at 3 months and thereafter, at least on an annual basis) in order to reassess symptoms and adherence to secondary prevention measures, and reinforce medical therapy and lifestyle changes when appropriate.	I	C
<b>Symptomatic patients</b>		
Coronary angiography is recommended in patients with intermediate- to high-risk findings <sup>c</sup> at stress testing.	I	C
An imaging stress test should be considered in patients with prior revascularization over stress ECG. <sup>786</sup>	Ila	B
<b>Asymptomatic patients</b>		
Surveillance by non-invasive imaging-based stress testing may be considered in high-risk patient subsets 6 months after revascularization.	Ilb	C
After high-risk PCI (e.g. unprotected LM stenosis), late (3-12 months) surveillance angiography may be considered, irrespective of symptoms.	Ilb	C
Routine non-invasive imaging-based stress testing may be considered 1 year after PCI and >5 years after CABG.	Ilb	C

AMI: acute myocardial infarction; CABG: coronary artery bypass grafting; ECG: electrocardiogram; LM: left main; PCI: percutaneous coronary intervention. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence. <sup>c</sup>Intermediate- and high-risk findings at stress imaging are ischaemia at low work-load with exercise stress testing, early-onset ischaemia with pharmacological stress testing, an inducible wall motion abnormality, or a reversible perfusion defect in ≥10% of LV myocardium.

Specific studies to clarify which subset of patients benefits more from a specific follow-up approach are missing. More studies are needed to assess the role of CT angiography in patient surveillance after myocardial revascularization.

## 20 Key messages

- (1) Myocardial revascularization is performed for the relief of symptoms of myocardial ischaemia and the improvement of prognosis. In SCAD, the prognostic benefit is dependent on the extent of myocardium subject to ischaemia.
- (2) The prognostic and symptomatic benefits of myocardial revascularization critically depend on the completeness of revascularization. Therefore, the ability to achieve complete revascularization is a key issue when choosing the appropriate treatment strategy.
- (3) Apart from issues of individual operative risk and technical feasibility, diabetes mellitus and the anatomical complexity of CAD determine the relative benefits of PCI and CABG.
- (4) The SYNTAX score is the recommended tool to gauge the anatomical complexity of coronary disease.
- (5) In some instances, both PCI and CABG are equally reasonable, or sometimes even equally problematic, options. This calls for the Heart Team to be consulted to develop individualized treatment concepts, with respect for the preferences of the patient who has been informed about early and late outcomes.
- (6) Timely PCI of the culprit lesion remains the mainstay of treatment of ACS.
- (7) After PCI of the culprit lesion in ACS, the choice of further revascularization modality should follow the criteria applied to patients with SCAD.
- (8) Radial access is preferred for any PCI irrespective of clinical presentation, unless there are overriding procedural considerations.
- (9) DES are recommended for any PCI irrespective of clinical presentation, lesion type, anticipated duration of DAPT, or concomitant anticoagulant therapy.
- (10) Even though 6 months of DAPT is generally recommended after PCI in SCAD and 12 months of DAPT after ACS, the type and duration of DAPT should be individualized according to the ischaemic and bleeding risks, and appropriately adapted during follow-up. Based on this judgement, treatment durations for DAPT after DES that are as short as 1 month or even as long as lifelong may be reasonable.
- (11) Off-pump surgery with no-touch aorta for high-risk patients should be considered when expertise exists.
- (12) Multiple arterial grafting should be considered using the radial artery for high-grade stenosis and/or BIMA grafting for patients who do not have an increased risk of sternal wound infection.

## 21 Evidence-based 'to do' and 'not to do' messages from the Guidelines

Risk models to assess short- and long-term outcomes after myocardial revascularization		Class <sup>a</sup>	Level <sup>b</sup>		
When evidence of ischaemia is not available, FFR or iwFR are recommended to assess the haemodynamic relevance of intermediate-grade stenosis.		I	A		
It is recommended that the STS score is calculated to assess in-hospital or 30 day mortality, and in-hospital morbidity, after CABG.		I	B		
In patients with LM or multivessel disease, it is recommended that the SYNTAX score is calculated to assess the anatomical complexity of CAD and the long-term risk of mortality and morbidity after PCI.		I	B		
Indications for revascularization in patients with stable angina or silent ischaemia					
For prognosis	LM disease with stenosis >50%. <sup>c</sup>	I	A		
	Any proximal LAD stenosis >50%. <sup>c</sup>	I	A		
	Two- or three-vessel disease with stenosis >50% <sup>c</sup> with impaired LV function (LVEF ≤35%). <sup>c</sup>	I	A		
	Large area of ischaemia detected by functional testing (>10% LV) or abnormal invasive FFR. <sup>d</sup>	I	B		
For symptoms	Any haemodynamically significant coronary stenosis in the presence of limiting angina or angina equivalent, with an insufficient response to optimized medical therapy.	I	A		
Type of revascularization (CABG or PCI) in patients with SCAD with suitable coronary anatomy for both procedures and low predicted surgical mortality					
Recommendations according to the extent of CAD		CABG		PCI	
		Class <sup>a</sup>	Level <sup>b</sup>	Class <sup>a</sup>	Level <sup>b</sup>
<b>One-vessel CAD</b>					
With proximal LAD stenosis		I	A	I	A
<b>Two-vessel CAD</b>					
With proximal LAD stenosis		I	B		
<b>LM CAD</b>					
LM with low SYNTAX score 0 - 22		I	A	I	A
LM with intermediate SYNTAX score >22 and ≤32		I	A		
LM with high SYNTAX score >32. <sup>e</sup>		I	A	III	B
<b>Three-vessel CAD without diabetes mellitus</b>					
Three-vessel disease with low SYNTAX score 0 - 22		I	A	I	A
Three-vessel disease with intermediate or high SYNTAX score >22 <sup>e</sup>		I	A	III	A
<b>Three-vessel CAD with diabetes mellitus</b>					
Three-vessel disease with low SYNTAX score 0 - 22		I	A		
Three-vessel disease with intermediate or high SYNTAX score >22 <sup>e</sup>		I	A	III	A

*continued*

<b>Invasive evaluation and revascularization in NSTEMI-ACS</b>		
An early invasive strategy (<24 h) is recommended in patients with at least one high-risk criterion (Figure 4).	I	A
An invasive strategy (<72 h after first presentation) is indicated in patients with at least one intermediate-risk criterion (Figure 4) or recurrent symptoms.	I	A
It is recommended that the revascularization strategy ( <i>ad hoc</i> culprit-lesion PCI/multivessel PCI/CABG) is based on the patient's clinical status and comorbidities, as well as the disease severity, i.e. distribution and angiographic lesion characteristics (e.g. SYNTAX score), according to the principles for SCAD.	I	B
In cardiogenic shock, routine revascularization of non-IRA lesions is not recommended during primary PCI.	III	B
<b>Primary PCI for myocardial reperfusion in STEMI</b>		
<b>Indication</b>		
Reperfusion therapy is indicated in all patients with time from symptom onset <12 h duration and persistent ST-segment elevation.	I	A
A primary PCI strategy is recommended over fibrinolysis within indicated timeframes.	I	A
<b>Logistics</b>		
It is recommended that the pre-hospital management of STEMI patients be based on regional networks that are designed to timely and effectively deliver reperfusion therapy, and to offer primary PCI to as many patients as possible.	I	B
It is recommended that primary PCI-capable centres deliver a 24 h/7 day service and ensure that primary PCI is performed as fast as possible.	I	B
Patients transferred to a PCI-capable centre for primary PCI should bypass the emergency department and be transferred directly to the catheterization laboratory.	I	B
<b>Strategy/technique</b>		
In cardiogenic shock, routine revascularization of non-IRA lesions is not recommended during primary PCI.	III	B
Routine use of thrombus aspiration is not recommended.	III	A
<b>Recommendations on revascularizations in patients with chronic heart failure and systolic LV dysfunction (EF ≤35%)</b>		
In patients with severe LV systolic dysfunction and coronary artery disease suitable for intervention, myocardial revascularization is recommended.	I	B
CABG is recommended as the first revascularization strategy choice in patients with multivessel disease and acceptable surgical risk.	I	B
<b>Revascularizations in patients with cardiogenic shock</b>		
Emergency invasive evaluation is indicated in patients with acute heart failure or cardiogenic shock complicating ACS.	I	B
Emergency PCI is indicated for patients with cardiogenic shock due to STEMI or NSTEMI-ACS, independent of time delay of symptom onset, if coronary anatomy is amenable.	I	B
Emergency CABG is recommended for patients with cardiogenic shock if the coronary anatomy is not amenable to PCI.	I	B
Routine use of IABP in patients with cardiogenic shock due to ACS is not recommended.	III	B
<b>Prevention of contrast-induced nephropathy</b>		
<b>Patients with moderate-to-severe CKD</b>		
Use of low- or iso-osmolar contrast media is recommended.	I	A
It is recommended that the volume of contrast media is minimized.	I	B
<b>Severe CKD</b>		
Haemodialysis therapy is not recommended as a preventative measure.	III	B
<b>Pre-operative strategies to reduce the incidence of stroke in patients undergoing CABG</b>		
In patients undergoing CABG, carotid DUS is recommended in patients with recent (<6 months) history of stroke/TIA.	I	B
<b>Disease progression and late graft failure</b>		
Repeat revascularization is indicated in patients with extensive ischaemia or severe symptoms despite medical therapy.	I	B
IMA is the conduit of choice for redo CABG in patients in whom the IMA was not used previously.	I	B
DES are recommended for the treatment of in-stent restenosis within BMS or DES.	I	A
Drug-coated balloons are recommended for the treatment of in-stent restenosis within BMS or DES.	I	A
<b>Prevention of ventricular arrhythmias by revascularization</b>		
A primary PCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG consistent with STEMI.	I	B
Perioperative oral β-blocker therapy is recommended for the prevention of post-operative AF after CABG surgery.	I	B
<b>Procedural aspects of CABG</b>		
Arterial grafting with an IMA to the LAD system is recommended.	I	B
Use of the radial artery is recommended over the saphenous vein in patients with high-degree stenosis.	I	A
Skeletonized IMA dissection is recommended in patients with high risk of sternal wound infection.	I	B
Minimization of aortic manipulation is recommended.	I	B
<b>Procedural aspects of PCI</b>		
DES are recommended over BMS for any PCI irrespective of: – clinical presentation – lesion type – planned non-cardiac surgery – anticipated duration of DAPT – concomitant anticoagulant therapy.	I	A

*continued*

Radial access is recommended as the standard approach, unless there are overriding procedural considerations.	I	A
Stent implantation in the main vessel only, followed by provisional balloon angioplasty with or without stenting of the side branch, is recommended for PCI of bifurcation lesions.	I	A
<b>Antithrombotic treatment in SCAD patients undergoing PCI</b>		
Treatment with 600 mg clopidogrel is recommended in elective PCI patients once anatomy is known and the decision has been made to proceed with PCI.	I	A
Aspirin is indicated before elective stenting.	I	A
Clopidogrel (600 mg loading dose and 75 mg daily maintenance dose) is recommended for elective stenting.	I	A
UFH is indicated as a standard anticoagulant (70-100 U/kg).	I	B
Life-long single antiplatelet therapy, usually aspirin, is recommended.	I	A
In patients with SCAD treated with coronary stent implantation, DAPT consisting of clopidogrel in addition to aspirin is generally recommended for 6 months, irrespective of the stent type.	I	A
<b>Antithrombotic treatment in NSTEMI-ACS patients undergoing PCI</b>		
Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150-300 mg (or 75-250 mg i.v.) and at a maintenance dose of 75-100 mg daily long-term, regardless of treatment strategy.	I	A
A P2Y <sub>12</sub> inhibitor is recommended in addition to aspirin, maintained over 12 months unless there are contraindications such as an excessive risk of bleeding. Options are:	I	A
Prasugrel in P2Y <sub>12</sub> -naïve patients who proceed to PCI (60 mg loading dose and 10 mg daily dose)	I	B
Ticagrelor irrespective of the pre-treatment and revascularization strategy (180 mg loading dose, 90 mg twice daily)	I	B
Clopidogrel (600 mg loading dose and 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.	I	B
Pre-treatment with GP IIb/IIIa antagonists in patients in whom coronary anatomy is not known is not recommended.	III	A
Administration of prasugrel to patients in whom coronary anatomy is not known is not recommended.	III	B
Peri-interventional anticoagulation is recommended for all patients in addition to antiplatelet therapy.	I	A
In patients on fondaparinux (2.5 mg daily s.c.), a single bolus UFH (85 IU/kg, or 60 IU in the case of concomitant use of GP IIb/IIIa receptor inhibitors) is indicated.	I	B
Crossover of UFH and LMWH is not recommended.	III	B
In patients with ACS treated with coronary stent implantation, DAPT with a P2Y <sub>12</sub> inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as an excessive risk of bleeding (e.g. PRECISE-DAPT ≥25).	I	A
<b>Antithrombotic treatment in STEMI patients undergoing PCI</b>		
Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150-300 mg (or 75-250 mg i.v.), and at a maintenance dose of 75-100 mg daily long-term regardless of treatment strategy.	I	A
A potent P2Y <sub>12</sub> inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at the time of PCI at the latest) PCI and should be maintained over 12 months, unless there are contraindications such as an excessive risk of bleeding.	I	A
<b>Strategies for follow-up and management</b>		
After CABG or PCI for AMI, participation in a cardiac rehabilitation programme is recommended to improve patient outcomes.	I	A
It is recommended that secondary prevention measures, including medical therapy and lifestyle changes, are started and reinforced after myocardial revascularization.	I	A

ACS: acute coronary syndrome; AF: atrial fibrillation; AMI: acute myocardial infarction; BMS: bare-metal stent; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CKD: chronic kidney disease; DAPT: dual antiplatelet therapy; DES: drug eluting stents; DUS: duplex ultrasound; ECG: electrocardiogram; EF: ejection fraction; FFR: fractional flow reserve; GP: glycoprotein; IABP: intra-aortic balloon pump; iwFR: instantaneous wave-free ratio; IMA: internal mammary artery; IRA: infarct-related artery; i.v.: intravenous; LAD: left anterior descending; LM: left main; LMWH: low-molecular-weight heparin; LV: left ventricular; LVEF: left ventricular ejection fraction; NSTEMI-ACS: non-ST-elevation acute coronary syndrome; PCI: percutaneous coronary intervention; PRECISE-DAPT: PREDicting bleeding Complications In patients undergoing Stent implantation and subSEquent Dual Anti Platelet Therapy; s.c.: subcutaneous; SCAD: stable coronary artery disease; STEMI: ST-elevation myocardial infarction; STS: Society of Thoracic Surgeons; SYNTAX: Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TIA: transient ischaemic attack; UFH: unfractionated heparin. <sup>a</sup>Class of recommendation. <sup>b</sup>Level of evidence. <sup>c</sup>With documented ischaemia, a haemodynamically relevant lesion defined by FFR ≤0.80 or iwFR ≤0.89, or >90% stenosis in a major coronary vessel. <sup>d</sup>Based on FFR <0.75 indicating a prognostically relevant lesion. <sup>e</sup>PCI should be considered, if the Heart Team is concerned about the surgical risk or if the patient refuses CABG after adequate counselling by the Heart Team. <sup>f</sup>These recommendations refer to stents that are supported by large-scale randomized trials with clinical endpoint evaluation leading to an unconditional CE mark.

## 22 Appendix

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## 23. References

- Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabate M, Senior R, Taggart DP, van der Wall EE, Vrints CJ. 2013 ESC guidelines on the management of stable coronary artery disease. *Eur Heart J*. 2013;34:2949-3003.
- Min JK, Leipsic J, Pencina MJ, Berman DS, Koo BK, van Mieghem C, Erglis A, Lin FY, Dunning AM, Apruzzese P, Budoff MJ, Cole JH, Jaffer FA, Leon MB, Malpeso J, Mancini GB, Park SJ, Schwartz RS, Shaw LJ, Mauri L. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA*. 2012;308:1237-1245.
- Norgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, Jensen JM, Mauri L, De Bruyne B, Bezerra H, Osawa K, Marwan M, Naber C, Erglis A, Park SJ, Christiansen EH, Kaltoft A, Lassen JF, Botker HE, Achenbach S, Group NXTTS. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: The NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol*. 2014;63: 1145-1155.
- Douglas PS, Pontone G, Hlatky MA, Patel MR, Norgaard BL, Byrne RA, Curzen N, Purcell I, Gutberlet M, Rioufol G, Hink U, Schuchlenz HW, Feuchtner G, Gilard M, Andreini D, Jensen JM, Hadamitzky M, Chiswell K, Cyr D, Wilk A, Wang F, Rogers C, De Bruyne B, PLATFORM Investigators. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: The prospective longitudinal trial of FFR(CT): Outcome and resource impacts study. *Eur Heart J*. 2015;36: 3359-3367.
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37: 2129-2200.
- Beanlands RS, Nichol G, Huszti E, Humen D, Racine N, Freeman M, Gulenchyn KY, Garrard L, deKemp R, Guo A, Ruddy TD, Benard F, Lamy A, Iwanochko RM; PARR-2 Investigators. F-18-fluorodeoxyglucose positron emission tomography imaging-assisted management of patients with severe left ventricular dysfunction and suspected coronary disease: A randomized, controlled trial (PARR-2). *J Am Coll Cardiol*. 2007;50: 2002-2012.
- Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, Danziger-Isakov L, Kirklin JK, Kirk R, Kushwaha SS, Lund LH, Potena L, Ross HJ, Taylor DO, Verschuuren EA, Zuckermann A, International Society for Heart Lung Transplantation Infectious Diseases Council, International Society for Heart Lung Transplantation Pediatric Transplantation Council, International Society for Heart Lung Transplantation Heart Failure, Transplantation Council. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. *J Heart Lung Transplant*. 2016;35:1-23.

8. Feldman D, Pamboukian SV, Teuteberg JJ, Birks E, Lietz K, Moore SA, Morgan JA, Arabia F, Bauman ME, Buchholz HW, Deng M, Dickstein ML, El-Banayosy A, Elliot T, Goldstein DJ, Grady KL, Jones K, Hryniewicz K, John R, Kaan A, Kusne S, Loebe M, Massicotte MP, Moazami N, Mohacsi P, Mooney M, Nelson T, Pagani F, Perry W, Potapov EV, Eduardo Rame J, Russell SD, Sorensen EN, Sun B, Strueber M, Mangi AA, Petty MG, Rogers J; International Society for Heart and Lung Transplantation. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: Executive summary. *J Heart Lung Transplant*. 2013;32:157-187.
9. Bonow RO, Maurer G, Lee KL, Holly TA, Binkley PF, Desvigne-Nickens P, Drozd J, Farsky PS, Feldman AM, Doenst T, Michler RE, Berman DS, Nicolau JC, Pellikka PA, Wrobel K, Alotti N, Asch FM, Favaloro LE, She L, Velazquez EJ, Jones RH, Panza JA; STICH Trial Investigators. Myocardial viability and survival in ischemic left ventricular dysfunction. *N Engl J Med*. 2011;364:1617-1625.
10. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: A meta-analysis. *J Am Coll Cardiol*. 2002;39:1151-1158.
11. Ling LF, Marwick TH, Flores DR, Jaber WA, Brunken RC, Cerqueira MD, Hachamovitch R. Identification of therapeutic benefit from revascularization in patients with left ventricular systolic dysfunction: Inducible ischemia versus hibernating myocardium. *Circ Cardiovasc Imaging*. 2013;6:363-372.
12. Ahn JM, Park DW, Shin ES, Koo BK, Nam CW, Doh JH, Kim JH, Chae IH, Yoon JH, Her SH, Seung KB, Chung WY, Yoo SY, Lee JB, Choi SW, Park K, Hong TJ, Lee SY, Han M, Lee PH, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, Park SJ; IRIS-FFR Investigators. Fractional flow reserve and cardiac events in coronary artery disease: Data from a prospective IRIS-FFR Registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve). *Circulation*. 2017;135:2241-2251.
13. Bech GJ, De Bruyne B, Bonnier HJ, Bartunek J, Wijns W, Peels K, Heyndrickx GR, Koolen JJ, Pijls NH. Long-term follow-up after deferral of percutaneous transluminal coronary angioplasty of intermediate stenosis on the basis of coronary pressure measurement. *J Am Coll Cardiol*. 1998;31:841-847.
14. Bech GJ, De Bruyne B, Pijls NH, de Muinck ED, Hoorntje JC, Escaned J, Stella PR, Boersma E, Bartunek J, Koolen JJ, Wijns W. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: A randomized trial. *Circulation*. 2001;103:2928-2934.
15. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bar F, Hoorntje J, Koolen J, Wijns W, de Bruyne B. Percutaneous coronary intervention of functionally non-significant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol*. 2007;49:2105-2111.
16. Adedj J, De Bruyne B, Flore V, Di Gioia G, Ferrara A, Pellicano M, Toth GG, Bartunek J, Vanderheyden M, Heyndrickx GR, Wijns W, Barbato E. Significance of intermediate values of fractional flow reserve in patients with coronary artery disease. *Circulation*. 2016;133:502-508.
17. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, Bhindi R, Lehman SJ, Walters D, Sapontis J, Janssens L, Vrints CJ, Khashaba A, Laine M, Van Belle E, Krackhardt F, Bojara W, Going O, Harle T, Indolfi C, Niccoli G, Ribichini F, Tanaka N, Yokoi H, Takashima H, Kikuta Y, Erglis A, Vinhas H, Canas Silva P, Baptista SB, Alghamdi A, Hellig F, Koo BK, Nam CW, Shin ES, Doh JH, Brugaletta S, Alegria-Barrero E, Meuwissen M, Piek JJ, van Royen N, Sezer M, Di Mario C, Gerber RT, Malik IS, Sharp ASP, Talwar S, Tang K, Samady H, Altman J, Seto AH, Singh J, Jeremias A, Matsuo H, Kharbada RK, Patel MR, Serruys P, Escaned J. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med*. 2017;376:1824-1834.
18. Gotberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, Olsson SE, Ohagen P, Olsson H, Omerovic E, Calais F, Lindroos P, Maeng M, Todt T, Venetsanos D, James SK, Karegren A, Nilsson M, Carlsson J, Hauer D, Jensen J, Karlsson AC, Panayi G, Erlinge D, Frobert O, iFR-SWEDEHEART Investigators. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med*. 2017;376:1813-1823.
19. Van Belle E, Rioufol G, Pouillot C, Cuisset T, Bougrini K, Teiger E, Champagne S, Belle L, Barreau D, Hanssen M, Besnard C, Dauphin R, Dallongeville J, El Hahi Y, Sideris G, Bretelle C, Lhoest N, Barnay P, Leborgne L, Dupouy P, Investigators of the Registre Francais de la FFR-R3F. Outcome impact of coronary revascularization strategy reclassification with fractional flow reserve at time of diagnostic angiography: Insights from a large French multicenter fractional flow reserve registry. *Circulation*. 2014;129:173-185.
20. Curzen N, Rana O, Nicholas Z, Golledge P, Zaman A, Oldroyd K, Hanratty C, Banning A, Wheatcroft S, Hobson A, Chitkara K, Hildick-Smith D, McKenzie D, Calver A, Dimitrov BD, Corbett S. Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain?: the RIPCORD study. *Circ Cardiovasc Interv*. 2014;7:248-255.
21. Baptista SB, Raposo L, Santos L, Ramos R, Cale R, Jorge E, Machado C, Costa M, Infante de Oliveira E, Costa J, Pipa J, Fonseca N, Guardado J, Silva B, Sousa MJ, Silva JC, Rodrigues A, Seca L, Fernandes R. Impact of routine fractional flow reserve evaluation during coronary angiography on management strategy and clinical outcome: One-year results of the POST-IT. *Circ Cardiovasc Interv*. 2016;9:e003288.
22. Van Belle E, Baptista SB, Raposo L, Henderson J, Rioufol G, Santos L, Pouillot C, Ramos R, Cuisset T, Cale R, Teiger E, Jorge E, Belle L, Machado C, Barreau D, Costa M, Hanssen M, Oliveira E, Besnard C, Costa J, Dallongeville J, Pipa J, Sideris G, Fonseca N, Bretelle C, Guardado J, Lhoest N, Silva B, Barnay P, Sousa MJ, Leborgne L, Silva JC, Vincent F, Rodrigues A, Seca L, Fernandes R, Dupouy P, PRIMER-FFR Study Group. Impact of Routine Fractional Flow Reserve on Management Decision and 1-Year Clinical Outcome of Patients With Acute Coronary Syndromes: PRIME-FFR (Insights From the POST-IT [Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease] and R3F [French FFR Registry] Integrated Multicenter Registries - Implementation of FFR [Fractional Flow Reserve] in Routine Practice). *Circ Cardiovasc Interv*. 2017;10:e004296.
23. Van Belle E, Dupouy P, Rioufol G. Routine fractional flow reserve combined to diagnostic coronary angiography as a one-stop procedure: Episode 3. *Circ Cardiovasc Interv*. 2016;9:e004137.

24. Johnson NP, Toth GG, Lai D, Zhu H, Acar G, Agostoni P, Appelman Y, Arslan F, Barbato E, Chen SL, Di Serafino L, Dominguez-Franco AJ, Dupouy P, Esen AM, Esen OB, Hamilos M, Iwasaki K, Jensen LO, Jimenez-Navarro MF, Katritsis DG, Kocaman SA, Koo BK, Lopez-Palop R, Lorin JD, Miller LH, Muller O, Nam CW, Oud N, Puymirat E, Rieber J, Rioufol G, Rodes-Cabau J, Sedlis SP, Takeishi Y, Tonino PA, Van Belle E, Verna E, Werner GS, Fearon WF, Pijls NH, De Bruyne B, Gould KL. Prognostic value of fractional flow reserve: Linking physiologic severity to clinical outcomes. *J Am Coll Cardiol.* 2014;64:1641-1654.
25. Mallidi J, Atreya AR, Cook J, Garb J, Jeremias A, Klein LW, Lotfi A. Long-term outcomes following fractional flow reserve-guided treatment of angiographically ambiguous left main coronary artery disease: A meta-analysis of prospective cohort studies. *Catheter Cardiovasc Interv.* 2015;86:12-18.
26. Hamilos M, Muller O, Cuisset T, Ntalianis A, Chlouverakis G, Sarno G, Nelis O, Bartunek J, Vanderheyden M, Wyffels E, Barbato E, Heyndrickx GR, Wijns W, De Bruyne B. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation.* 2009;120:1505-1512.
27. Yong AS, Daniels D, De Bruyne B, Kim HS, Ikeno F, Lyons J, Pijls NH, Fearon WF. Fractional flow reserve assessment of left main stenosis in the presence of downstream coronary stenoses. *Circ Cardiovasc Interv.* 2013;6:161-165.
28. Toth G, De Bruyne B, Casselman F, De Vroey F, Pyxaras S, Di Serafino L, Van Praet F, Van Mieghem C, Stockman B, Wijns W, Degrieck I, Barbato E. Fractional flow reserve-guided versus angiography-guided coronary artery bypass graft surgery. *Circulation.* 2013;128:1405-1411.
29. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van't Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med.* 2009;360:213-224.
30. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, van't Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, De Bruyne B; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol.* 2010;56:177-184.
31. van Nunen LX, Zimmermann FM, Tonino PA, Barbato E, Baumbach A, Engstrom T, Klauss V, MacCarthy PA, Manoharan G, Oldroyd KG, Ver Lee PN, van't Veer M, Fearon WF, De Bruyne B, Pijls NH; FAME study Investigators. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. *Lancet.* 2015;386:1853-1860.
32. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Juni P, Fearon WF; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med.* 2012;367:991-1001.
33. Fearon WF, Nishi T, De Bruyne B, Boothroyd DB, Barbato E, Tonino P, Juni P, Pijls NHJ, Hlatky MA; FAME 2 Trial Investigators. Clinical outcomes and cost-effectiveness of fractional flow reserve-guided percutaneous coronary intervention in patients with stable coronary artery disease: Three-year follow-up of the FAME 2 trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation). *Circulation.* 2018;137:480-487.
34. Escaned J, Collet C, Ryan N, De Maria GL, Walsh S, Sabate M, Davies J, Lesiak M, Moreno R, Cruz-Gonzalez I, Hoole SP, Ej West N, Piek JJ, Zaman A, Fath-Ordoubadi F, Stables RH, Appleby C, van Mieghem N, van Geuns RJ, Uren N, Zueco J, Buszman P, Iniguez A, Goicolea J, Hildick-Smith D, Ochala A, Dudek D, Hanratty C, Cavalcante R, Kappetein AP, Taggart DP, van Es GA, Morel MA, de Vries T, Onuma Y, Farooq V, Serruys PW, Banning AP. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. *Eur Heart J.* 2017;38:3124-3134.
- 34a. Waksman R, Legutko J, Singh J, Orlando Q, Marso S, Schloss T, Tugaoen J, DeVries J, Palmer N, Haude M, Swymelar S, Torguson R. FIRST: Fractional Flow Reserve and Intravascular Ultrasound Relationship Study. *J Am Coll Cardiol.* 2013;61:917-923.
35. Park SJ, Kim YH, Park DW, Lee SW, Kim WJ, Suh J, Yun SC, Lee CW, Hong MK, Lee JH, Park SW; MAIN-COMPARE Investigators. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. *Circ Cardiovasc Interv.* 2009;2:167-177.
36. Fassa AA, Wagatsuma K, Higano ST, Mathew V, Barsness GW, Lennon RJ, Holmes DR Jr, Lerman A. Intravascular ultrasound-guided treatment for angiographically indeterminate left main coronary artery disease: A long-term follow-up study. *J Am Coll Cardiol.* 2005;45:204-211.
37. de la Torre Hernandez JM, Hernandez Hernandez F, Alfonso F, Rumoroso JR, Lopez-Palop R, Sadaba M, Carrillo P, Rondan J, Lozano I, Ruiz Nodar JM, Baz JA, Fernandez Nofrerias E, Pajin F, Garcia Camarero T, Gutierrez H, LITRO Study Group. Prospective application of pre-defined intravascular ultrasound criteria for assessment of intermediate left main coronary artery lesions results from the multicenter LITRO study. *J Am Coll Cardiol.* 2011;58:351-358.
38. Park SJ, Ahn JM, Kang SJ, Yoon SH, Koo BK, Lee JY, Kim WJ, Park DW, Lee SW, Kim YH, Lee CW, Park SW. Intravascular ultrasound-derived minimal lumen area criteria for functionally significant left main coronary artery stenosis. *JACC Cardiovasc Interv.* 2014;7:868-874.
39. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JKJJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med.* 1996;334:1703-1708.
40. Ayton DR, Barker AL, Peeters G, Berkovic DE, Lefkovits J, Brennan A, Evans S, Zalceberg J, Reid C, Stoelwinder JJ, McNeil J. Exploring patient-reported outcomes following percutaneous coronary intervention: A qualitative study. *Health Expect.* 2018;21:457-465.
41. Myles PS. Meaningful outcome measures in cardiac surgery. *J Extra Corpor Technol.* 2014;46:23-27.
42. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I,

- Hall MS, Hobbs FDR, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S; Scientific Document ESC Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37:2315-2381.
43. Head SJ, Kaul S, Mack MJ, Serruys PW, Taggart DP, Holmes DR Jr, Leon MB, Marco J, Bogers AJ, Kappetein AP. The rationale for Heart Team decision-making for patients with stable, complex coronary artery disease. *Eur Heart J*. 2013;34:2510-2518.
44. Filardo G, Maggioni AP, Mura G, Valagussa F, Valagussa L, Schweiger C, Ballard DJ, Liberati A. The consequences of under-use of coronary revascularization; Results of a cohort study in Northern Italy. *Eur Heart J*. 2001;22:654-662.
45. Yates MT, Soppa GK, Valencia O, Jones S, Firoozi S, Jahangiri M. Impact of European Society of Cardiology and European Association for Cardiothoracic Surgery Guidelines on Myocardial Revascularization on the activity of percutaneous coronary intervention and coronary artery bypass graft surgery for stable coronary artery disease. *J Thorac Cardiovasc Surg*. 2014;147:606-610.
46. Organisation for Economic Co-operation and Development. Health at a glance. <http://www.oecd.org/health/health-systems/health-at-a-glance-19991312.htm> accessed July 21, 2018.
47. Bradley SM, Bohn CM, Malenka DJ, Graham MM, Bryson CL, McCabe JM, Curtis JP, Lambert-Kerzner A, Maynard C. Temporal trends in percutaneous coronary intervention appropriateness: Insights from the clinical outcomes assessment program. *Circulation*. 2015;132:20-26.
48. Hannan EL, Samadashvili Z, Cozzens K, Gesten F, Osinaga A, Fish DG, Donahue CL, Bass RJ, Walford G, Jacobs AK, Venditti FJ, Stamato NJ, Berger PB, Sharma S, King SB III. Changes in percutaneous coronary interventions deemed “inappropriate” by appropriate use criteria. *J Am Coll Cardiol*. 2017;69:1234-1242.
49. Denvir MA, Pell JP, Lee AJ, Rysdale J, Prescott RJ, Eteiba H, Walker A, Mankad P, Starkey IR. Variations in clinical decision-making between cardiologists and cardiac surgeons; A case for management by multidisciplinary teams? *J Cardiothorac Surg*. 2006;1:2.
50. Pavlidis AN, Perera D, Karamasis GV, Bapat V, Young C, Clapp BR, Blauth C, Roxburgh J, Thomas MR, Redwood SR. Implementation and consistency of Heart Team decision-making in complex coronary revascularisation. *Int J Cardiol*. 2016;206:37-41.
51. Sanchez CE, Dota A, Badhwar V, Kliner D, Smith AJ, Chu D, Toma C, Wei L, Marroquin OC, Schindler J, Lee JS, Mulukutla SR. Revascularization heart team recommendations as an adjunct to appropriate use criteria for coronary revascularization in patients with complex coronary artery disease. *Catheter Cardiovasc Interv*. 2016;88:E103-E112.
52. Sobolev BG, Fradet G, Kuramoto L, Rogula B. The occurrence of adverse events in relation to time after registration for coronary artery bypass surgery: A population-based observational study. *J Cardiothorac Surg*. 2013;8:74.
53. Head SJ, da Costa BR, Beumer B, Stefanini GG, Alfonso F, Clemmensen PM, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Kappetein AP, Kastrati A, Knuuti J, Kolh P, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauer P, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A, Windecker S, Juni P, Sousa-Uva M. Adverse events while awaiting myocardial revascularization: A systematic review and meta-analysis. *Eur J Cardiothorac Surg*. 2017;52:206-217.
54. Graham MM, Knudtson ML, O’Neill BJ, Ross DB, Canadian Cardiovascular Society Access to Care Working Group. Treating the right patient at the right time: Access to cardiac catheterization, percutaneous coronary intervention and cardiac surgery. *Can J Cardiol*. 2006;22:679-683.
55. Truffa MA, Alves GM, Bernardi F, Esteves Filho A, Ribeiro E, Galon MZ, Spadaro A, Kajita LJ, Arrieta R, Lemos PA. Does ad hoc coronary intervention reduce radiation exposure? - Analysis of 568 patients. *Arq Bras Cardiol*. 2015;105:487-492.
56. Hannan EL, Samadashvili Z, Walford G, Holmes DR, Jacobs A, Sharma S, Katz S, King SB III. Predictors and outcomes of ad hoc versus non-ad hoc percutaneous coronary interventions. *JACC Cardiovasc Interv*. 2009;2:350-356.
57. RITA-2 Trial Participants. Coronary angioplasty versus medical therapy for angina: The second Randomised Intervention Treatment of Angina (RITA-2) trial. RITA-2 trial participants. *Lancet*. 1997;350:461-468.
58. TIME Investigators. Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): A randomised trial. *Lancet*. 2001;358:951-957.
59. Boden WE, O’Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503-1516.
60. Erne P, Schoenenberger AW, Burckhardt D, Zuber M, Kiowski W, Buser PT, Dubach P, Resink TJ, Pfisterer M. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: The SWISSI II randomized controlled trial. *JAMA*. 2007;297:1985-1991.
61. BARI Study Group 2D, Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, Orchard TJ, Chaitman BR, Genuth SM, Goldberg SH, Hlatky MA, Jones TL, Molitch ME, Nesto RW, Sako EY, Sobel BE. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;360:2503-2515.
62. Hueb W, Lopes N, Gersh BJ, Soares PR, Ribeiro EE, Pereira AC, Favarato D, Rocha AS, Hueb AC, Ramires JA. Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): A randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation*. 2010;122:949-957.
63. Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, Keeble T, Mielewicz M, Kaprielian R, Malik IS, Nijjer SS, Petraco R, Cook C, Ahmad Y, Howard J, Baker C, Sharp A, Gerber R, Talwar S, Assomull R, Mayet J, Wensel R, Collier D, Shun-Shin M, Thom SA, Davies JE, Francis DP, ORBITA Investigators. Percutaneous coronary intervention in stable angina

(ORBITA): A double-blind, randomised controlled trial. *Lancet*. 2018;391:31-40.

64. Chaitman BR, Mori Brooks M, Fox K, Luscher TF. ORBITA revisited: what it really means and what it does not? *Eur Heart J*. 2018;39:963-965.

65. Baron SJ, Chinnakondepalli K, Magnuson EA, Kandzari DE, Puskas JD, Ben-Yehuda O, van Es GA, Taggart DP, Morice MC, Lembo NJ, Brown WM III, Banning A, Simonton CA, Kappetein AP, Sabik JF, Serruys PW, Stone GW, Cohen DJ, EXCEL Investigators. Quality-of-life after everolimus-eluting stents or bypass surgery for left-main disease: Results from the EXCEL trial. *J Am Coll Cardiol*. 2017;70:3113-3122.

66. Abdallah MS, Wang K, Magnuson EA, Osnabrugge RL, Kappetein AP, Morice MC, Mohr FA, Serruys PW, Cohen DJ, SYNTAX Trial Investigators. Quality of life after surgery or DES in patients with 3-vessel or left main disease. *J Am Coll Cardiol*. 2017;69:2039-2050.

67. Abdallah MS, Wang K, Magnuson EA, Spertus JA, Farkouh ME, Fuster V, Cohen DJ; FREEDOM Trial Investigators. Quality of life after PCI vs CABG among patients with diabetes and multivessel coronary artery disease: A randomized clinical trial. *JAMA*. 2013;310:1581-1590.

68. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, Davis K, Killip T, Passamani E, Norris R, et al. Effect of coronary artery bypass graft surgery on survival: Overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet*. 1994;344:563-570.

69. Bittl JA, He Y, Jacobs AK, Yancy CW, Normand SL, American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Bayesian methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. *Circulation*. 2013;127:2177-2185.

70. Dzavik V, Ghali WA, Norris C, Mitchell LB, Koshal A, Saunders LD, Galbraith PD, Hui W, Faris P, Knudtson ML, Alberta for Provincial Project in Outcome Assessment Coronary Heart Disease Investigators. Long-term survival in 11,661 patients with multivessel coronary artery disease in the era of stenting: A report from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. *Am Heart J*. 2001;142:119-126.

71. Lee PH, Ahn JM, Chang M, Baek S, Yoon SH, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, Park DW, Park SJ. Left main coronary artery disease: Secular trends in patient characteristics, treatments, and outcomes. *J Am Coll Cardiol*. 2016;68:1233-1246.

72. Smith PK, Califf RM, Tuttle RH, Shaw LK, Lee KL, Delong ER, Lilly RE, Sketch MH Jr, Peterson ED, Jones RH. Selection of surgical or percutaneous coronary intervention provides differential longevity benefit. *Ann Thorac Surg*. 2006;82:1420-1428; discussion 1428-1429.

73. Hannan EL, Wu C, Walford G, Culliford AT, Gold JP, Smith CR, Higgins RS, Carlson RE, Jones RH. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. *N Engl J Med*. 2008;358:331-341.

74. Hannan EL, Samadashvili Z, Cozzens K, Walford G, Jacobs AK, Holmes DR Jr, Stamato NJ, Gold JP, Sharma S, Venditti FJ, Powell T, King SB III. Comparative outcomes for

patients who do and do not undergo percutaneous coronary intervention for stable coronary artery disease in New York. *Circulation*. 2012;125:1870-1879.

75. Caracciolo EA, Davis KB, Sopko G, Kaiser GC, Corley SD, Schaff H, Taylor HA, Chaitman BR. Comparison of surgical and medical group survival in patients with left main equivalent coronary artery disease. Long-term CASS experience. *Circulation*. 1995;91:2335-2344.

76. Chaitman BR, Hardison RM, Adler D, Gebhart S, Grogan M, Ocampo S, Sopko G, Ramires JA, Schneider D, Frye RL; Bypass Angioplasty Revascularization Investigation 2 Diabetes Study G. The Bypass Angioplasty Revascularization Investigation 2 Diabetes randomized trial of different treatment strategies in type 2 diabetes mellitus with stable ischemic heart disease: Impact of treatment strategy on cardiac mortality and myocardial infarction. *Circulation*. 2009;120:2529-2540.

77. Passamani E, Davis KB, Gillespie MJ, Killip T. A randomized trial of coronary artery bypass surgery. Survival of patients with a low ejection fraction. *N Engl J Med*. 1985;312:1665-1671.

78. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, Ali IS, Pohost G, Gradinac S, Abraham WT, Yii M, Prabhakaran D, Szwed H, Ferrazzi P, Petrie MC, O'Connor CM, Panchavinnin P, She L, Bonow RO, Rankin GR, Jones RH, Rouleau JL; STICH Investigators. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med*. 2011;364:1607-1616.

79. Jones RH, Kesler K, Phillips HR III, Mark DB, Smith PK, Nelson CL, Newman MF, Reves JG, Anderson RW, Califf RM. Long-term survival benefits of coronary artery bypass grafting and percutaneous transluminal angioplasty in patients with coronary artery disease. *J Thorac Cardiovasc Surg*. 1996;111:1013-1025.

80. Baker DW, Jones R, Hodges J, Massie BM, Konstam MA, Rose EA. Management of heart failure. III. The role of revascularization in the treatment of patients with moderate or severe left ventricular systolic dysfunction. *JAMA*. 1994;272:1528-1534.

81. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, Michler RE, Bonow RO, Doenst T, Petrie MC, Oh JK, She L, Moore VL, Desvigne-Nickens P, Sopko G, Rouleau JL; STICHES Investigators. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med*. 2016;374:1511-1520.

82. Panza JA, Velazquez EJ, She L, Smith PK, Nicolau JC, Favaloro RR, Gradinac S, Chrzanowski L, Prabhakaran D, Howlett JG, Jasinski M, Hill JA, Szwed H, Larbalestier R, Desvigne-Nickens P, Jones RH, Lee KL, Rouleau JL. Extent of coronary and myocardial disease and benefit from surgical revascularization in ischemic LV dysfunction [Corrected]. *J Am Coll Cardiol*. 2014;64:553-561.

83. Petrie MC, Jhund PS, She L, Adlbrecht C, Doenst T, Panza JA, Hill JA, Lee KL, Rouleau JL, Prior DL, Ali IS, Maddury J, Golba KS, White HD, Carson P, Chrzanowski L, Romanov A, Miller AB, Velazquez EJ, STICH Trial Investigators. Ten-year outcomes after coronary artery bypass grafting according to age in patients with heart failure and left ventricular systolic dysfunction: An analysis of the extended follow-up of the STICH trial (Surgical Treatment for Ischemic Heart Failure). *Circulation*. 2016;134:1314-1324.

84. Hachamovitch R, Rozanski A, Shaw LJ, Stone GW, Thomson LE, Friedman JD, Hayes SW, Cohen I, Germano G,

- Berman DS. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J*. 2011;32:1012-1024.
85. Davies RF, Goldberg AD, Forman S, Pepine CJ, Knatterud GL, Geller N, Sopko G, Pratt C, Deanfield J, Conti CR. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: Outcomes of patients randomized to initial strategies of medical therapy versus revascularization. *Circulation*. 1997;95:2037-2043.
86. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE; COURAGE Investigators. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: Results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation*. 2008;117(10):1283-1291.
87. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003;107:2900-2907.
88. Gada H, Kirtane AJ, Kereiakes DJ, Bangalore S, Moses JW, Genereux P, Mehran R, Dangas GD, Leon MB, Stone GW. Meta-analysis of trials on mortality after percutaneous coronary intervention compared with medical therapy in patients with stable coronary heart disease and objective evidence of myocardial ischemia. *Am J Cardiol*. 2015;115:1194-1199.
89. Stergiopoulos K, Boden WE, Hartigan P, Mobius-Winkler S, Hambrecht R, Hueb W, Hardison RM, Abbott JD, Brown DL. Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: A collaborative meta-analysis of contemporary randomized clinical trials. *JAMA Intern Med*. 2014;174:232-240.
90. Nishigaki K, Yamazaki T, Kitabatake A, Yamaguchi T, Kanmatsuse K, Kodama I, Takekoshi N, Tomoike H, Hori M, Matsuzaki M, Takeshita A, Shimbo T, Fujiwara H; Japanese Stable Angina Pectoris Study Investigators. Percutaneous coronary intervention plus medical therapy reduces the incidence of acute coronary syndrome more effectively than initial medical therapy only among patients with low-risk coronary artery disease a randomized, comparative, multicenter study. *JACC Cardiovasc Interv*. 2008;1:469-479.
91. Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: A meta-analysis. *Circulation*. 2005;111:2906-2912.
92. Schomig A, Mehilli J, de Waha A, Seyfarth M, Pache J, Kastrati A. A meta-analysis of 17 randomized trials of a percutaneous coronary intervention-based strategy in patients with stable coronary artery disease. *J Am Coll Cardiol*. 2008;52:894-904.
93. Trikalinos TA, Alsheikh-Ali AA, Tatsioni A, Nallamothu BK, Kent DM. Percutaneous coronary interventions for non-acute coronary artery disease: A quantitative 20-year synopsis and a network meta-analysis. *Lancet*. 2009;373:911-918.
94. Bangalore S, Pursnani S, Kumar S, Bagos PG. Percutaneous coronary intervention versus optimal medical therapy for prevention of spontaneous myocardial infarction in subjects with stable ischemic heart disease. *Circulation*. 2013;127:769-781.
95. Pursnani S, Korley F, Gopaul R, Kanade P, Chandra N, Shaw RE, Bangalore S. Percutaneous coronary intervention versus optimal medical therapy in stable coronary artery disease: A systematic review and meta-analysis of randomized clinical trials. *Circ Cardiovasc Interv*. 2012;5:476-490.
96. Thomas S, Gokhale R, Boden WE, Devereaux PJ. A meta-analysis of randomized controlled trials comparing percutaneous coronary intervention with medical therapy in stable angina pectoris. *Can J Cardiol*. 2013;29:472-482.
97. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd K, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Limacher A, Nuesch E, Juni P; FAME-2 Trial Investigators. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med*. 2014;371:1208-1217.
98. Bucher HC, Hengstler P, Schindler C, Guyatt GH. Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: Meta-analysis of randomised controlled trials. *BMJ*. 2000;321:73-77.
99. Stergiopoulos K, Brown DL. Initial coronary stent implantation with medical therapy vs medical therapy alone for stable coronary artery disease: Meta-analysis of randomized controlled trials. *Arch Intern Med*. 2012;172:312-319.
100. Windecker S, Stortecky S, Stefanini GG, da Costa BR, Rutjes AW, Di Nisio M, Siletta MG, Maione A, Alfonso F, Clemmensen PM, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head S, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter D, Schauerte P, Sousa Uva M, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A, Kolh P, Juni P. Revascularisation versus medical treatment in patients with stable coronary artery disease: Network meta-analysis. *BMJ*. 2014;348:g3859.
101. Jeremias A, Kaul S, Rosengart TK, Gruberg L, Brown DL. The impact of revascularization on mortality in patients with nonacute coronary artery disease. *Am J Med*. 2009;122:152-161.
102. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW; SYNTAX Investigators S. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961-972.
103. Boudriot E, Thiele H, Walther T, Liebetrau C, Boeckstegers P, Pohl T, Reichart B, Mudra H, Beier F, Gansera B, Neumann FJ, Gick M, Zietak T, Desch S, Schuler G, Mohr FW. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. *J Am Coll Cardiol*. 2011;57:538-545.
104. Park SJ, Kim YH, Park DW, Yun SC, Ahn JM, Song HG, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Chung CH, Lee JW, Lim DS, Rha SW, Lee SG, Gwon HC, Kim HS, Chae IH, Jang Y, Jeong MH, Tahk SJ, Seung KB. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med*. 2011;364:1718-1727.

105. Park SJ, Ahn JM, Kim YH, Park DW, Yun SC, Lee JY, Kang SJ, Lee SW, Lee CW, Park SW, Choo SJ, Chung CH, Lee JW, Cohen DJ, Yeung AC, Hur SH, Seung KB, Ahn TH, Kwon HM, Lim DS, Rha SW, Jeong MH, Lee BK, Tresukosol D, Fu GS, Ong TK; BEST Trial Investigators. Trial of everolimus-eluting stents or bypass surgery for coronary disease. *N Engl J Med*. 2015; 372:1204-1212.
106. Makikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IB, Trovik T, Eskola M, Romppanen H, Kellerth T, Ravkilde J, Jensen LO, Kalinauskas G, Linder RB, Pentikainen M, Hervold A, Banning A, Zaman A, Cotton J, Eriksen E, Margus S, Sorensen HT, Nielsen PH, Niemela M, Kervinen K, Lassen JF, Maeng M, Oldroyd K, Berg G, Walsh SJ, Hanratty CG, Kumsars I, Stradins P, Steigen TK, Frobert O, Graham AN, Endresen PC, Corbascio M, Kajander O, Trivedi U, Hartikainen J, Anttila V, Hildick-Smith D, Thuesen L, Christiansen EH; NOBLE Study Investigators. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet*. 2016;388:2743-2752.
107. Stone GW, Sabik JF, Serruys PW, Simonton CA, Genereux P, Puskas J, Kandzari DE, Morice MC, Lembo N, Brown WM III, Taggart DP, Banning A, Merkely B, Horkay F, Boonstra PW, van Boven AJ, Ungi I, Bogats G, Mansour S, Noiseux N, Sabate M, Pomar J, Hickey M, Gershlick A, Buszman P, Bochenek A, Schampaert E, Page P, Dressler O, Kosmidou I, Mehran R, Pocock SJ, Kappetein AP; EXCEL Trial Investigators. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med*. 2016;375:2223-2235.
108. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. EuroSCORE II. *Eur J Cardiothorac Surg*. 2012;41:734-744; discussion 744-745.
109. Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand SL, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP, Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: Part 1-coronary artery bypass grafting surgery. *Ann Thorac Surg*. 2009; 88:S2-S22.
110. Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand SL, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP; Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: Part 3-valve plus coronary artery bypass grafting surgery. *Ann Thorac Surg*. 2009;88: S43-S62.
111. Biancari F, Vasques F, Mikkola R, Martin M, Lahtinen J, Heikkinen J. Validation of EuroSCORE II in patients undergoing coronary artery bypass surgery. *Ann Thorac Surg*. 2012;93: 1930-1935.
112. Osnabrugge RL, Speir AM, Head SJ, Fonner CE, Fonner E, Kappetein AP, Rich JB. Performance of EuroSCORE II in a large US database: Implications for transcatheter aortic valve implantation. *Eur J Cardiothorac Surg*. 2014;46:400-408.
113. Sullivan PG, Wallach JD, Ioannidis JP. Meta-analysis comparing established risk prediction models (EuroSCORE II, STS Score, and ACEF Score) for perioperative mortality during cardiac surgery. *Am J Cardiol*. 2016;118:1574-1582.
114. Kirmani BH, Mazhar K, Fabri BM, Pullan DM. Comparison of the EuroSCORE II and Society of Thoracic Surgeons 2008 risk tools. *Eur J Cardiothorac Surg*. 2013;44:999-1005.
115. Velicki L, Cemerlic-Adijic N, Pavlovic K, Mihajlovic BB, Bankovic D, Mihajlovic B, Fabri M. Clinical performance of the EuroSCORE II compared with the previous EuroSCORE iterations. *Thorac Cardiovasc Surg*. 2014;62:288-297.
116. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: An angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. 2005; 1:219-227.
117. Wykrzykowska JJ, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. *J Am Coll Cardiol*. 2010;56:272-277.
118. Garg S, Serruys PW, Silber S, Wykrzykowska J, van Geuns RJ, Richardt G, Buszman PE, Kelbaek H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Van Remortel E, Ronden J, Windecker S. The prognostic utility of the SYNTAX score on 1-year outcomes after revascularization with zotarolimus- and everolimus-eluting stents: a substudy of the RESOLUTE All Comers Trial. *JACC Cardiovasc Interv*. 2011;4: 432-441.
119. Zhao M, Stampf S, Valina C, Kienzle RP, Ferenc M, Gick M, Essang E, Nuhrenberg T, Buttner HJ, Schumacher M, Neumann FJ. Role of euroSCORE II in predicting long-term outcome after percutaneous catheter intervention for coronary triple vessel disease or left main stenosis. *Int J Cardiol*. 2013;168:3273-3279.
120. Cavalcante R, Sotomi Y, Mancone M, Whan Lee C, Ahn JM, Onuma Y, Lemos PA, van Geuns RJ, Park SJ, Serruys PW. Impact of the SYNTAX scores I and II in patients with diabetes and multi-vessel coronary disease: A pooled analysis of patient level data from the SYNTAX, PRECOMBAT, and BEST trials. *Eur Heart J*. 2017;38:1969-1977.
121. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR Jr, Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet*. 2013;381:629-638.
122. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR, Choi JW, Ruzyllo W, Religa G, Huang J, Roy K, Dawkins KD, Mohr F. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation*. 2014;129:2388-2394.
123. Head SJ, Davierwala PM, Serruys PW, Redwood SR, Colombo A, Mack MJ, Morice MC, Holmes DR Jr, Feldman TE, Stahle E, Underwood P, Dawkins KD, Kappetein AP, Mohr FW. Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: Final five-year follow-up of the SYNTAX trial. *Eur Heart J*. 2014;35:2821-2830.

124. Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH, Domanski MJ, Farkouh ME, Flather M, Fuster V, Hlatky MA, Holm NR, Hueb WA, Kamalesh M, Kim YH, Makikallio T, Mohr FW, Papageorgiou G, Park SJ, Rodriguez AE, Sabik JF III, Stables RH, Stone GW, Serruys PW, Kappetein AP. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: A pooled analysis of individual patient data. *Lancet*. 2018;391:939-948.
125. Zhang YJ, Iqbal J, Campos CM, Klaveren DV, Bourantas CV, Dawkins KD, Banning AP, Escaned J, de Vries T, Morel MA, Farooq V, Onuma Y, Garcia-Garcia HM, Stone GW, Steyerberg EW, Mohr FW, Serruys PW. Prognostic value of site SYNTAX score and rationale for combining anatomic and clinical factors in decision making: Insights from the SYNTAX trial. *J Am Coll Cardiol*. 2014;64:423-432.
126. Medina A, Suarez de Lezo J, Pan M. [A new classification of coronary bifurcation lesions]. *Rev Esp Cardiol*. 2006;59:183.
127. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr, Mack M, Feldman T, Morice MC, Stahle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: Development and validation of SYNTAX score II. *Lancet*. 2013;381:639-650.
128. Campos CM, Garcia-Garcia HM, van Klaveren D, Ishibashi Y, Cho YK, Valgimigli M, Raber L, Jonker H, Onuma Y, Farooq V, Garg S, Windecker S, Morel MA, Steyerberg EW, Serruys PW. Validity of SYNTAX score II for risk stratification of percutaneous coronary interventions: A patient-level pooled analysis of 5,433 patients enrolled in contemporary coronary stent trials. *Int J Cardiol*. 2015;187:111-115.
129. Sotomi Y, Cavalcante R, van Klaveren D, Ahn JM, Lee CW, de Winter RJ, Wykrzykowska JJ, Onuma Y, Steyerberg EW, Park SJ, Serruys PW. Individual long-term mortality prediction following either coronary stenting or bypass surgery in patients with multivessel and/or unprotected left main disease: An external validation of the SYNTAX Score II model in the 1,480 patients of the BEST and PRECOMBAT randomized controlled trials. *JACC Cardiovasc Interv*. 2016;9:1564-1572.
130. Campos CM, van Klaveren D, Farooq V, Simonton CA, Kappetein AP, Sabik JF III, Steyerberg EW, Stone GW, Serruys PW, Investigators ET. Long-term forecasting and comparison of mortality in the Evaluation of the Xience Everolimus Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial: Prospective validation of the SYNTAX Score II. *Eur Heart J*. 2015;36:1231-1241.
131. Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas CV, Holmes DR, Mack M, Feldman T, Morice MC, Stahle E, James S, Colombo A, Diletti R, Papafaklis MI, de Vries T, Morel MA, van Es GA, Mohr FW, Dawkins KD, Kappetein AP, Sianos G, Boersma E. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: The SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol*. 2013;61:282-294.
132. Garcia S, Sandoval Y, Roukoz H, Adabag S, Canoniero M, Yannopoulos D, Brilakis ES. Outcomes after complete versus incomplete revascularization of patients with multivessel coronary artery disease: A meta-analysis of 89,883 patients enrolled in randomized clinical trials and observational studies. *J Am Coll Cardiol*. 2013;62:1421-1431.
133. Zimarino M, Ricci F, Romanello M, Di Nicola M, Corazzini A, De Caterina R. Complete myocardial revascularization confers a larger clinical benefit when performed with state-of-the-art techniques in high-risk patients with multivessel coronary artery disease: A meta-analysis of randomized and observational studies. *Catheter Cardiovasc Interv*. 2016;87:3-12.
134. Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, Holmes DR, Mack M, Morice MC, Stahle E, Colombo A, de Vries T, Morel MA, Dawkins KD, Kappetein AP, Mohr FW. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation*. 2013;128:141-151.
135. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J, Hannan EL. Everolimus-eluting stents or bypass surgery for multivessel coronary disease. *N Engl J Med*. 2015;372:1213-1222.
136. Ahn JM, Park DW, Lee CW, Chang M, Cavalcante R, Sotomi Y, Onuma Y, Tenekecioglu E, Han M, Lee PH, Kang SJ, Lee SW, Kim YH, Park SW, Serruys PW, Park SJ. Comparison of stenting versus bypass surgery according to the completeness of revascularization in severe coronary artery disease: Patient-level pooled analysis of the SYNTAX, PRECOMBAT, and BEST Trials. *JACC Cardiovasc Interv*. 2017;10:1415-1424.
137. Layland J, Oldroyd KG, Curzen N, Sood A, Balachandran K, Das R, Junejo S, Ahmed N, Lee MM, Shaikat A, O'Donnell A, Nam J, Briggs A, Henderson R, McConnachie A, Berry C, FAMOUS-NSTEMI Investigators. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: The British Heart Foundation FAMOUS-NSTEMI randomized trial. *Eur Heart J*. 2015;36:100-111.
138. Ad N, Holmes SD, Patel J, Pritchard G, Shuman DJ, Halpin L. Comparison of EuroSCORE II, original EuroSCORE, and The Society of Thoracic Surgeons Risk Score in cardiac surgery patients. *Ann Thorac Surg*. 2016;102:573-579.
139. Aziz O, Rao C, Panesar SS, Jones C, Morris S, Darzi A, Athanasiou T. Meta-analysis of minimally invasive internal thoracic artery bypass versus percutaneous revascularisation for isolated lesions of the left anterior descending artery. *BMJ*. 2007;334:617.
140. Kapoor JR, Gienger AL, Ardehali R, Varghese R, Perez MV, Sundaram V, McDonald KM, Owens DK, Hlatky MA, Bravata DM. Isolated disease of the proximal left anterior descending artery comparing the effectiveness of percutaneous coronary interventions and coronary artery bypass surgery. *JACC Cardiovasc Interv*. 2008;1:483-491.
141. Blazek S, Holzhey D, Jungert C, Borger MA, Fuernau G, Desch S, Eitel I, de Waha S, Lurz P, Schuler G, Mohr FW, Thiele H. Comparison of bare-metal stenting with minimally invasive bypass surgery for stenosis of the left anterior descending coronary artery:

- 10-year follow-up of a randomized trial. *JACC Cardiovasc Interv.* 2013;6:20-26.
142. Hannan EL, Zhong Y, Walford G, Holmes DR Jr, Venditti FJ, Berger PB, Jacobs AK, Stamato NJ, Curtis JP, Sharma S, King SB III. Coronary artery bypass graft surgery versus drug-eluting stents for patients with isolated proximal left anterior descending disease. *J Am Coll Cardiol.* 2014;64:2717-2126.
143. Blazek S, Rossbach C, Borger MA, Fuernau G, Desch S, Eitel I, Stiermaier T, Lurz P, Holzhey D, Schuler G, Mohr FW, Thiele H. Comparison of sirolimus-eluting stenting with minimally invasive bypass surgery for stenosis of the left anterior descending coronary artery: 7-year follow-up of a randomized trial. *JACC Cardiovasc Interv.* 2015;8:30-38.
144. Thiele H, Neumann-Schriedewind P, Jacobs S, Boudriot E, Walther T, Mohr FW, Schuler G, Falk V. Randomized comparison of minimally invasive direct coronary artery bypass surgery versus sirolimus-eluting stenting in isolated proximal left anterior descending coronary artery stenosis. *J Am Coll Cardiol.* 2009;53:2324-2331.
145. Capodanno D, Stone GW, Morice MC, Bass TA, Tamburino C. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: A meta-analysis of randomized clinical data. *J Am Coll Cardiol.* 2011;58:1426-1432.
146. Ahn JM, Roh JH, Kim YH, Park DW, Yun SC, Lee PH, Chang M, Park HW, Lee SW, Lee CW, Park SW, Choo SJ, Chung C, Lee J, Lim DS, Rha SW, Lee SG, Gwon HC, Kim HS, Chae IH, Jang Y, Jeong MH, Tahk SJ, Seung KB, Park SJ. Randomized trial of stents versus bypass surgery for left main coronary artery disease: 5-Year outcomes of the PRECOMBAT study. *J Am Coll Cardiol.* 2015;65:2198-2206.
147. Cavalcante R, Sotomi Y, Lee CW, Ahn JM, Farooq V, Tateishi H, Tenekecioglu E, Zeng Y, Suwannasom P, Collet C, Albuquerque FN, Onuma Y, Park SJ, Serruys PW. Outcomes after percutaneous coronary intervention or bypass surgery in patients with unprotected left main disease. *J Am Coll Cardiol.* 2016;68:999-1009.
148. Giacoppo D, Colleran R, Cassese S, Frangieh AH, Wiebe J, Joner M, Schunkert H, Kastrati A, Byrne RA. Percutaneous coronary intervention vs coronary artery bypass grafting in patients with left main coronary artery stenosis: A systematic review and meta-analysis. *JAMA Cardiol.* 2017;2:1079-1088.
149. Chang M, Ahn JM, Lee CW, Cavalcante R, Sotomi Y, Onuma Y, Tenekecioglu E, Han M, Park DW, Kang SJ, Lee SW, Kim YH, Park SW, Serruys PW, Park SJ. Long-term mortality after coronary revascularization in nondiabetic patients with multivessel disease. *J Am Coll Cardiol.* 2016;68:29-36.
150. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S III, Bertrand M, Fuster V; FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med.* 2012;367:2375-2384.
151. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J, Hannan EL. Everolimus eluting stents versus coronary artery bypass graft surgery for patients with diabetes mellitus and multivessel disease. *Circ Cardiovasc Interv.* 2015;8:e002626.
152. Hakeem A, Garg N, Bhatti S, Rajpurohit N, Ahmed Z, Uretsky BF. Effectiveness of percutaneous coronary intervention with drug-eluting stents compared with bypass surgery in diabetics with multivessel coronary disease: Comprehensive systematic review and meta-analysis of randomized clinical data. *J Am Heart Assoc.* 2013;2:e000354.
153. Herbison P, Wong CK. Has the difference in mortality between percutaneous coronary intervention and coronary artery bypass grafting in people with heart disease and diabetes changed over the years? A systematic review and meta-regression. *BMJ Open.* 2015;5:e010055.
154. Kamalesh M, Sharp TG, Tang XC, Shunk K, Ward HB, Walsh J, King S III, Colling C, Moritz T, Stroupe K, Reda D; CARDS Investigators VA. Percutaneous coronary intervention versus coronary bypass surgery in United States veterans with diabetes. *J Am Coll Cardiol.* 2013;61:808-816.
155. Kappetein AP, Head SJ, Morice MC, Banning AP, Serruys PW, Mohr FW, Dawkins KD, Mack MJ, Investigators S. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *Eur J Cardiothorac Surg.* 2013;43:1006-1013.
156. Kapur A, Hall RJ, Malik IS, Qureshi AC, Butts J, de Belder M, Baumbach A, Angelini G, de Belder A, Oldroyd KG, Flather M, Roughton M, Nihoyannopoulos P, Bagger JP, Morgan K, Beatt KJ. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. *J Am Coll Cardiol.* 2010;55:432-440.
157. Koskinas KC, Siontis GC, Piccolo R, Franzone A, Haynes A, Rat-Wirtzler J, Silber S, Serruys PW, Pilgrim T, Raber L, Heg D, Juni P, Windecker S. Impact of diabetic status on outcomes after revascularization with drug-eluting stents in relation to coronary artery disease complexity: Patient-level pooled analysis of 6081 patients. *Circ Cardiovasc Interv.* 2016;9:e003255.
158. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S; Scientific Document ESC Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2016;37:267-315.
159. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med.* 2000;343:915-922.
160. Shishebor MH, Venkatachalam S, Sun Z, Rajeswaran J, Kapadia SR, Bajzer C, Gornik HL, Gray BH, Bartholomew JR, Clair DG, Sabik JF III, Blackstone EH. A direct comparison of early and late outcomes with three approaches to carotid revascularization and open heart surgery. *J Am Coll Cardiol.* 2013;62:1948-1956.
161. Cheruvu PK, Finn AV, Gardner C, Caplan J, Goldstein J, Stone GW, Virmani R, Muller JE. Frequency and distribution of

- thin-cap fibroatheroma and ruptured plaques in human coronary arteries: A pathologic study. *J Am Coll Cardiol.* 2007;50:940-949.
162. Kerensky RA, Wade M, Deedwania P, Boden WE, Pepine CJ, Veterans Affairs Non-Q-Wave Infarction Strategies in-Hospital (VANQWISH) Trial Investigators. Revisiting the culprit lesion in non-Q-wave myocardial infarction. Results from the VANQWISH trial angiographic core laboratory. *J Am Coll Cardiol.* 2002;39:1456-1463.
163. Kastrati A, Neumann FJ, Schulz S, Massberg S, Byrne RA, Ferenc M, Laugwitz KL, Pache J, Ott I, Hausleiter J, Seyfarth M, Gick M, Antoniucci D, Schomig A, Berger PB, Mehilli J; ISAR-REACT 4 Trial Investigators. Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. *N Engl J Med.* 2011;365:1980-1989.
164. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, Afzal R, Chrolavicius S, Jolly SS, Widimsky P, Avezum A, Rupprecht HJ, Zhu J, Col J, Natarajan MK, Horsman C, Fox KA, Yusuf S; TIMACS Investigators. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med.* 2009;360:2165-2175.
165. Montalescot G, Bolognese L, Dudek D, Goldstein P, Hamm C, Tanguay JF, ten Berg JM, Miller DL, Costigan TM, Goedicke J, Silvain J, Angioli P, Legutko J, Niethammer M, Motovska Z, Jakubowski JA, Cayla G, Visconti LO, Vicaut E, Widimsky P; ACCOAST Investigators. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med.* 2013;369:999-1010.
166. Thiele H, Rach J, Klein N, Pfeiffer D, Hartmann A, Hambrecht R, Sick P, Eitel I, Desch S, Schuler G; LIPSIA-NSTEMI Trial Group. Optimal timing of invasive angiography in stable non-ST-elevation myocardial infarction: The Leipzig Immediate versus early and late Percutaneous coronary Intervention trial in NSTEMI (LIPSIA-NSTEMI Trial). *Eur Heart J.* 2012;33:2035-2043.
167. Tanaka A, Shimada K, Tearney GJ, Kitabata H, Taguchi H, Fukuda S, Kashiwagi M, Kubo T, Takarada S, Hirata K, Mizukoshi M, Yoshikawa J, Bouma BE, Akasaka T. Conformational change in coronary artery structure assessed by optical coherence tomography in patients with vasospastic angina. *J Am Coll Cardiol.* 2011;58:1608-1613.
168. Kato M, Dote K, Sasaki S, Kagawa E, Nakano Y, Watanabe Y, Higashi A, Itakura K, Ochiuami Y, Takiguchi Y. Presentations of acute coronary syndrome related to coronary lesion morphologies as assessed by intravascular ultrasound and optical coherence tomography. *Int J Cardiol.* 2013;165:506-511.
169. Motreff P, Malcles G, Combaret N, Barber-Chamoux N, Bouajila S, Pereira B, Amonchot A, Citron B, Lusson JR, Eschaliere R, Souteyrand G. How and when to suspect spontaneous coronary artery dissection: Novel insights from a single-centre series on prevalence and angiographic appearance. *EuroIntervention.* 2017;12:e2236-e2243.
170. Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: A meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol.* 2006;48:1319-1325.
171. Fox KA, Clayton TC, Damman P, Pocock SJ, de Winter RJ, Tijssen JG, Lagerqvist B, Wallentin L, FIR Collaboration. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome: a meta-analysis of individual patient data. *J Am Coll Cardiol.* 2010;55:2435-2445.
172. Valgimigli M, Gagnor A, Calabro P, Frigoli E, Leonardi S, Zaro T, Rubartelli P, Briguori C, Ando G, Repetto A, Limbruno U, Cortese B, Sganzerla P, Lupi A, Galli M, Colangelo S, Ierna S, Ausiello A, Presbitero P, Sardella G, Varbella F, Esposito G, Santarelli A, Tresoldi S, Nazzaro M, Zingarelli A, de Cesare N, Rigattieri S, Tosi P, Palmieri C, Brugaletta S, Rao SV, Heg D, Rothenbuhler M, Vranckx P, Juni P; MATRIX Investigators. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: A randomised multicentre trial. *Lancet.* 2015;385:2465-2476.
173. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrie D, Naber C, Lipiecki J, Richardt G, Iniguez A, Brunel P, Valdes-Chavarri M, Garot P, Talwar S, Berland J, Abdellaoui M, Eberli F, Oldroyd K, Zambahari R, Gregson J, Greene S, Stoll HP, Morice MC; LEADERS FREE Investigators. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med.* 2015;373:2038-2047.
174. Katritsis DG, Siontis GC, Kastrati A, van't Hof AW, Neumann FJ, Siontis KC, Ioannidis JP. Optimal timing of coronary angiography and potential intervention in non-ST-elevation acute coronary syndromes. *Eur Heart J.* 2011;32:32-40.
175. Navarese EP, Gurbel PA, Andreotti F, Tantry U, Jeong YH, Kozinski M, Engstrom T, Di Pasquale G, Kochman W, Ardissino D, Kedhi E, Stone GW, Kubica J. Optimal timing of coronary invasive strategy in non-ST-segment elevation acute coronary syndromes: A systematic review and meta-analysis. *Ann Intern Med.* 2013;158:261-270.
176. Jobs A, Mehta SR, Montalescot G, Vicaut E, Van't Hof AWJ, Badings EA, Neumann FJ, Kastrati A, Sciahbasi A, Reuter PG, Lapostolle F, Milosevic A, Stankovic G, Milasinovic D, Vonthein R, Desch S, Thiele H. Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: A meta-analysis of randomised trials. *Lancet.* 2017;390:737-746.
177. Raber L, Kelback H, Ostojic M, Baumbach A, Heg D, Tuller D, von Birgelen C, Roffi M, Moschovitis A, Khattab AA, Wenaweser P, Bonvini R, Pedrazzini G, Kornowski R, Weber K, Trelle S, Luscher TF, Taniwaki M, Matter CM, Meier B, Juni P, Windecker S; COMFORTABLE AMI Trial Investigators. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: The COMFORTABLE AMI randomized trial. *JAMA.* 2012;308:777-787.
178. Sabate M, Raber L, Heg D, Brugaletta S, Kelback H, Cequier A, Ostojic M, Iniguez A, Tuller D, Serra A, Baumbach A, von Birgelen C, Hernandez-Antolin R, Roffi M, Mainar V, Valgimigli M, Serruys PW, Juni P, Windecker S. Comparison of newer-generation drug-eluting with bare-metal stents in patients with acute ST-segment elevation myocardial infarction: A pooled analysis of the EXAMINATION (clinical Evaluation of the Xience-V stent in Acute Myocardial InfARction) and COMFORTABLE-AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) trials. *JACC Cardiovasc Interv.* 2014;7:55-63.
179. Valgimigli M, Tebaldi M, Borghesi M, Vranckx P, Campo G, Tumscitz C, Cangiano E, Minarelli M, Scalone A, Cavazza C,

- Marchesini J, Parrinello G; PRODIGY Investigators. Two-year outcomes after first- or second-generation drug-eluting or bare-metal stent implantation in all-comer patients undergoing percutaneous coronary intervention: A pre-specified analysis from the PRODIGY study (PROlonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia studY). *JACC Cardiovasc Interv.* 2014;7:20-28.
180. Thiele H, de Waha S, Zeymer U, Desch S, Scheller B, Lauer B, Geisler T, Gawaz M, Gunkel O, Bruch L, Klein N, Pfeiffer D, Schuler G, Eitel I. Effect of aspiration thrombectomy on microvascular obstruction in NSTEMI patients: The TATORT-NSTEMI trial. *J Am Coll Cardiol.* 2014;64:1117-1124.
181. Hakeem A, Edupuganti MM, Almomani A, Pothineni NV, Payne J, Abualsuod AM, Bhatti S, Ahmed Z, Uretsky BF. Long-term prognosis of deferred acute coronary syndrome lesions based on nonischemic fractional flow reserve. *J Am Coll Cardiol.* 2016;68:1181-1191.
182. Wallentin L, Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: The FRISC II invasive randomised trial. FRISC II Investigators. Fast Revascularisation during Instability in Coronary artery disease. *Lancet.* 2000;3:9-16.
183. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann FJ, Robertson DH, DeLuca PT, DiBattiste PM, Gibson CM, Braunwald E, TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)-Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med.* 2001;344:1879-1887.
184. Genereux P, Palmerini T, Caixeta A, Cristea E, Mehran R, Sanchez R, Lazar D, Jankovic I, Corral MD, Dressler O, Fahy MP, Parise H, Lansky AJ, Stone GW. SYNTAX score reproducibility and variability between interventional cardiologists, core laboratory technicians, and quantitative coronary measurements. *Circ Cardiovasc Interv.* 2011;4:553-561.
185. Sardella G, Lucisano L, Garbo R, Pennacchi M, Cavallo E, Stio RE, Calcagno S, Ugo F, Bocuzzi G, Fedele F, Mancone M. Single-staged compared with multi-staged PCI in multivessel NSTEMI patients: The SMILE Trial. *J Am Coll Cardiol.* 2016;67:264-272.
186. Tricoci P, Huang Z, Held C, Moliterno DJ, Armstrong PW, Van de Werf F, White HD, Aylward PE, Wallentin L, Chen E, Lokhnygina Y, Pei J, Leonardi S, Rorick TL, Kilian AM, Jennings LH, Ambrosio G, Bode C, Cequier A, Cornel JH, Diaz R, Erkan A, Huber K, Hudson MP, Jiang L, Jukema JW, Lewis BS, Lincoff AM, Montalescot G, Nicolau JC, Ogawa H, Pfisterer M, Prieto JC, Ruzyllo W, Sinnaeve PR, Storey RF, Valgimigli M, Whellan DJ, Widimsky P, Strony J, Harrington RA, Mahaffey KW; TRACER Investigators. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. *N Engl J Med.* 2012;366:20-33.
187. Lindholm D, Varenhorst C, Cannon CP, Harrington RA, Himmelmann A, Maya J, Husted S, Steg PG, Cornel JH, Storey RF, Stevens SR, Wallentin L, James SK. Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: Results from the PLATO trial. *Eur Heart J.* 2014;35:2083-2093.
188. Curtis JP, Schreiner G, Wang Y, Chen J, Spertus JA, Rumsfeld JS, Brindis RG, Krumholz HM. All-cause readmission and repeat revascularization after percutaneous coronary intervention in a cohort of medicare patients. *J Am Coll Cardiol.* 2009;54:903-907.
189. Meadows ES, Bae JP, Zagar A, Sugihara T, Ramaswamy K, McCracken R, Heiselman D. Rehospitalization following percutaneous coronary intervention for commercially insured patients with acute coronary syndrome: A retrospective analysis. *BMC Res Notes.* 2012;5:342.
190. Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, Nordbeck P, Geisler T, Landmesser U, Skurk C, Fach A, Lapp H, Piek JJ, Noc M, Goslar T, Felix SB, Maier LS, Stepinska J, Oldroyd K, Serpytis P, Montalescot G, Barthelemy O, Huber K, Windecker S, Savonitto S, Torremante P, Vrints C, Schneider S, Desch S, Zeymer U; CULPRIT-SHOCK Investigators. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med.* 2017;377:2419-2432.
191. Ranasinghe I, Alprandi-Costa B, Chow V, Elliott JM, Waites J, Counsell JT, Lopez-Sendon J, Avezum A, Goodman SG, Granger CB, Brieger D. Risk stratification in the setting of non-ST elevation acute coronary syndromes. 1999-2007. *Am J Cardiol.* 2011;108:617-624.
192. Fukui T, Tabata M, Morita S, Takanashi S. Early and long-term outcomes of coronary artery bypass grafting in patients with acute coronary syndrome versus stable angina pectoris. *J Thorac Cardiovasc Surg.* 2013;145:1577-1583.
193. Malm CJ, Hansson EC, Akesson J, Andersson M, Hesse C, Shams Hakimi C, Jeppsson A. Preoperative platelet function predicts perioperative bleeding complications in ticagrelor-treated cardiac surgery patients: A prospective observational study. *Br J Anaesth.* 2016;117:309-315.
194. Chang M, Lee CW, Ahn JM, Cavalcante R, Sotomi Y, Onuma Y, Han M, Park DW, Kang SJ, Lee SW, Kim YH, Park SW, Serruys PW, Park SJ. Comparison of outcome of coronary artery bypass grafting versus drug-eluting stent implantation for non-ST-elevation acute coronary syndrome. *Am J Cardiol.* 2017;120:380-386.
195. Palmerini T, Genereux P, Caixeta A, Cristea E, Lansky A, Mehran R, Dangas G, Lazar D, Sanchez R, Fahy M, Xu K, Stone GW. Prognostic value of the SYNTAX score in patients with acute coronary syndromes undergoing percutaneous coronary intervention: Analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *J Am Coll Cardiol.* 2011;57:2389-2397.
196. Ramanathan K, Abel JG, Park JE, Fung A, Mathew V, Taylor CM, Mancini GBJ, Gao M, Ding L, Verma S, Humphries KH, Farkouh ME. Surgical versus percutaneous coronary revascularization in patients with diabetes and acute coronary syndromes. *J Am Coll Cardiol.* 2017;70:2995-3006.
197. Kolte D, Khera S, Dabhadkar KC, Agarwal S, Aronow WS, Timmermans R, Jain D, Cooper HA, Frishman WH, Menon V, Bhatt DL, Abbott JD, Fonarow GC, Panza JA. Trends in coronary angiography, revascularization, and outcomes of cardiogenic shock complicating non-ST-elevation myocardial infarction. *Am J Cardiol.* 2016;117:1-9.
198. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevanos JA,

- Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P, ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119-177.
199. Scholz KH, Maier SKG, Maier LS, Lengenfelder B, Jacobshagen C, Jung J, Fleischmann C, Werner GS, Olbrich HG, Ott R, Mudra H, Seidl K, Schulze PC, Weiss C, Haimerl J, Friede T, Meyer T. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic instability: Results from the German prospective, multicentre FITT-STEMI trial. *Eur Heart J*. 2018;39:1065-1074.
200. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: Quantitative review of randomised trials. *Lancet*. 2006;367:579-588.
201. Boersma E, Primary Coronary Angioplasty vs. Thrombolysis Group. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J*. 2006;27:779-788.
202. Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: A meta-analysis. *JAMA*. 2000;283:2686-2692.
203. Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY, Cattan S, Boullenger E, Machecourt J, Lacroute JM, Cassagnes J, Dissait F, Touboul P. Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction study group. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: A randomised study. *Lancet*. 2002;360:825-829.
204. Bonnefoy E, Steg PG, Boutitie F, Dubien PY, Lapostolle F, Roncalli J, Dissait F, Vanzetto G, Leizorowicz A, Kirkorian G, CAPTIM Investigators, Mercier C, McFadden EP, Touboul P. Comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial: a 5-year follow-up. *Eur Heart J*. 2009;30:1598-1606.
205. Pinto DS, Frederick PD, Chakrabarti AK, Kirtane AJ, Ullman E, Dejam A, Miller DP, Henry TD, Gibson CM; National Registry of Investigators Myocardial Infarction. Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. *Circulation*. 2011;124:2512-2251.
206. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Rosell Ortiz F, Ostojic M, Welsh RC, Carvalho AC, Nanas J, Arntz HR, Halvorsen S, Huber K, Grajek S, Fresco C, Bluhmki E, Regelin A, Vandenberghe K, Bogaerts K, Van de Werf F; STZREAM Investigative Team. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;368:1379-1387.
207. Park DW, Clare RM, Schulte PJ, Pieper KS, Shaw LK, Califf RM, Ohman EM, Van de Werf F, Hirji S, Harrington RA, Armstrong PW, Granger CB, Jeong MH, Patel MR. Extent, location, and clinical significance of non-infarct-related coronary artery disease among patients with ST-elevation myocardial infarction. *JAMA*. 2014;312:2019-2027.
208. Kornowski R, Mehran R, Dangas G, Nikolsky E, Assali A, Claessen BE, Gersh BJ, Wong SC, Witzienbichler B, Guagliumi G, Dudek D, Fahy M, Lansky AJ, Stone GW, HORIZONS-AMI Trial Investigators. Prognostic impact of staged versus “one-time” multi-vessel percutaneous intervention in acute myocardial infarction: Analysis from the HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial. *J Am Coll Cardiol*. 2011;58:704-711.
209. Politi L, Sgura F, Rossi R, Monopoli D, Guerri E, Leuzzi C, Bursi F, Sangiorgi GM, Modena MG. A randomised trial of target-vessel versus multi-vessel revascularisation in ST-elevation myocardial infarction: Major adverse cardiac events during long-term follow-up. *Heart*. 2010;96:662-667.
210. Di Mario, C Mara, S Flavio, A Imad, S Antonio, M Anna, P Emanuela, P Stefano, DS Angelo, R Stefania, C Anna, F Carmelo, C Antonio, C Monzini, N, Bonardi, MA. Single vs multivessel treatment during primary angioplasty: Results of the multicentre randomised HEpacoat for cuLPrit or multivessel stenting for Acute Myocardial Infarction (HELP AMI) Study. *Int J Cardiovasc Intervent*. 2004;6:128-133.
211. Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, Berry C, Oldroyd KG; PRAMI Investigators. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med*. 2013;369:1115-1123.
212. Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, Blackman DJ, Dalby M, Fairbrother KL, Banya W, Wang D, Flather M, Hetherington SL, Kelion AD, Talwar S, Gunning M, Hall R, Swanton H, McCann GP. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: The CvLPRI trial. *J Am Coll Cardiol*. 2015;65:963-972.
213. Engstrom T, Kelbaek H, Helqvist S, Hofsten DE, Klovgaard L, Holmvang L, Jorgensen E, Pedersen F, Saunamaki K, Clemmensen P, De Backer O, Ravkilde J, Tilsted HH, Villadsen AB, Aaroe J, Jensen SE, Raungaard B, Kober L, DANAMI-PRIMULTI Investigators. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI): An open-label, randomised controlled trial. *Lancet*. 2015;386:665-671.
214. Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Ong PJ, Hambrecht R, Angeras O, Richardt G, Omerovic E, Compare-Acute Investigators. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med*. 2017;376:1234-1244.
215. Elgendy IY, Mahmoud AN, Kumbhani DJ, Bhatt DL, Bavry AA. Complete or culprit-only revascularization for patients with multivessel coronary artery disease undergoing percutaneous coronary intervention: A pairwise and network meta-analysis of randomized trials. *JACC Cardiovasc Interv*. 2017;10:315-324.
216. Kastrati A, Dibra A, Spaulding C, Laarman GJ, Menicelli M, Valgimigli M, Di Lorenzo E, Kaiser C, Tierala I, Mehilli J, Seyfarth M, Varenne O, Dirksen MT, Percoco G, Varricchio A,

- Pittl U, Syvanne M, Suttorp MJ, Violini R, Schomig A. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. *Eur Heart J*. 2007;28:2706-2713.
217. Sabate M, Cequier A, Iniguez A, Serra A, Hernandez-Antolin R, Mainar V, Valgimigli M, Tsepili M, den Heijer P, Bethencourt A, Vazquez N, Gomez-Hospital JA, Baz JA, Martin-Yuste V, van Geuns RJ, Alfonso F, Bordes P, Tebaldi M, Masotti M, Silvestro A, Backx B, Brugaletta S, van Es GA, Serruys PW. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet*. 2012;380:1482-1490.
218. Sabate M, Brugaletta S, Cequier A, Iniguez A, Serra A, Jimenez-Quevedo P, Mainar V, Campo G, Tsepili M, den Heijer P, Bethencourt A, Vazquez N, van Es GA, Backx B, Valgimigli M, Serruys PW. Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial. *Lancet*. 2016;387:357-366.
219. Belle L, Motreff P, Mangin L, Range G, Marcaggi X, Marie A, Ferrier N, Dubreuil O, Zémour G, Souteyrand G, Caussin C, Amabile N, Isaaq K, Dauphin R, Koning R, Robin C, Faurie B, Bonello L, Champin S, Delhaye C, Cuilleret F, Mewton N, Genty C, Viallon M, Bosson JL, Croisille P, MIMI Investigators. Comparison of immediate with delayed stenting using the Minimalist Immediate Mechanical Intervention approach in acute ST-segment-elevation myocardial infarction: The MIMI study. *Circ Cardiovasc Interv*. 2016;9:e003388.
220. Carrick D, Oldroyd KG, McEntegart M, Haig C, Petrie MC, Eteiba H, Hood S, Owens C, Watkins S, Layland J, Lindsay M, Peat E, Rae A, Behan M, Sood A, Hillis WS, Mordi I, Mahrous A, Ahmed N, Wilson R, Lasalle L, Genereux P, Ford I, Berry C. A randomized trial of deferred stenting versus immediate stenting to prevent no- or slow-reflow in acute ST-segment elevation myocardial infarction (DEFER-STEMI). *J Am Coll Cardiol*. 2014;63:2088-2098.
221. Kelbaek H, Hofsten DE, Kober L, Helqvist S, Klovgaard L, Holmvang L, Jorgensen E, Pedersen F, Saunamaki K, De Backer O, Bang LE, Kofoed KF, Lonborg J, Ahtarovski K, Vejlsstrup N, Botker HE, Terkelsen CJ, Christiansen EH, Ravkilde J, Tilsted HH, Villadsen AB, Aaroe J, Jensen SE, Raungaard B, Jensen LO, Clemmensen P, Grande P, Madsen JK, Torp-Pedersen C, Engstrom T. Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER): An open-label, randomised controlled trial. *Lancet*. 2016;387:2199-2206.
222. De Luca G, Navarese EP, Suryapranata H. A meta-analytic overview of thrombectomy during primary angioplasty. *Int J Cardiol*. 2013;166:606-612.
223. Frobert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, Aasa M, Angeras O, Calais F, Danielewicz M, Erlinge D, Hellsten L, Jensen U, Johansson AC, Karegren A, Nilsson J, Robertson L, Sandhall L, Sjogren I, Ostlund O, Harnek J, James SK; TASTE Trial Investigators. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;369:1587-1597.
224. Lagerqvist B, Frobert O, Olivecrona GK, Gudnason T, Maeng M, Alstrom P, Andersson J, Calais F, Carlsson J, Collste O, Gotberg M, Hardhammar P, Ioanes D, Kallryd A, Linder R, Lundin A, Odenstedt J, Omerovic E, Puskas V, Todt T, Zellerroth E, Ostlund O, James SK. Outcomes 1 year after thrombus aspiration for myocardial infarction. *N Engl J Med*. 2014;371:1111-1120.
225. Jolly SS, Cairns JA, Yusuf S, Meeks B, Pogue J, Rokoss MJ, Kedev S, Thabane L, Stankovic G, Moreno R, Gershlick A, Chowdhary S, Lavi S, Niemela K, Steg PG, Bernat I, Xu Y, Cantor WJ, Overgaard CB, Naber CK, Cheema AN, Welsh RC, Bertrand OF, Avezum A, Bhindi R, Pancholy S, Rao SV, Natarajan MK, ten Berg JM, Shestakovska O, Gao P, Widimsky P, Dzavik V, TOTAL Investigators. Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med*. 2015;372(15):1389-1398.
226. Jolly SS, Cairns JA, Yusuf S, Rokoss MJ, Gao P, Meeks B, Kedev S, Stankovic G, Moreno R, Gershlick A, Chowdhary S, Lavi S, Niemela K, Bernat I, Cantor WJ, Cheema AN, Steg PG, Welsh RC, Sheth T, Bertrand OF, Avezum A, Bhindi R, Natarajan MK, Horak D, Leung RC, Kassam S, Rao SV, El-Omar M, Mehta SR, Velianou JL, Pancholy S, Dzavik V; TOTAL Investigators. Outcomes after thrombus aspiration for ST elevation myocardial infarction: 1-year follow-up of the prospective randomised TOTAL trial. *Lancet*. 2016;387:127-135.
227. Jolly SS, Cairns JA, Yusuf S, Meeks B, Gao P, Hart RG, Kedev S, Stankovic G, Moreno R, Horak D, Kassam S, Rokoss MJ, Leung RC, El-Omar M, Romppanen HO, Alazzoni A, Alak A, Fung A, Alexopoulos D, Schwalm JD, Valettas N, Dzavik V, TOTAL Investigators. Stroke in the TOTAL trial: A randomized trial of routine thrombectomy vs. percutaneous coronary intervention alone in ST elevation myocardial infarction. *Eur Heart J*. 2015;36:2364-2372.
228. Jolly SS, James S, Dzavik V, Cairns JA, Mahmoud KD, Zijlstra F, Yusuf S, Olivecrona GK, Renlund H, Gao P, Lagerqvist B, Alazzoni A, Kedev S, Stankovic G, Meeks B, Frobert O. Thrombus aspiration in ST-segment-elevation myocardial infarction: An individual patient meta-analysis: Thrombectomy Trialists Collaboration. *Circulation*. 2017;135(2):143-152.
229. Bohmer E, Hoffmann P, Abdelnoor M, Arnesen H, Halvorsen S. Efficacy and safety of immediate angioplasty versus ischemia-guided management after thrombolysis in acute myocardial infarction in areas with very long transfer distances results of the NORDISTEMI (NORwegian study on DIstrict treatment of ST-elevation myocardial infarction). *J Am Coll Cardiol*. 2010;55:102-110.
230. Cantor WJ, Fitchett D, Borgundvaag B, Ducas J, Heffernan M, Cohen EA, Morrison LJ, Langer A, Dzavik V, Mehta SR, Lazzam C, Schwartz B, Casanova A, Goodman SG; TRANSFER-AMI Investigators. Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Engl J Med*. 2009;360:2705-2718.
231. Di Mario C, Dudek D, Piscione F, Mielecki W, Savonitto S, Murena E, Dimopoulos K, Manari A, Gaspardone A, Ochala A, Zmudka K, Bolognese L, Steg PG, Flather M; CARES-in-AMI Investigators. Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): An open, prospective, randomised, multicentre trial. *Lancet*. 2008;371:559-568.
232. Gershlick AH, Stephens-Lloyd A, Hughes S, Abrams KR, Stevens SE, Uren NG, de Belder A, Davis J, Pitt M, Banning A,

- Baumbach A, Shiu MF, Schofield P, Dawkins KD, Henderson RA, Oldroyd KG, Wilcox R; REACT Trial Investigators. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. *N Engl J Med*. 2005;353:2758-2768.
233. Schomig A, Mehilli J, Antoniucci D, Ndrepepa G, Markwardt C, Di Pede F, Nekolla SG, Schlotterbeck K, Schuhlen H, Pache J, Seyfarth M, Martinoff S, Benzer W, Schmitt C, Dirschinger J, Schwaiger M, Kastrati A; Beyond 12 hours Reperfusion AlternatiVe Evaluation Trial Investigators. Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptom onset: A randomized controlled trial. *JAMA*. 2005;293:2865-2872.
234. Busk M, Kaltoft A, Nielsen SS, Bottcher M, Rehling M, Thuesen L, Botker HE, Lassen JF, Christiansen EH, Krusell LR, Andersen HR, Nielsen TT, Kristensen SD. Infarct size and myocardial salvage after primary angioplasty in patients presenting with symptoms for <12 h vs. 12-72 h. *Eur Heart J*. 2009;30:1322-1330.
235. Hochman JS, Lamas GA, Buller CE, Dzavik V, Reynolds HR, Abramsky SJ, Forman S, Ruzyllo W, Maggioni AP, White H, Sadowski Z, Carvalho AC, Rankin JM, Renkin JP, Steg PG, Mascette AM, Sopko G, Pfisterer ME, Leor J, Fridrich V, Mark DB, Knatterud GL; Occluded Artery Trial Investigators. Coronary intervention for persistent occlusion after myocardial infarction. *N Engl J Med*. 2006;355:2395-2407.
236. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: Reappraisal of the golden hour. *Lancet*. 1996;348:771-775.
237. Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, Abildgaard U, Pedersen F, Madsen JK, Grande P, Villadsen AB, Krusell LR, Haghfelt T, Lomholt P, Husted SE, Vigholt E, Kjaergard HK, Mortensen LS; DANAMI-2 Investigators. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med*. 2003;349:733-742.
238. Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: A meta-analysis. *Circulation*. 2003;108:1809-1814.
239. Mehilli J, Kastrati A, Schulz S, Frungel S, Nekolla SG, Moshage W, Dotzer F, Huber K, Pache J, Dirschinger J, Seyfarth M, Martinoff S, Schwaiger M, Schomig A, Bavarian Reperfusion Alternatives Evaluation-Study 3 I. Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: A randomized double-blind trial. *Circulation*. 2009;119:1933-1940.
240. Kalla K, Christ G, Karnik R, Malzer R, Norman G, Prachar H, Schreiber W, Unger G, Glogar HD, Kaff A, Laggner AN, Maurer G, Mlczoch J, Slany J, Weber HS, Huber K, Vienna SRG. Implementation of guidelines improves the standard of care: The Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI registry). *Circulation*. 2006;113:2398-2405.
241. Henry TD, Sharkey SW, Burke MN, Chavez IJ, Graham KJ, Henry CR, Lips DL, Madison JD, Menssen KM, Mooney MR, Newell MC, Pedersen WR, Poulouse AK, Traverse JH, Unger BT, Wang YL, Larson DM. A regional system to provide timely access to percutaneous coronary intervention for ST-elevation myocardial infarction. *Circulation*. 2007;116:721-728.
242. Nallamothu BK, Krumholz HM, Ko DT, LaBresh KA, Rathore S, Roe MT, Schwamm L. Development of systems of care for ST-elevation myocardial infarction patients: Gaps, barriers, and implications. *Circulation*. 2007;116:e68-e72.
243. Widimsky P, Wijns W, Fajadet J, de Belder M, Knot J, Aaberge L, Andrikopoulos G, Baz JA, Betriu A, Claeys M, Danchin N, Djambazov S, Erne P, Hartikainen J, Huber K, Kala P, Klinecva M, Kristensen SD, Ludman P, Ferre JM, Merkely B, Milicic D, Morais J, Noc M, Opolski G, Ostojic M, Radovanovic D, De Servi S, Stenestrand U, Studencan M, Tubaro M, Vasiljevic Z, Weidinger F, Witkowski A, Zeymer U, European Association for Percutaneous Cardiovascular Interventions. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: Description of the current situation in 30 countries. *Eur Heart J*. 2010;31:943-957.
244. Knot J, Widimsky P, Wijns W, Stenestrand U, Kristensen SD, Van THA, Weidinger F, Janzon M, Norgaard BL, Soerensen JT, van de Wetering H, Thygesen K, Bergsten PA, Digerfeldt C, Potgieter A, Tomer N, Fajadet J. How to set up an effective national primary angioplasty network: Lessons learned from five European countries. *EuroIntervention*. 2009;5:299, 301-309.
245. Bradley EH, Herrin J, Wang Y, Barton BA, Webster TR, Mattern JA, Roumanis SA, Curtis JP, Nallamothu BK, Magid DJ, McNamara RL, Parkosewich J, Loeb JM, Krumholz HM. Strategies for reducing the door-to-balloon time in acute myocardial infarction. *N Engl J Med*. 2006;355:2308-2320.
246. Pinto DS, Kirtane AJ, Nallamothu BK, Murphy SA, Cohen DJ, Laham RJ, Cutlip DE, Bates ER, Frederick PD, Miller DP, Carrozza JP Jr, Antman EM, Cannon CP, Gibson CM. Hospital delays in reperfusion for ST-elevation myocardial infarction: Implications when selecting a reperfusion strategy. *Circulation*. 2006;114:2019-2025.
247. Steg PG, Cambou JP, Goldstein P, Durand E, Sauval P, Kadri Z, Blanchard D, Lablanche JM, Gueret P, Cottin Y, Juliard JM, Hanania G, Vaur L, Danchin N; USIC. 2000 Investigators. Bypassing the emergency room reduces delays and mortality in ST elevation myocardial infarction: The USIC 2000 registry. *Heart*. 2006;92:1378-1383.
248. Wolff G, Dimitroulis D, Andreotti F, Kolodziejczak M, Jung C, Scicchitano P, Devito F, Zito A, Occhipinti M, Castiglioni B, Calveri G, Maisano F, Ciccone MM, De Servi S, Navarese EP. Survival benefits of invasive versus conservative strategies in heart failure in patients with reduced ejection fraction and coronary artery disease: A meta-analysis. *Circ Heart Fail*. 2017;10:e003255.
249. Wrobel K, Stevens SR, Jones RH, Selzman CH, Lamy A, Beaver TM, Djokovic LT, Wang N, Velazquez EJ, Sopko G, Kron IL, DiMaio JM, Michler RE, Lee KL, Yii M, Leng CY, Zembala M, Rouleau JL, Daly RC, Al-Khalidi HR. Influence of baseline characteristics, operative conduct, and postoperative course on 30-day outcomes of coronary artery bypass grafting among patients with left ventricular dysfunction: Results from the Surgical Treatment for Ischemic Heart Failure (STICH) Trial. *Circulation*. 2015;132:720-730.
250. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Hannan EL. Revascularization in patients with multivessel coronary artery disease and severe left ventricular systolic dysfunction: Everolimus-eluting stents versus coronary artery bypass graft surgery. *Circulation*. 2016;133:2132-2140.

251. Nagendran J, Bozso SJ, Norris CM, McAlister FA, Appoo JJ, Moon MC, Freed DH, Nagendran J. Coronary artery bypass surgery improves outcomes in patients with diabetes and left ventricular dysfunction. *J Am Coll Cardiol*. 2018;71:819-827.
252. Jones RH, Velazquez EJ, Michler RE, Sopko G, Oh JK, O'Connor CM, Hill JA, Menicanti L, Sadowski Z, Desvigne-Nickens P, Rouleau JL, Lee KL, STICH Hypothesis 2 Investigators. Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med*. 2009;360:1705-1717.
253. Oh JK, Velazquez EJ, Menicanti L, Pohost GM, Bonow RO, Lin G, Hellkamp AS, Ferrazzi P, Wos S, Rao V, Berman D, Bochenek A, Cherniavsky A, Rogowski J, Rouleau JL, Lee KL, STICH Investigators. Influence of baseline left ventricular function on the clinical outcome of surgical ventricular reconstruction in patients with ischaemic cardiomyopathy. *Eur Heart J*. 2013;34:39-47.
254. Dor V, Civaia F, Alexandrescu C, Sabatier M, Montiglio F. Favorable effects of left ventricular reconstruction in patients excluded from the Surgical Treatments for Ischemic Heart Failure (STICH) trial. *J Thorac Cardiovasc Surg*. 2011;141:905-916, 916 e1-e4.
255. Killip T, Passamani E, Davis K. Coronary artery surgery study (CASS): A randomized trial of coronary bypass surgery. Eight years follow-up and survival in patients with reduced ejection fraction. *Circulation*. 1985;72:V102-V109.
256. Di Donato M, Castelvechio S, Menicanti L. End-systolic volume following surgical ventricular reconstruction impacts survival in patients with ischaemic dilated cardiomyopathy. *Eur J Heart Fail*. 2010;12:375-381.
257. Michler RE, Rouleau JL, Al-Khalidi HR, Bonow RO, Pellikka PA, Pohost GM, Holly TA, Oh JK, Dagenais F, Milano C, Wrobel K, Pirk J, Ali IS, Jones RH, Velazquez EJ, Lee KL, Di Donato M, STICH Trial Investigators. Insights from the STICH trial: Change in left ventricular size after coronary artery bypass grafting with and without surgical ventricular reconstruction. *J Thorac Cardiovasc Surg*. 2013;146:1139-1145.e6.
258. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med*. 1999;341:625-634.
259. White HD, Assmann SF, Sanborn TA, Jacobs AK, Webb JG, Sleeper LA, Wong CK, Stewart JT, Aylward PE, Wong SC, Hochman JS. Comparison of percutaneous coronary intervention and coronary artery bypass grafting after acute myocardial infarction complicated by cardiogenic shock: Results from the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial. *Circulation*. 2005;112:1992-2001.
260. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, de Waha A, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Lauer B, Bohm M, Ebel H, Schneider S, Werdan K, Schuler G; Intraaortic Balloon Pump in cardiogenic shock II (IABP-SHOCK II) Trial Investigators. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): Final 12 month results of a randomised, open-label trial. *Lancet*. 2013;382:1638-1645.
261. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Bohm M, Ebel H, Schneider S, Schuler G, Werdan K; IABP-SHOCK II Trial Investigators I-SIT. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med*. 2012;367:1287-1296.
262. Unverzagt S, Buerke M, de Waha A, Haerting J, Pietzner D, Seyfarth M, Thiele H, Werdan K, Zeymer U, Prondzinsky R. Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock. *Cochrane Database Syst Rev*. 2015;3:CD007398.
263. Ouweneel DM, Schotborgh JV, Limpens J, Sjauw KD, Engstrom AE, Lagrand WK, Cherpanath TGV, Driessen AHG, de Mol B, Henriques JPS. Extracorporeal life support during cardiac arrest and cardiogenic shock: a systematic review and meta-analysis. *Intensive Care Med*. 2016;42:1922-1934.
264. Burkhoff D, Cohen H, Brunckhorst C, O'Neill WW; TandemHeart Investigators Group. A randomized multicenter clinical study to evaluate the safety and efficacy of the TandemHeart percutaneous ventricular assist device versus conventional therapy with intraaortic balloon pumping for treatment of cardiogenic shock. *Am Heart J*. 2006;152:469.e1-469.e8.
265. Seyfarth M, Sibbing D, Bauer I, Frohlich G, Bott-Flugel L, Byrne R, Dirschinger J, Kastrati A, Schomig A. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. *J Am Coll Cardiol*. 2008;52:1584-1588.
266. Thiele H, Jobs A, Ouweneel DM, Henriques JPS, Seyfarth M, Desch S, Eitel I, Poss J, Fuernau G, de Waha S. Percutaneous short-term active mechanical support devices in cardiogenic shock: A systematic review and collaborative meta-analysis of randomized trials. *Eur Heart J*. 2017;38:3523-3531.
267. O'Neill WW, Kleiman NS, Moses J, Henriques JP, Dixon S, Massaro J, Palacios I, Maini B, Mulukutla S, Dzavik V, Popma J, Douglas PS, Ohman M. A prospective, randomized clinical trial of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention: The PROTECT II study. *Circulation*. 2012;126:1717-1727.
268. Acharya D, Loyaga-Rendon RY, Pamboukian SV, Tallaj JA, Holman WL, Cantor RS, Naftel DC, Kirklin JK. Ventricular assist device in acute myocardial infarction. *J Am Coll Cardiol*. 2016;67:1871-1880.
269. Hochman JS, Sleeper LA, Webb JG, Dzavik V, Buller CE, Aylward P, Col J, White HD; SHOCK Investigators. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *JAMA*. 2006;295:2511-2515.
270. Hammoud T, Tanguay JF, Bourassa MG. Management of coronary artery disease: Therapeutic options in patients with diabetes. *J Am Coll Cardiol*. 2000;36:355-365.
271. Haffner SM, Lehto S, Ronnema T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229-234.
272. Luscher TF, Creager MA, Beckman JA, Cosentino F. Diabetes and vascular disease: Pathophysiology, clinical consequences, and medical therapy: Part II. *Circulation*. 2003;108:1655-1661.

273. Ledru F, Ducimetiere P, Battaglia S, Courbon D, Beverelli F, Guize L, Guernonprez JL, Diebold B. New diagnostic criteria for diabetes and coronary artery disease: Insights from an angiographic study. *J Am Coll Cardiol*. 2001;37:1543-1550.
274. Moreno PR, Murcia AM, Palacios IF, Leon MN, Bernardi VH, Fuster V, Fallon JT. Coronary composition and macrophage infiltration in atherectomy specimens from patients with diabetes mellitus. *Circulation*. 2000;102:2180-2184.
275. Marso SP, Mercado N, Maehara A, Weisz G, Mintz GS, McPherson J, Schiele F, Dudek D, Fahy M, Xu K, Lansky A, Templin B, Zhang Z, de Bruyne B, Serruys PW, Stone GW. Plaque composition and clinical outcomes in acute coronary syndrome patients with metabolic syndrome or diabetes. *JACC Cardiovasc Imaging*. 2012;5:S42-S52.
276. Silva JA, Escobar A, Collins TJ, Ramee SR, White CJ. Unstable angina. A comparison of angioscopic findings between diabetic and nondiabetic patients. *Circulation*. 1995;92:1731-1736.
277. O'Donoghue ML, Vaidya A, Afsal R, Alfredsson J, Boden WE, Braunwald E, Cannon CP, Clayton TC, de Winter RJ, Fox KA, Lagerqvist B, McCullough PA, Murphy SA, Spacek R, Swahn E, Windhausen F, Sabatine MS. An invasive or conservative strategy in patients with diabetes mellitus and non-ST-segment elevation acute coronary syndromes: A collaborative meta-analysis of randomized trials. *J Am Coll Cardiol*. 2012;60: 106-111.
278. Schwartz L, Bertolet M, Feit F, Fuentes F, Sako EY, Toosi MS, Davidson CJ, Ikeno F, King SB III. Impact of completeness of revascularization on long-term cardiovascular outcomes in patients with type 2 diabetes mellitus: Results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D). *Circ Cardiovasc Interv*. 2012;5:166-173.
279. Dangas GD, Farkouh ME, Sleeper LA, Yang M, Schoos MM, Macaya C, Abizaid A, Buller CE, Devlin G, Rodriguez AE, Lansky AJ, Siami FS, Domanski M, Fuster V; FREEDOM Investigators. Long-term outcome of PCI versus CABG in insulin and non-insulin-treated diabetic patients: Results from the FREEDOM trial. *J Am Coll Cardiol*. 2014;64:1189-1197.
280. Goergen SK, Rumbold G, Compton G, Harris C. Systematic review of current guidelines, and their evidence base, on risk of lactic acidosis after administration of contrast medium for patients receiving metformin. *Radiology*. 2010;254:261-269.
281. Milojevic M, Head SJ, Mack MJ, Mohr FW, Morice MC, Dawkins KD, Holmes DR Jr, Serruys PW, Kappetein AP. The impact of chronic kidney disease on outcomes following percutaneous coronary intervention versus coronary artery bypass grafting in patients with complex coronary artery disease: Five-year follow-up of the SYNTAX trial. *EuroIntervention*. 2018;14:102-111.
282. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: Development and initial validation. *J Am Coll Cardiol*. 2004;44:1393-1399.
283. Ohno Y, Maekawa Y, Miyata H, Inoue S, Ishikawa S, Sueyoshi K, Noma S, Kawamura A, Kohsaka S, Fukuda K. Impact of periprocedural bleeding on incidence of contrast-induced acute kidney injury in patients treated with percutaneous coronary intervention. *J Am Coll Cardiol*. 2013;62:1260-1266.
284. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ, Nephrotoxicity in High-Risk Patients Study of I-O, Low-Osmolar Non-Ionic Contrast Media Study Investigators. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med*. 2003;348:491-499.
285. Jo SH, Youn TJ, Koo BK, Park JS, Kang HJ, Cho YS, Chung WY, Joo GW, Chae IH, Choi DJ, Oh BH, Lee MM, Park YB, Kim HS. Renal toxicity evaluation and comparison between visipaque (iodixanol) and hexabrix (ioxaglate) in patients with renal insufficiency undergoing coronary angiography: The RECOVER study: A randomized controlled trial. *J Am Coll Cardiol*. 2006;48: 924-930.
286. Solomon RJ, Natarajan MK, Doucet S, Sharma SK, Staniloae CS, Katholi RE, Gelormini JL, Labinaz M, Moreyra AE; Investigators of the CARE Study. Cardiac Angiography in Renally Impaired Patients (CARE) study: A randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease. *Circulation*. 2007;115:3189-3196.
287. Marenzi G, Assanelli E, Campodonico J, Lauri G, Marana I, De Metrio M, Moltrasio M, Grazi M, Rubino M, Veglia F, Fabbicocchi F, Bartorelli AL. Contrast volume during primary percutaneous coronary intervention and subsequent contrast-induced nephropathy and mortality. *Ann Intern Med*. 2009;150:170-177.
288. Laskey WK, Jenkins C, Selzer F, Marroquin OC, Wilensky RL, Glaser R, Cohen HA, Holmes DR Jr, Investigators NDR. Volume-to-creatinine clearance ratio: A pharmacokinetically based risk factor for prediction of early creatinine increase after percutaneous coronary intervention. *J Am Coll Cardiol*. 2007;50:584-590.
289. Mueller C, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, Marsch S, Roskamm H. Prevention of contrast media-associated nephropathy: Randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med*. 2002;162:329-336.
290. Merten GJ, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, Bersin RM, Van Moore A, Simonton CA III, Rittase RA, Norton HJ, Kennedy TP. Prevention of contrast-induced nephropathy with sodium bicarbonate: A randomized controlled trial. *JAMA*. 2004;291:2328-2334.
291. Brar SS, Shen AY, Jorgensen MB, Kotlewski A, Aharonian VJ, Desai N, Ree M, Shah AI, Burchette RJ. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: A randomized trial. *JAMA*. 2008;300:1038-1046.
292. Nijssen EC, Rennenberg RJ, Nelemans PJ, Essers BA, Janssen MM, Vermeeren MA, Ommen VV, Wildberger JE. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): A prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. *Lancet*. 2017;389:1312-1322.
293. Giacoppo D, Gargiulo G, Buccheri S, Aruta P, Byrne RA, Cassese S, Dangas G, Kastrati A, Mehran R, Tamburino C, Capodanno D. Preventive strategies for contrast-induced acute kidney injury in patients undergoing percutaneous coronary procedures: Evidence from a hierarchical Bayesian network meta-analysis of 124 trials and 28 240 patients. *Circ Cardiovasc Interv*. 2017;10:e004383.
294. Weisbord SD, Gallagher M, Jneid H, Garcia S, Cass A, Thwin SS, Conner TA, Chertow GM, Bhatt DL, Shunk K, Parikh CR, McFalls EO, Brophy M, Ferguson R, Wu H,

- Androsenko M, Myles J, Kaufman J, Palevsky PM; PRESERVE Trial Group. Outcomes after angiography with sodium bicarbonate and acetylcysteine. *N Engl J Med.* 2018;378:603-614.
295. Qian G, Fu Z, Guo J, Cao F, Chen Y. Prevention of contrast-induced nephropathy by central venous pressure-guided fluid administration in chronic kidney disease and congestive heart failure patients. *JACC Cardiovasc Interv.* 2016;9:89-96.
296. Briguori C, Visconti G, Focaccio A, Airoidi F, Valgimigli M, Sangiorgi GM, Golia B, Ricciardelli B, Condorelli G; REMEDIAL II Investigators. Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard System in high-risk patients for contrast-induced acute kidney injury. *Circulation.* 2011;124:1260-1269.
297. Putzu A, Boscolo Berto M, Belletti A, Pasotti E, Cassina T, Moccetti T, Pedrazzini G. Prevention of contrast-induced acute kidney injury by furosemide with matched hydration in patients undergoing interventional procedures: A systematic review and meta-analysis of randomized trials. *JACC Cardiovasc Interv.* 2017;10:355-363.
298. Marenzi G, Marana I, Lauri G, Assanelli E, Grazi M, Campodonico J, Trabattoni D, Fabbiochi F, Montorsi P, Bartorelli AL. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med.* 2003;349:1333-1340.
299. Marenzi G, Lauri G, Campodonico J, Marana I, Assanelli E, De Metrio M, Grazi M, Veglia F, Fabbiochi F, Montorsi P, Bartorelli AL. Comparison of two hemofiltration protocols for prevention of contrast-induced nephropathy in high-risk patients. *Am J Med.* 2006;119:155-162.
300. Cruz DN, Goh CY, Marenzi G, Corradi V, Ronco C, Perazella MA. Renal replacement therapies for prevention of radiocontrast-induced nephropathy: A systematic review. *Am J Med.* 2012;125:66-78 e3.
301. Vogt B, Ferrari P, Schonholzer C, Marti HP, Mohaupt M, Wiederkehr M, Cereghetti C, Serra A, Huynh-Do U, Uehlinger D, Frey FJ. Prophylactic hemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful. *Am J Med.* 2001;111:692-698.
302. Scarsini R, Pesarini G, Zivelonghi C, Piccoli A, Ferrero V, Lunardi M, Barbierato M, Caprioglio F, Vassanelli C, Ribichini F. Coronary physiology in patients with severe aortic stenosis: Comparison between fractional flow reserve and instantaneous wave-free ratio. *Int J Cardiol.* 2017;243:40-46.
303. Scarsini R, Pesarini G, Zivelonghi C, Piccoli A, Ferrero V, Lunardi M, Gottin L, Zanetti C, Faggian G, Ribichini F. Physiologic evaluation of coronary lesions using instantaneous wave-free ratio (iFR) in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. *EuroIntervention.* 2018;13:1512-1519.
304. Di Gioia G, Scarsini R, Strisciuglio T, De Biase C, Zivelonghi C, Franco D, De Bruyne B, Ribichini F, Barbato E. Correlation between angiographic and physiologic evaluation of coronary artery narrowings in patients with aortic valve stenosis. *Am J Cardiol.* 2017;120:106-110.
305. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Munoz D, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL, ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J.* 2017;38:2739-2791.
306. Yamashita K, Fujita T, Hata H, Shimahara Y, Kume Y, Matsumoto Y, Kobayashi J. Long-term outcome of isolated off-pump coronary artery bypass grafting in patients with coronary artery disease and mild to moderate aortic stenosis. *J Cardiol.* 2017;70:48-54.
307. Goldstein D, Moskowitz AJ, Gelijns AC, Ailawadi G, Parides MK, Perrault LP, Hung JW, Voisine P, Dagenais F, Gillinov AM, Thourani V, Argenziano M, Gammie JS, Mack M, Demers P, Atluri P, Rose EA, O'Sullivan K, Williams DL, Bagiella E, Michler RE, Weisel RD, Miller MA, Geller NL, Taddei-Peters WC, Smith PK, Moquete E, Overbey JR, Kron IL, O'Gara PT, Acker MA, Ctsn. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. *N Engl J Med.* 2016;374:344-353.
308. Smith PK, Puskas JD, Ascheim DD, Voisine P, Gelijns AC, Moskowitz AJ, Hung JW, Parides MK, Ailawadi G, Perrault LP, Acker MA, Argenziano M, Thourani V, Gammie JS, Miller MA, Page P, Overbey JR, Bagiella E, Dagenais F, Blackstone EH, Kron IL, Goldstein DJ, Rose EA, Moquete EG, Jeffries N, Gardner TJ, O'Gara PT, Alexander JH, Michler RE; Cardiothoracic Surgical Trials Network Investigators. Surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med.* 2014;371:2178-2188.
309. Michler RE, Smith PK, Parides MK, Ailawadi G, Thourani V, Moskowitz AJ, Acker MA, Hung JW, Chang HL, Perrault LP, Gillinov AM, Argenziano M, Bagiella E, Overbey JR, Moquete EG, Gupta LN, Miller MA, Taddei-Peters WC, Jeffries N, Weisel RD, Rose EA, Gammie JS, DeRose JJ Jr, Puskas JD, Dagenais F, Burks SG, El-Hamamsy I, Milano CA, Atluri P, Voisine P, O'Gara PT, Gelijns AC, Ctsn. Two-year outcomes of surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med.* 2016;374:1932-1941.
310. Chan KM, Punjabi PP, Flather M, Wage R, Symmonds K, Roussin I, Rahman-Haley S, Pennell DJ, Kilner PJ, Dreyfus GD, Pepper JR, Investigators R. Coronary artery bypass surgery with or without mitral valve annuloplasty in moderate functional ischemic mitral regurgitation: final results of the Randomized Ischemic Mitral Evaluation (RIME) trial. *Circulation.* 2012;126(21):2502-2510.
311. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, Badano L, Zamorano JL, Scientific Document Committee of the European Association of Cardiovascular Imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: An executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2013;14:611-644.
312. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, Little SH, Shah DJ, Shernan S, Thavendiranathan P, Thomas JD, Weissman NJ. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A report from the American Society of Echocardiography developed in collaboration with the society for cardiovascular magnetic resonance. *J Am Soc Echocardiogr.* 2017;30:303-371.
313. Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH, Domanski MJ, Farkouh ME, Flather M, Fuster V,

- Hlatky MA, Holm NR, Hueb WA, Kamallesh M, Kim YH, Mäkikallio T, Mohr FW, Papageorgiou W, Park SJ, Rodriguez AE, Sabik III JF, Stables RH, Stone GW, Serruys PW, Kappetein AP. Stroke rates following surgical versus percutaneous coronary revascularization. *J Am Coll Cardiol*. 2018;72:386-398.
314. Naylor AR, Bown MJ. Stroke after cardiac surgery and its association with asymptomatic carotid disease: An updated systematic review and meta-analysis. *Eur J Vasc Endovasc Surg*. 2011;41:607-624.
315. Masabni K, Raza S, Blackstone EH, Gornik HL, Sabik JF III. Does preoperative carotid stenosis screening reduce perioperative stroke in patients undergoing coronary artery bypass grafting? *J Thorac Cardiovasc Surg*. 2015;149:1253-1260.
316. Naylor AR. Does the risk of post-CABG stroke merit staged or synchronous reconstruction in patients with symptomatic or asymptomatic carotid disease? *J Cardiovasc Surg (Torino)*. 2009;50:71-81.
317. Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Rother J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I, ESC Scientific Document Group. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries Endorsed by: The European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J*. 2018;39:763-816.
318. Lee R, Matsutani N, Polimenakos AC, Levers LC, Lee M, Johnson RG. Preoperative noncontrast chest computed tomography identifies potential aortic emboli. *Ann Thorac Surg*. 2007;84:38-41.
319. Naylor AR, Cuffe RL, Rothwell PM, Bell PR. A systematic review of outcomes following staged and synchronous carotid endarterectomy and coronary artery bypass. *Eur J Vasc Endovasc Surg*. 2003;25:380-389.
320. Paraskevas KI, Nduwayo S, Saratzis AN, Naylor AR. Carotid stenting prior to coronary bypass surgery: An updated systematic review and meta-analysis. *Eur J Vasc Endovasc Surg*. 2017;53:309-319.
321. Lin JC, Kabbani LS, Peterson EL, Masabni K, Morgan JA, Brooks S, Wertella KP, Paone G. Clinical utility of carotid duplex ultrasound prior to cardiac surgery. *J Vasc Surg*. 2016;63:710-714.
322. Aboyans V, Lacroix P. Indications for carotid screening in patients with coronary artery disease. *Presse Med*. 2009;38:977-986.
323. Zhao DX, Leacche M, Balaguer JM, Boudoulas KD, Damp JA, Greelish JP, Byrne JG; Writing Group of the Cardiac Surgery, Cardiac Anesthesiology, and Interventional Cardiology Groups at the Vanderbilt Heart and Vascular Institute, Ahmad RM, Ball SK, Cleator JH, Deegan RJ, Eagle SS, Fong PP, Fredi JL, Hoff SJ, Jennings HS III, McPherson JA, Piana RN, Pretorius M, Robbins MA, Slosky DA, Thompson A. Routine intraoperative completion angiography after coronary artery bypass grafting and 1-stop hybrid revascularization results from a fully integrated hybrid catheterization laboratory/operating room. *J Am Coll Cardiol*. 2009;53:232-241.
324. Thielmann M, Massoudy P, Jaeger BR, Neuhauser M, Marggraf G, Sack S, Erbel R, Jakob H. Emergency re-revascularization with percutaneous coronary intervention, reoperation, or conservative treatment in patients with acute perioperative graft failure following coronary artery bypass surgery. *Eur J Cardiothorac Surg*. 2006;30:117-125.
325. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Writing Group on the Joint/ACCF/AHA/Task Force for the Universal Definition of Myocardial Infarction WHF, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghide M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, ESC Committee for Practice Guidelines. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33:2551-2567.
326. Davierwala PM, Verevkin A, Leontyev S, Misfeld M, Borger MA, Mohr FW. Impact of expeditious management of perioperative myocardial ischemia in patients undergoing isolated coronary artery bypass surgery. *Circulation*. 2013;128:S226-S234.
327. Laflamme M, DeMey N, Bouchard D, Carrier M, Demers P, Pellerin M, Couture P, Perrault LP. Management of early postoperative coronary artery bypass graft failure. *Interact Cardiovasc Thorac Surg*. 2012;14:452-456.
328. Gaudino M, Nesta M, Burzotta F, Trani C, Coluccia V, Crea F, Massetti M. Results of emergency postoperative re-angiography after cardiac surgery procedures. *Ann Thorac Surg*. 2015;99:1576-1582.
329. Thielmann M, Sharma V, Al-Attar N, Bulluck H, Bisleri G, Bunge JH, Czerny M, Ferdinandy P, Frey UH, Heusch G, Holfeld J, Kleinbongard P, Kunst G, Lang I, Lentini S, Madonna R, Meybohm P, Muneretto C, Obadia JF, Perrino C, Prunier F, Sluijter JPG, Van Laake LW, Sousa-Uva M, Hausenloy DJ. ESC Joint Working Groups on Cardiovascular Surgery and the Cellular Biology of the Heart Position Paper: Perioperative myocardial injury and infarction in patients undergoing coronary artery bypass graft surgery. *Eur Heart J*. 2017;38:2392-2407.
330. Seshadri N, Whitlow PL, Acharya N, Houghtaling P, Blackstone EH, Ellis SG. Emergency coronary artery bypass surgery in the contemporary percutaneous coronary intervention era. *Circulation*. 2002;106:2346-2350.
331. Mattichak SJ, Dixon SR, Shannon F, Boura JA, Safian RD. Failed percutaneous coronary intervention: A decade of experience in 21,000 patients. *Catheter Cardiovasc Interv*. 2008;71:131-137.
332. Davierwala PM, Leontyev S, Verevkin A, Rastan AJ, Mohr M, Bakhtiyari F, Misfeld M, Mohr FW. Temporal trends in predictors of early and late mortality after emergency coronary artery bypass grafting for cardiogenic shock complicating acute myocardial infarction. *Circulation*. 2016;134:1224-1237.
333. Axelsson TA, Mennander A, Malmberg M, Gunn J, Jeppsson A, Gudbjartsson T. Is emergency and salvage coronary

- artery bypass grafting justified? The Nordic Emergency/ Salvage coronary artery bypass grafting study. *Eur J Cardiothorac Surg.* 2016;49:1451-1456.
334. Parasca CA, Head SJ, Milojevic M, Mack MJ, Serruys PW, Morice MC, Mohr FW, Feldman TE, Colombo A, Dawkins KD, Holmes DR Jr, Kappetein PA; SYNTAX Investigators. Incidence, characteristics, predictors, and outcomes of repeat revascularization after percutaneous coronary intervention and coronary artery bypass grafting: The SYNTAX trial at 5 years. *JACC Cardiovasc Interv.* 2016;9:2493-2507.
335. Cassese S, Byrne RA, Tada T, Piniack S, Joner M, Ibrahim T, King LA, Fusaro M, Laugwitz KL, Kastrati A. Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography. *Heart.* 2014;100:153-159.
336. Tada T, Byrne RA, Simunovic I, King LA, Cassese S, Joner M, Fusaro M, Schneider S, Schulz S, Ibrahim T, Ott I, Massberg S, Laugwitz KL, Kastrati A. Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: Results from a registry of 18,334 patients. *JACC Cardiovasc Interv.* 2013;6:1267-1274.
337. Sabik JF III, Blackstone EH, Houghtaling PL, Walts PA, Lytle BW. Is reoperation still a risk factor in coronary artery bypass surgery? *Ann Thorac Surg.* 2005;80:1719-1727.
338. Yap CH, Sposato L, Akowuah E, Theodore S, Dinh DT, Shardey GC, Skillington PD, Tatoulis J, Yui M, Smith JA, Mohajeri M, Pick A, Seevanayagam S, Reid CM. Contemporary results show repeat coronary artery bypass grafting remains a risk factor for operative mortality. *Ann Thorac Surg.* 2009;87:1386-1391.
339. Fosbol EL, Zhao Y, Shahian DM, Grover FL, Edwards FH, Peterson ED. Repeat coronary revascularization after coronary artery bypass surgery in older adults: The Society of Thoracic Surgeons' national experience, 1991-2007. *Circulation.* 2013;127:1656-1663.
340. Brener SJ, Lytle BW, Casserly IP, Ellis SG, Topol EJ, Lauer MS. Predictors of revascularization method and long-term outcome of percutaneous coronary intervention or repeat coronary bypass surgery in patients with multivessel coronary disease and previous coronary bypass surgery. *Eur Heart J.* 2006;27:413-418.
341. Morrison DA, Sethi G, Sacks J, Henderson WG, Grover F, Sedlis S, Esposito R; Investigators of the Department of Veterans Affairs Cooperative Study #385. Angina With Extremely Serious Operative Mortality Evaluation. Percutaneous coronary intervention versus repeat bypass surgery for patients with medically refractory myocardial ischemia: AWESOME randomized trial and registry experience with post-CABG patients. *J Am Coll Cardiol.* 2002;40:1951-1954.
342. Morrison DA, Sethi G, Sacks J, Henderson W, Grover F, Sedlis S, Esposito R, Ramanathan K, Weiman D, Saucedo J, Antakli T, Paramesh V, Pett S, Vernon S, Birjiniuk V, Welt F, Krucoff M, Wolfe W, Lucke JC, Mediratta S, Booth D, Barbieri C, Lewis D; Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: A multicenter, randomized trial. Investigators of the Department of Veterans Affairs Cooperative Study #385, the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). *J Am Coll Cardiol.* 2001;38:143-149.
343. Harskamp RE, Beijk MA, Damman P, Kuijt WJ, Woudstra P, Grundeken MJ, Kloek JJ, Tijssen JG, de Mol BA, de Winter RJ. Clinical outcome after surgical or percutaneous revascularization in coronary bypass graft failure. *J Cardiovasc Med (Hagerstown).* 2013;14:438-445.
344. Sabik JF III, Raza S, Blackstone EH, Houghtaling PL, Lytle BW. Value of internal thoracic artery grafting to the left anterior descending coronary artery at coronary reoperation. *J Am Coll Cardiol.* 2013;61:302-310.
345. Nwaejike N, Tennyson C, Mosca R, Venkateswaran R. Reusing the patent internal mammary artery as a conduit in redo coronary artery bypass surgery. *Interact Cardiovasc Thorac Surg.* 2016;22:346-350.
346. Coolong A, Baim DS, Kuntz RE, O'Malley AJ, Marulkar S, Cutlip DE, Popma JJ, Mauri L. Saphenous vein graft stenting and major adverse cardiac events: A predictive model derived from a pooled analysis of 3958 patients. *Circulation.* 2008;117:790-797.
347. Baim DS, Wahr D, George B, Leon MB, Greenberg J, Cutlip DE, Kaya U, Popma JJ, Ho KK, Kuntz RE; Saphenous vein graft Angioplasty Free of Emboli Randomized (SAFER) Trial Investigators. Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. *Circulation.* 2002;105:1285-1290.
348. Paul TK, Bhatheja S, Panchal HB, Zheng S, Banerjee S, Rao SV, Guzman L, Beohar N, Zhao D, Mehran R, Mukherjee D. Outcomes of saphenous vein graft intervention with and without embolic protection device: A comprehensive review and meta-analysis. *Circ Cardiovasc Interv.* 2017;10:e005538.
349. Brennan JM, Al-Hejily W, Dai D, Shaw RE, Trilesskaya M, Rao SV, Brilakis ES, Anstrom KJ, Messenger JC, Peterson ED, Douglas PS, Sketch MH Jr. Three-year outcomes associated with embolic protection in saphenous vein graft intervention: Results in 49 325 senior patients in the Medicare-linked National Cardiovascular Data Registry CathPCI Registry. *Circ Cardiovasc Interv.* 2015;8:e001403.
350. Stone GW, Rogers C, Hermiller J, Feldman R, Hall P, Haber R, Masud A, Cambier P, Caputo RP, Turco M, Kovach R, Brodie B, Herrmann HC, Kuntz RE, Popma JJ, Ramee S, Cox DA; FilterWire EX Randomized Evaluation Investigators. Randomized comparison of distal protection with a filter-based catheter and a balloon occlusion and aspiration system during percutaneous intervention of diseased saphenous vein aorto-coronary bypass grafts. *Circulation.* 2003;108:548-553.
351. Mauri L, Cox D, Hermiller J, Massaro J, Wahr J, Tay SW, Jonas M, Popma JJ, Pavliska J, Wahr D, Rogers C. The PROXIMAL trial: Proximal protection during saphenous vein graft intervention using the Proxis Embolic Protection System: A randomized, prospective, multicenter clinical trial. *J Am Coll Cardiol.* 2007;50:1442-1449.
352. Schächinger V, Hamm CW, Munzel T, Haude M, Baldus S, Grube E, Bonzel T, Konorza T, Koster R, Arnold R, Haase J, Probst P, vom Dahl J, Neumann FJ, Mudra H, Hennen B, Thiele L, Zeiher AM; STENTS (STents IN Grafts) Investigators. A randomized trial of polytetrafluoroethylene-membrane-covered stents compared with conventional stents in aortocoronary saphenous vein grafts. *J Am Coll Cardiol.* 2003;42:1360-1369.

353. Stankovic G, Colombo A, Presbitero P, van den Branden F, Inglese L, Cernigliaro C, Niccoli L, Bartorelli AL, Rubartelli P, Reifart N, Heyndrickx GR, Saunamaki K, Morice MC, Sgura FA, Di Mario C; Randomized Evaluation of polytetrafluoroethylene COVERed stent in Saphenous vein grafts Investigators. Randomized evaluation of polytetrafluoroethylene-covered stent in saphenous vein grafts: The Randomized Evaluation of polytetrafluoroethylene COVERed stent in Saphenous vein grafts (RECOVERS) Trial. *Circulation*. 2003;108:37-42.
354. Mehilli J, Pache J, Abdel-Wahab M, Schulz S, Byrne RA, Tiroch K, Hausleiter J, Seyfarth M, Ott I, Ibrahim T, Fusaro M, Laugwitz KL, Massberg S, Neumann FJ, Richardt G, Schomig A, Kastrati A, Is Drug-Eluting-Stenting Associated with Improved Results in Coronary Artery Bypass Grafts? (ISAR CABG) Investigators. Drug-eluting versus bare-metal stents in saphenous vein graft lesions (ISAR-CABG): A randomised controlled superiority trial. *Lancet*. 2011;378:1071-1078.
355. Brilakis ES, Lichtenwalter C, de Lemos JA, Roesle M, Obel O, Haagen D, Saeed B, Gadiparthi C, Bissett JK, Sachdeva R, Voudris VV, Karyofillis P, Kar B, Rossen J, Fasseas P, Berger P, Banerjee S. A randomized controlled trial of a paclitaxel-eluting stent versus a similar bare-metal stent in saphenous vein graft lesions the SOS (Stenting of Saphenous Vein Grafts) trial. *J Am Coll Cardiol*. 2009;53:919-928.
356. Vermeersch P, Agostoni P, Verheye S, Van den Heuvel P, Convens C, Bruining N, Van den Branden F, Van Langenhove G; DELAYED RRISC Investigators. Randomized double-blind comparison of sirolimus-eluting stent versus bare-metal stent implantation in diseased saphenous vein grafts: Six-month angiographic, intravascular ultrasound, and clinical follow-up of the RRISC Trial. *J Am Coll Cardiol*. 2006;48:2423-2431.
357. Colleran R, Kufner S, Mehilli J, Rosenbeiger C, Schupke S, Hoppmann P, Joner M, Mankerious N, Fusaro M, Cassese S, Abdel-Wahab M, Neumann FJ, Richardt G, Ibrahim T, Schunkert H, Laugwitz KL, Kastrati A, Byrne RA; ISAR-CABG Investigators. Efficacy over time with drug-eluting stents in saphenous vein graft lesions. *J Am Coll Cardiol*. 2018;71:1973-1982.
358. Brilakis ES, Lichtenwalter C, Abdel-karim AR, de Lemos JA, Obel O, Addo T, Roesle M, Haagen D, Rangan BV, Saeed B, Bissett JK, Sachdeva R, Voudris VV, Karyofillis P, Kar B, Rossen J, Fasseas P, Berger P, Banerjee S. Continued benefit from paclitaxel-eluting compared with bare-metal stent implantation in saphenous vein graft lesions during long-term follow-up of the SOS (Stenting of Saphenous Vein Grafts) trial. *JACC Cardiovasc Interv*. 2011;4:176-182.
359. Vermeersch P, Agostoni P, Verheye S, Van den Heuvel P, Convens C, Van den Branden F, Van Langenhove G; DELAYED RRISC (Death and Events at Long-term follow-up ANALYsis: Extended Duration of the Reduction of Restenosis in Saphenous vein grafts with Cypher stent) Investigators. Increased late mortality after sirolimus-eluting stents versus bare-metal stents in diseased saphenous vein grafts: Results from the randomized DELAYED RRISC Trial. *J Am Coll Cardiol*. 2007;50:261-267.
360. Mehilli J, Byrne RA, Tiroch K, Piniack S, Schulz S, Kufner S, Massberg S, Laugwitz KL, Schomig A, Kastrati A; ISAR-DESIRE 2 Investigators. Randomized trial of paclitaxel-versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents: The ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) study. *J Am Coll Cardiol*. 2010;55:2710-2716.
361. Kastrati A, Mehilli J, von Beckerath N, Dibra A, Hausleiter J, Pache J, Schühlen H, Schmitt C, Dirschinger J, Schomig A; ISAR-DESIRE Investigators. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: A randomized controlled trial. *JAMA*. 2005;293:165-171.
362. Alfonso F, Perez-Vizcayno MJ, Hernandez R, Bethencourt A, Marti V, Lopez-Minguez JR, Angel J, Mantilla R, Moris C, Cequier A, Sabate M, Escaned J, Moreno R, Banuelos C, Suarez A, Macaya C; RIBS-II Investigators. A randomized comparison of sirolimus-eluting stent with balloon angioplasty in patients with in-stent restenosis: Results of the Restenosis Intra-stent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting (RIBS-II) trial. *J Am Coll Cardiol*. 2006;47:2152-2160.
363. Alfonso F, Zueco J, Cequier A, Mantilla R, Bethencourt A, Lopez-Minguez JR, Angel J, Auge JM, Gomez-Recio M, Moris C, Seabra-Gomes R, Perez-Vizcayno MJ, Macaya C, Restenosis Intra-stent: Balloon Angioplasty Versus Elective Stenting (RIBS) Investigators. A randomized comparison of repeat stenting with balloon angioplasty in patients with in-stent restenosis. *J Am Coll Cardiol*. 2003;42:796-805.
364. Dibra A, Kastrati A, Alfonso F, Seyfarth M, Perez-Vizcayno MJ, Mehilli J, Schomig A. Effectiveness of drug-eluting stents in patients with bare-metal in-stent restenosis: Meta-analysis of randomized trials. *J Am Coll Cardiol*. 2007;49:616-623.
365. Scheller B, Clever YP, Kelsch B, Hehrlein C, Bocksch W, Rutsch W, Haghi D, Dietz U, Speck U, Bohm M, Cremers B. Long-term follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *JACC Cardiovasc Interv*. 2012;5:323-330.
366. Scheller B, Hehrlein C, Bocksch W, Rutsch W, Haghi D, Dietz U, Bohm M, Speck U. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med*. 2006;355:2113-2124.
367. Habara S, Iwabuchi M, Inoue N, Nakamura S, Asano R, Nanto S, Hayashi Y, Shiode N, Saito S, Ikari Y, Kimura T, Hosokawa J, Nakamura M, Kotani J, Kozuma K, Mitsudo K. A multicenter randomized comparison of paclitaxel-coated balloon catheter with conventional balloon angioplasty in patients with bare-metal stent restenosis and drug-eluting stent restenosis. *Am Heart J*. 2013;166:527-533.
368. Unverdorben M, Vallbracht C, Cremers B, Heuer H, Hengstenberg C, Maikowski C, Werner GS, Antoni D, Kleber FX, Bocksch W, Leschke M, Ackermann H, Boxberger M, Speck U, Degenhardt R, Scheller B. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation*. 2009;119:2986-2994.
369. Rittger H, Brachmann J, Sinha AM, Waliszewski M, Ohlow M, Brugger A, Thiele H, Birkemeyer R, Kurowski V, Breithardt OA, Schmidt M, Zimmermann S, Lonke S, von Cranach M, Nguyen TV, Daniel WG, Wöhrle J. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: The PEPCAD-DES study. *J Am Coll Cardiol*. 2012;59:1377-1382.
370. Habara S, Mitsudo K, Kadota K, Goto T, Fujii S, Yamamoto H, Katoh H, Oka N, Fuku Y, Hosogi S, Hirono A, Maruo T, Tanaka H,

- Shigemoto Y, Hasegawa D, Tasaka H, Kusunose M, Otsuru S, Okamoto Y, Saito N, Tsujimoto Y, Eguchi H, Miyake K, Yoshino M. Effectiveness of paclitaxel-eluting balloon catheter in patients with sirolimus-eluting stent restenosis. *JACC Cardiovasc Interv.* 2011;4:149-154.
371. Byrne RA, Neumann FJ, Mehilli J, Piniack S, Wolff B, Tiroch K, Schulz S, Fusaro M, Ott I, Ibrahim T, Hausleiter J, Valina C, Pache J, Laugwitz KL, Massberg S, Kastrati A; ISAR-DESIRE 3 Investigators. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): A randomised, open-label trial. *Lancet.* 2013;381:461-467.
372. Indermuehle A, Bahl R, Lansky AJ, Froehlich GM, Knapp G, Timmis A, Meier P. Drug-eluting balloon angioplasty for in-stent restenosis: A systematic review and meta-analysis of randomised controlled trials. *Heart.* 2013;99:327-333.
373. Alfonso F, Perez-Vizcayno MJ, Cardenas A, Garcia Del Blanco B, Seidelberger B, Iniguez A, Gomez-Recio M, Masotti M, Velazquez MT, Sanchis J, Garcia-Touchard A, Zueco J, Bethencourt A, Melgares R, Cequier A, Dominguez A, Mainar V, Lopez-Minguez JR, Moreu J, Marti V, Moreno R, Jimenez-Quevedo P, Gonzalo N, Fernandez C, Macaya C; RIBS V Study Investigators, under the auspices of the Working Group on Interventional Cardiology of the Spanish Society of Cardiology. A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent-in-stent restenosis: The RIBS V Clinical Trial (Restenosis Intra-stent of Bare Metal Stents: Paclitaxel-eluting balloon vs. everolimus-eluting stent). *J Am Coll Cardiol.* 2014;63:1378-1386.
374. Pleva L, Kukla P, Kusnierova P, Zapletalova J, Hlinomaz O. Comparison of the efficacy of paclitaxel-eluting balloon catheters and everolimus-eluting stents in the treatment of coronary in-stent restenosis: The treatment of in-stent restenosis study. *Circ Cardiovasc Interv.* 2016;9:e003316.
375. Alfonso F, Perez-Vizcayno MJ, Cardenas A, Garcia del Blanco B, Garcia-Touchard A, Lopez-Minguez JR, Benedicto A, Masotti M, Zueco J, Iniguez A, Velazquez M, Moreno R, Mainar V, Dominguez A, Pomar F, Melgares R, Rivero F, Jimenez-Quevedo P, Gonzalo N, Fernandez C, Macaya C, RIBS IV Investigators. A prospective randomized trial of drug-eluting balloons versus everolimus-eluting stents in patients with in-stent restenosis of drug-eluting stents: The RIBS IV randomized clinical trial. *J Am Coll Cardiol.* 2015;66:23-33.
376. Baan J Jr, Claessen BE, Dijk KB, Vendrik J, van der Schaaf RJ, Meuwissen M, van Royen N, Gosselink ATM, van Wely MH, Dirkali A, Arkenbout EK, de Winter RJ, Koch KT, Sjaauw KD, Beijk MA, Vis MM, Wykrzykowska JJ, Piek JJ, Tijssen JGP, Henriques JPS. A randomized comparison of paclitaxel-eluting balloon versus everolimus-eluting stent for the treatment of any in-stent restenosis: The DARE trial. *JACC Cardiovasc Interv.* 2018;11:275-283.
377. Kufner S, Joner M, Schneider S, Tolg R, Zrenner B, Repp J, Starkmann A, Xhepa E, Ibrahim T, Cassese S, Fusaro M, Ott I, Hengstenberg C, Schunkert H, Abdel-Wahab M, Laugwitz KL, Kastrati A, Byrne RA; ISAR-DESIRE 4 Investigators. Neointimal modification with scoring balloon and efficacy of drug-coated balloon therapy in patients with restenosis in drug-eluting coronary stents: A randomized controlled trial. *JACC Cardiovasc Interv.* 2017;10:1332-1340.
378. Siontis GC, Stefanini GG, Mavridis D, Siontis KC, Alfonso F, Perez-Vizcayno MJ, Byrne RA, Kastrati A, Meier B, Salanti G, Juni P, Windecker S. Percutaneous coronary interventional strategies for treatment of in-stent restenosis: A network meta-analysis. *Lancet.* 2015;386:655-664.
379. Giacoppo D, Gargiulo G, Aruta P, Capranzano P, Tamburino C, Capodanno D. Treatment strategies for coronary in-stent restenosis: Systematic review and hierarchical Bayesian network meta-analysis of 24 randomised trials and 4880 patients. *BMJ.* 2015;351:h5392.
380. Kufner S, Cassese S, Valeskini M, Neumann FJ, Schulz-Schupke S, Hoppmann P, Fusaro M, Schunkert H, Laugwitz KL, Kastrati A, Byrne RA; ISAR-DESIRE 3 Investigators. Long-term efficacy and safety of paclitaxel-eluting balloon for the treatment of drug-eluting stent restenosis: 3-year results of a randomized controlled trial. *JACC Cardiovasc Interv.* 2015;8:877-884.
381. Xu B, Qian J, Ge J, Wang J, Chen F, Chen J, Wei M, Chen Y, Yang Y, Gao R; PEPCAD China ISR Investigators. Two-year results and subgroup analyses of the PEPCAD China in-stent restenosis trial: A prospective, multicenter, randomized trial for the treatment of drug-eluting stent in-stent restenosis. *Catheter Cardiovasc Interv.* 2016;87:624-629.
382. Byrne RA, Cassese S, Windisch T, King LA, Joner M, Tada T, Mehilli J, Pache J, Kastrati A. Differential relative efficacy between drug-eluting stents in patients with bare metal and drug-eluting stent restenosis; Evidence in support of drug resistance: Insights from the ISAR-DESIRE and ISAR-DESIRE 2 trials. *EuroIntervention.* 2013;9:797-802.
383. Zellweger MJ, Kaiser C, Jeger R, Brunner-La Rocca HP, Buser P, Bader F, Mueller-Brand J, Pfisterer M. Coronary artery disease progression late after successful stent implantation. *J Am Coll Cardiol.* 2012;59:793-799.
384. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med.* 2011;364:226-235.
385. Chechi T, Vecchio S, Vittori G, Giuliani G, Lilli A, Spaziani G, Consoli L, Baldereschi G, Biondi-Zoccai GG, Sheiban I, Margheri M. ST-segment elevation myocardial infarction due to early and late stent thrombosis a new group of high-risk patients. *J Am Coll Cardiol.* 2008;51:2396-23402.
386. Alfonso F, Dutary J, Paulo M, Gonzalo N, Perez-Vizcayno MJ, Jimenez-Quevedo P, Escaned J, Banuelos C, Hernandez R, Macaya C. Combined use of optical coherence tomography and intravascular ultrasound imaging in patients undergoing coronary interventions for stent thrombosis. *Heart.* 2012;98:1213-1220.
387. Adriaenssens T, Joner M, Godschalk TC, Malik N, Alfonso F, Xhepa E, De Cock D, Komukai K, Tada T, Cuesta J, Sirbu V, Feldman LJ, Neumann FJ, Goodall AH, Heestermans T, Buyschaert I, Hlinomaz O, Belmans A, Desmet W, Ten Berg JM, Gershlick AH, Massberg S, Kastrati A, Guagliumi G, Byrne RA; Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort (PRESTIGE) Investigators. Optical coherence tomography findings in patients with coronary stent thrombosis: A report of the PRESTIGE Consortium (Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort). *Circulation.* 2017;136:1007-1021.

388. Armstrong EJ, Feldman DN, Wang TY, Kaltenbach LA, Yeo KK, Wong SC, Spertus J, Shaw RE, Minutello RM, Moussa I, Ho KK, Rogers JH, Shunk KA. Clinical presentation, management, and outcomes of angiographically documented early, late, and very late stent thrombosis. *JACC Cardiovasc Interv.* 2012;5:131-140.
389. Holmes DR Jr, Davis KB, Mock MB, Fisher LD, Gersh BJ, Killip T III, Pettinger M. The effect of medical and surgical treatment on subsequent sudden cardiac death in patients with coronary artery disease: A report from the Coronary Artery Surgery Study. *Circulation.* 1986;73:1254-1263.
390. Long-term results of prospective randomised study of coronary artery bypass surgery in stable angina pectoris. European Coronary Surgery Study Group. *Lancet.* 1982;2:1173-80.
391. Veenhuyzen GD, Singh SN, McAreavey D, Shelton BJ, Exner DV. Prior coronary artery bypass surgery and risk of death among patients with ischemic left ventricular dysfunction. *Circulation.* 2001;104:1489-1493.
392. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML; Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* 2002;346:877-883.
393. Al-Khatib SM, Hellkamp AS, Lee KL, Anderson J, Poole JE, Mark DB, Bardy GH; SCD-HeFT Investigators. Implantable cardioverter defibrillator therapy in patients with prior coronary revascularization in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *J Cardiovasc Electrophysiol.* 2008;19:1059-1065.
394. Sesselberg HW, Moss AJ, McNitt S, Zareba W, Daubert JP, Andrews ML, Hall WJ, McClintic B, Huang DT; MADIT II Research Group. Ventricular arrhythmia storms in postinfarction patients with implantable defibrillators for primary prevention indications: A MADIT-II substudy. *Heart Rhythm.* 2007;4: 1395-1402.
395. Spaulding CM, Joly LM, Rosenberg A, Monchi M, Weber SN, Dhainaut JF, Carli P. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *N Engl J Med.* 1997;336:1629-1633.
396. Kern KB. Optimal treatment of patients surviving out-of-hospital cardiac arrest. *JACC Cardiovasc Interv.* 2012;5:597-605.
397. Garot P, Lefevre T, Eltchaninoff H, Morice MC, Tamion F, Abry B, Lesault PF, Le Tarnec JY, Pouges C, Margenet A, Monchi M, Laurent I, Dumas P, Garot J, Louvard Y. Six-month outcome of emergency percutaneous coronary intervention in resuscitated patients after cardiac arrest complicating ST-elevation myocardial infarction. *Circulation.* 2007;115:1354-1362.
398. Radsel P, Knafelj R, Kocjancic S, Noc M. Angiographic characteristics of coronary disease and postresuscitation electrocardiograms in patients with aborted cardiac arrest outside a hospital. *Am J Cardiol.* 2011;108:634-638.
399. Anyfantakis ZA, Baron G, Aubry P, Himbert D, Feldman LJ, Juliard JM, Ricard-Hibon A, Burnod A, Cokkinos DV, Steg PG. Acute coronary angiographic findings in survivors of out-of-hospital cardiac arrest. *Am Heart J.* 2009;157:312-318.
400. Dumas F, Cariou A, Manzo-Silberman S, Grimaldi D, Vivien B, Rosencher J, Empana JP, Carli P, Mira JP, Jouven X, Spaulding C. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: Insights from the PROCAT (Parisian Region Out of hospital Cardiac Arrest) registry. *Circ Cardiovasc Interv.* 2010;3:200-207.
401. Cronier P, Vignon P, Bouferrache K, Aegerter P, Charron C, Templier F, Castro S, El Mahmoud R, Lory C, Pichon N, Dubourg O, Vieillard-Baron A. Impact of routine percutaneous coronary intervention after out-of-hospital cardiac arrest due to ventricular fibrillation. *Crit Care.* 2011;15:R122.
402. Geri G, Dumas F, Bougouin W, Varenne O, Daviaud F, Pene F, Lambhaut L, Chiche JD, Spaulding C, Mira JP, Empana JP, Cariou A. Immediate percutaneous coronary intervention is associated with improved short- and long-term survival after out-of-hospital cardiac arrest. *Circ Cardiovasc Interv.* 2015;8:e002303.
403. Vyas A, Chan PS, Cram P, Nallamothu BK, McNally B, Girotra S. Early coronary angiography and survival after out-of-hospital cardiac arrest. *Circ Cardiovasc Interv.* 2015;8:e002321.
404. Noc M, Fajadet J, Lassen JF, Kala P, MacCarthy P, Olivecrona GK, Windecker S, Spaulding C. Invasive coronary treatment strategies for out-of-hospital cardiac arrest: A consensus statement from the European Association for Percutaneous Cardiovascular Interventions (EAPCI)/Stent for Life (SFL) groups. *EuroIntervention.* 2014;10:31-37.
405. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37: 2893-2962.
406. Chan W, Ajani AE, Clark DJ, Stub D, Andrianopoulos N, Brennan AL, New G, Sebastian M, Johnston R, Walton A, Reid CM, Dart AM, Duffy SJ, Melbourne Interventional Group Investigators. Impact of periprocedural atrial fibrillation on short-term clinical outcomes following percutaneous coronary intervention. *Am J Cardiol.* 2012;109:471-477.
407. Lopes RD, Elliott LE, White HD, Hochman JS, Van de Werf F, Ardissino D, Nielsen TT, Weaver WD, Widimsky P, Armstrong PW, Granger CB. Antithrombotic therapy and outcomes of patients with atrial fibrillation following primary percutaneous coronary intervention: Results from the APEX-AMI trial. *Eur Heart J.* 2009;30:2019-2028.
408. Mrdovic I, Savic L, Krljanac G, Perunicic J, Asanin M, Lasica R, Antonijevic N, Kocev N, Marinkovic J, Vasiljevic Z, Ostojic M. Incidence, predictors, and 30-day outcomes of new-onset atrial fibrillation after primary percutaneous coronary intervention: Insight into the RISK-PCI trial. *Coron Artery Dis.* 2012;23:1-8.
409. Pilgrim T, Kalesan B, Zanchin T, Pulver C, Jung S, Mattle H, Carrel T, Moschovitis A, Stortecky S, Wenaweser P, Stefanini GG, Raber L, Meier B, Juni P, Windecker S. Impact of atrial fibrillation on clinical outcomes among patients with coronary artery disease undergoing revascularisation with drug-eluting stents. *EuroIntervention.* 2013;8:1061-1071.
410. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the

- European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018;39:213-260.
411. Ahlsson AJ, Bodin L, Lundblad OH, Englund AG. Postoperative atrial fibrillation is not correlated to C-reactive protein. *Ann Thorac Surg*. 2007;83:1332-1337.
412. Arsenault KA, Yusuf AM, Crystal E, Healey JS, Morillo CA, Nair GM, Whitlock RP. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. *Cochrane Database Syst Rev*. 2013;1:CD003611.
413. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, Barash PG, Hsu PH, Mangano DT; Investigators of the Ischemia Research and Education Foundation; Multicenter Study of Perioperative Ischemia Research Group. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA*. 2004;291:1720-1729.
414. Shen J, Lall S, Zheng V, Buckley P, Damiano RJ Jr, Schuessler RB. The persistent problem of new-onset postoperative atrial fibrillation: A single-institution experience over two decades. *J Thorac Cardiovasc Surg*. 2011;141:559-570.
415. LaPar DJ, Speir AM, Crosby IK, Fonner E Jr, Brown M, Rich JB, Quader M, Kern JA, Kron IL, Ailawadi G, Investigators for the Virginia Cardiac Surgery Quality Initiative. Postoperative atrial fibrillation significantly increases mortality, hospital readmission, and hospital costs. *Ann Thorac Surg*. 2014;98: 527-533.
416. Saxena A, Dinh DT, Smith JA, Shardey GC, Reid CM, Newcomb AE. Usefulness of postoperative atrial fibrillation as an independent predictor for worse early and late outcomes after isolated coronary artery bypass grafting (multicenter Australian study of 19,497 patients). *Am J Cardiol*. 2012;109:219-225.
417. Steinberg BA, Zhao Y, He X, Hernandez AF, Fullerton DA, Thomas KL, Mills R, Klaskala W, Peterson ED, Piccini JP. Management of postoperative atrial fibrillation and subsequent outcomes in contemporary patients undergoing cardiac surgery: Insights from the Society of Thoracic Surgeons CAPS-Care Atrial Fibrillation Registry. *Clin Cardiol*. 2014;37:7-13.
418. Ahlsson A, Bodin L, Fengsrud E, Englund A. Patients with postoperative atrial fibrillation have a doubled cardiovascular mortality. *Scand Cardiovasc J*. 2009;43:330-336.
419. Ahlsson A, Fengsrud E, Bodin L, Englund A. Postoperative atrial fibrillation in patients undergoing aortocoronary bypass surgery carries an eightfold risk of future atrial fibrillation and a doubled cardiovascular mortality. *Eur J Cardiothorac Surg*. 2010;37:1353-1359.
420. Gialdini G, Nearing K, Bhavé PD, Bonuccelli U, Iadecola C, Healey JS, Kamel H. Perioperative atrial fibrillation and the long-term risk of ischemic stroke. *JAMA*. 2014;312:616-622.
421. Mariscalco G, Klersy C, Zanobini M, Banach M, Ferrarese S, Borsani P, Cantore C, Biglioli P, Sala A. Atrial fibrillation after isolated coronary surgery affects late survival. *Circulation*. 2008;118:1612-1618.
422. Villareal RP, Hariharan R, Liu BC, Kar B, Lee VV, Elayda M, Lopez JA, Rasekh A, Wilson JM, Massumi A. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. *J Am Coll Cardiol*. 2004;43:742-748.
423. Burgess DC, Kilborn MJ, Keech AC. Interventions for prevention of post-operative atrial fibrillation and its complications after cardiac surgery: A meta-analysis. *Eur Heart J*. 2006;27:2846-2857.
424. Connolly SJ, Cybulsky I, Lamy A, Roberts RS, O'Brien B, Carroll S, Crystal E, Thorpe KE, Gent M, Beta-Blocker Length Of Stay (BLOS) study. Double-blind, placebo-controlled, randomized trial of prophylactic metoprolol for reduction of hospital length of stay after heart surgery: the beta-Blocker Length Of Stay (BLOS) study. *Am Heart J*. 2003;145:226-232.
425. Crystal E, Connolly SJ, Sleik K, Ginger TJ, Yusuf S. Interventions on prevention of postoperative atrial fibrillation in patients undergoing heart surgery: A meta-analysis. *Circulation*. 2002;106:75-80.
426. Dunning J, Treasure T, Versteegh M, Nashef SA; EACTS Audit and Guidelines Committee. Guidelines on the prevention and management of de novo atrial fibrillation after cardiac and thoracic surgery. *Eur J Cardiothorac Surg*. 2006;30:852-872.
427. Koniari I, Apostolakis E, Rogkakou C, Baikoussis NG, Dougenis D. Pharmacologic prophylaxis for atrial fibrillation following cardiac surgery: A systematic review. *J Cardiothorac Surg*. 2010;5:121.
428. Lucio Ede A, Flores A, Blacher C, Leaes PE, Lucchese FA, Ribeiro JP. Effectiveness of metoprolol in preventing atrial fibrillation and flutter in the postoperative period of coronary artery bypass graft surgery. *Arq Bras Cardiol*. 2004;82:42-46, 37-41.
429. Tsuboi J, Kawazoe K, Izumoto H, Okabayashi H. Postoperative treatment with carvedilol, a beta-adrenergic blocker, prevents paroxysmal atrial fibrillation after coronary artery bypass grafting. *Circ J*. 2008;72:588-591.
430. Anderson E, Dyke C, Levy JH. Anticoagulation strategies for the management of postoperative atrial fibrillation. *Clin Lab Med*. 2014;34:537-561.
431. El-Chami MF, Kilgo P, Thourani V, Lattouf OM, Delurgio DB, Guyton RA, Leon AR, Puskas JD. New-onset atrial fibrillation predicts long-term mortality after coronary artery bypass graft. *J Am Coll Cardiol*. 2010;55:1370-1376.
432. Melduni RM, Schaff HV, Lee HC, Gersh BJ, Noseworthy PA, Bailey KR, Ammash NM, Cha SS, Fatema K, Wysokinski WE, Seward JB, Packer DL, Rihal CS, Asirvatham SJ. Impact of left atrial appendage closure during cardiac surgery on the occurrence of early postoperative atrial fibrillation, stroke, and mortality: A propensity score-matched analysis of 10 633 patients. *Circulation*. 2017;135:366-378.
433. Tsai YC, Phan K, Munkholm-Larsen S, Tian DH, La Meir M, Yan TD. Surgical left atrial appendage occlusion during cardiac surgery for patients with atrial fibrillation: A meta-analysis. *Eur J Cardiothorac Surg*. 2015;47:847-854.
434. Friedman DJ, Piccini JP, Wang T, Zheng J, Malaisrie SC, Holmes DR, Suri RM, Mack MJ, Badhwar V, Jacobs JP, Gaca JG, Chow SC, Peterson ED, Brennan JM. Association between left atrial appendage occlusion and readmission for thromboembolism among patients with atrial fibrillation undergoing concomitant cardiac surgery. *JAMA*. 2018;319:365-374.
435. Whitlock R, Healey J, Vincent J, Brady K, Teoh K, Royse A, Shah P, Guo Y, Alings M, Folkeringa RJ, Paparella D, Colli A, Meyer SR, Legare JF, Lamontagne F, Reents W, Boning A, Connolly S. Rationale and design of the Left Atrial Appendage Occlusion Study (LAAOS) III. *Ann Cardiothorac Surg*. 2014;3:45-54.
436. Kern KB, Rahman O. Emergent percutaneous coronary intervention for resuscitated victims of out-of-hospital cardiac arrest. *Catheter Cardiovasc Interv*. 2010;75:616-624.

437. Garcia-Tejada J, Jurado-Roman A, Rodriguez J, Velazquez M, Hernandez F, Albarran A, Martin-Asenjo R, Granda-Nistal C, Coma R, Tascon J. Post-resuscitation electrocardiograms, acute coronary findings and in-hospital prognosis of survivors of out-of-hospital cardiac arrest. *Resuscitation*. 2014;85:1245-1250.
438. Khan MF, Wendel CS, Movahed MR. Prevention of post-coronary artery bypass grafting (CABG) atrial fibrillation: Efficacy of prophylactic beta-blockers in the modern era: A meta-analysis of latest randomized controlled trials. *Ann Noninvasive Electrocardiol*. 2013;18:58-68.
439. Chatterjee S, Sardar P, Mukherjee D, Lichstein E, Aikat S. Timing and route of amiodarone for prevention of postoperative atrial fibrillation after cardiac surgery: A network regression meta-analysis. *Pacing Clin Electrophysiol*. 2013;36:1017-1023.
440. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: The Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012;33:1500-1510.
441. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The euro heart survey on atrial fibrillation. *Chest*. 2010;137:263-272.
442. Gillinov AM, Bagiella E, Moskowitz AJ, Raiten JM, Groh MA, Bowdish ME, Ailawadi G, Kirkwood KA, Perrault LP, Parides MK, Smith RL II, Kern JA, Dussault G, Hackmann AE, Jeffries NO, Miller MA, Taddei-Peters WC, Rose EA, Weisel RD, Williams DL, Mangusan RF, Argenziano M, Moquete EG, O'Sullivan KL, Pellerin M, Shah KJ, Gammie JS, Mayer ML, Voisine P, Gelijns AC, O'Gara PT, Mack MJ, CTSN. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. *N Engl J Med*. 2016;374:1911-1921.
443. Head SJ, Milojevic M, Taggart DP, Puskas JD. Current practice of state-of-the-art surgical coronary revascularization. *Circulation*. 2017;136:1331-1345.
444. Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA), Boer C, Meesters MI, Milojevic M, Benedetto U, Bolliger D, von Heymann C, Jeppsson A, Koster A, Osnabrugge RL, Ranucci M, Ravn HB, Vonk ABA, Wahba A, Pagano D. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. *J Cardiothorac Vasc Anesth*. 2018;32:88-120.
445. Head SJ, Mack MJ, Holmes DR Jr, Mohr FW, Morice MC, Serruys PW, Kappetein AP. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: A subgroup analysis of 3-year SYNTAX data. *Eur J Cardiothorac Surg*. 2012;41:535-541.
446. Kim YH, Park DW, Lee JY, Kim WJ, Yun SC, Ahn JM, Song HG, Oh JH, Park JS, Kang SJ, Lee SW, Lee CW, Park SW, Park SJ. Impact of angiographic complete revascularization after drug-eluting stent implantation or coronary artery bypass graft surgery for multivessel coronary artery disease. *Circulation*. 2011;123:2373-2381.
447. Mohammadi S, Kalavrouziotis D, Dagenais F, Voisine P, Charbonneau E. Completeness of revascularization and survival among octogenarians with triple-vessel disease. *Ann Thorac Surg*. 2012;93:1432-1437.
448. Rastan AJ, Walther T, Falk V, Kempfert J, Merk D, Lehmann S, Holzhey D, Mohr FW. Does reasonable incomplete surgical revascularization affect early or long-term survival in patients with multivessel coronary artery disease receiving left internal mammary artery bypass to left anterior descending artery? *Circulation*. 2009;120:S70-S77.
449. Yi G, Youn YN, Joo HC, Hong S, Yoo KJ. Association of incomplete revascularization with long-term survival after off-pump coronary artery bypass grafting. *J Surg Res*. 2013;185:166-173.
450. Scott R, Blackstone EH, McCarthy PM, Lytle BW, Loop FD, White JA, Cosgrove DM. Isolated bypass grafting of the left internal thoracic artery to the left anterior descending coronary artery: Late consequences of incomplete revascularization. *J Thorac Cardiovasc Surg*. 2000;120:173-184.
451. Melby SJ, Saint LL, Balsara K, Itoh A, Lawton JS, Maniar H, Pasque MK, Damiano RJ Jr, Moon MR. Complete coronary revascularization improves survival in octogenarians. *Ann Thorac Surg*. 2016;102:505-511.
452. Botman CJ, Schonberger J, Koolen S, Penn O, Botman H, Dib N, Eeckhout E, Pijls N. Does stenosis severity of native vessels influence bypass graft patency? A prospective fractional flow reserve-guided study. *Ann Thorac Surg*. 2007;83:2093-2097.
453. Boylan MJ, Lytle BW, Loop FD, Taylor PC, Borsh JA, Goormastic M, Cosgrove DM. Surgical treatment of isolated left anterior descending coronary stenosis. Comparison of left internal mammary artery and venous autograft at 18 to 20 years of follow-up. *J Thorac Cardiovasc Surg*. 1994;107:657-662.
454. Sabik JF III, Blackstone EH, Gillinov AM, Banbury MK, Smedira NG, Lytle BW. Influence of patient characteristics and arterial grafts on freedom from coronary reoperation. *J Thorac Cardiovasc Surg*. 2006;131:90-98.
455. Schmitto JD, Rajab TK, Cohn LH. Prevalence and variability of internal mammary graft use in contemporary multivessel coronary artery bypass graft. *Curr Opin Cardiol*. 2010;25:609-612.
456. Hess CN, Lopes RD, Gibson CM, Hager R, Wojdyla DM, Englum BR, Mack MJ, Califf RM, Kouchoukos NT, Peterson ED, Alexander JH. Saphenous vein graft failure after coronary artery bypass surgery: Insights from PREVENT IV. *Circulation*. 2014;130:1445-1451.
457. Benedetto U, Raja SG, Albanese A, Amrani M, Biondi-Zoccai G, Frati G. Searching for the second best graft for coronary artery bypass surgery: A network meta-analysis of randomized controlled trials. *Eur J Cardiothorac Surg*. 2015;47:59-65.
458. Dorman MJ, Kurlansky PA, Traad EA, Galbut DL, Zucker M, Ebra G. Bilateral internal mammary artery grafting enhances survival in diabetic patients: A 30-year follow-up of propensity score-matched cohorts. *Circulation*. 2012;126:2935-2942.
459. Galbut DL, Kurlansky PA, Traad EA, Dorman MJ, Zucker M, Ebra G. Bilateral internal thoracic artery grafting improves long-term survival in patients with reduced ejection fraction: A propensity-matched study with 30-year follow-up. *J Thorac Cardiovasc Surg*. 2012;143:844-853.e4.
460. Grau JB, Ferrari G, Mak AW, Shaw RE, Brizzio ME, Mindich BP, Strobeck J, Zapolanski A. Propensity matched analysis of bilateral internal mammary artery versus single left internal

- mammary artery grafting at 17-year follow-up: Validation of a contemporary surgical experience. *Eur J Cardiothorac Surg.* 2012;41:770-775.
461. Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M, Ebra G. Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups. *Ann Thorac Surg.* 2010;90:101-108.
462. Lytle BW. Bilateral internal thoracic artery grafting. *Ann Cardiothorac Surg.* 2013;2:485-492.
463. Ruttman E, Fischler N, Sakic A, Chevchik O, Alber H, Schistek R, Ulmer H, Grimm M. Second internal thoracic artery versus radial artery in coronary artery bypass grafting: A long-term, propensity score-matched follow-up study. *Circulation.* 2011;124:1321-1329.
464. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: A systematic review of studies comparing bilateral and single internal mammary arteries. *Lancet.* 2001;358:870-875.
465. Weiss AJ, Zhao S, Tian DH, Taggart DP, Yan TD. A meta-analysis comparing bilateral internal mammary artery with left internal mammary artery for coronary artery bypass grafting. *Ann Cardiothorac Surg.* 2013;2:390-400.
466. Gaudino M, Di Franco A, Rahouma M, Tam DY, Iannaccone M, Deb S, D'Ascenzo F, Abouarab AA, Girardi LN, Taggart DP, Fremes SE. Unmeasured confounders in observational studies comparing bilateral versus single internal thoracic artery for coronary artery bypass grafting: A meta-analysis. *J Am Heart Assoc.* 2018;7:e008010.
467. Taggart DP, Altman DG, Gray AM, Lees B, Gerry S, Benedetto U, Flather M; Arterial Revascularization Trial Investigators. Randomized trial of bilateral versus single internal-thoracic-artery grafts. *N Engl J Med.* 2016;375:2540-2549.
468. Gaudino M, Tranbaugh R, Fremes S. Bilateral versus single internal-thoracic-artery grafts. *N Engl J Med.* 2017;376:e37.
469. Raza S, Blackstone EH, Sabik JF, III. Bilateral versus single internal-thoracic-artery grafts. *N Engl J Med.* 2017;376:e37.
470. Royse A, Eccleston D, Royse C; iGRAFT Collaborators. Bilateral versus single internal-thoracic-artery grafts. *N Engl J Med.* 2017;376:e37.
471. Deo SV, Shah IK, Dunlay SM, Erwin PJ, Locker C, Altarabsheh SE, Boilson BA, Park SJ, Joyce LD. Bilateral internal thoracic artery harvest and deep sternal wound infection in diabetic patients. *Ann Thorac Surg.* 2013;95:862-869.
472. Elmistekawy EM, Gawad N, Bourke M, Mesana T, Boodhwani M, Rubens FD. Is bilateral internal thoracic artery use safe in the elderly? *J Card Surg.* 2012;27:1-5.
473. Hemo E, Mohr R, Uretzky G, Katz G, Popovits N, Pevni D, Medalion B. Long-term outcomes of patients with diabetes receiving bilateral internal thoracic artery grafts. *J Thorac Cardiovasc Surg.* 2013;146:586-592.
474. Taggart DP, Lees B, Gray A, Altman DG, Flather M, Channon K; ART Investigators. Protocol for the Arterial Revascularisation Trial (ART). A randomised trial to compare survival following bilateral versus single internal mammary grafting in coronary revascularisation [ISRCTN46552265]. *Trials.* 2006;7:7.
475. Toumpoulis IK, Theakos N, Dunning J. Does bilateral internal thoracic artery harvest increase the risk of mediastinitis? *Interact Cardiovasc Thorac Surg.* 2007;6:787-791.
476. Benedetto U, Altman DG, Gerry S, Gray A, Lees B, Pawlaczyk R, Flather M, Taggart DP; Arterial Revascularization Trial Investigators. Pedicled and skeletonized single and bilateral internal thoracic artery grafts and the incidence of sternal wound complications: Insights from the Arterial Revascularization Trial. *J Thorac Cardiovasc Surg.* 2016;152:270-276.
477. Hayward PA, Gordon IR, Hare DL, Matalanis G, Horrigan ML, Rosalion A, Buxton BF. Comparable patencies of the radial artery and right internal thoracic artery or saphenous vein beyond 5 years: Results from the Radial Artery Patency and Clinical Outcomes trial. *J Thorac Cardiovasc Surg.* 2010;139:60-5; discussion 65-67.
478. Schwann TA, Engoren M, Bonnell M, Clancy C, Habib RH. Comparison of late coronary artery bypass graft survival effects of radial artery versus saphenous vein grafting in male and female patients. *Ann Thorac Surg.* 2012;94:1485-1491.
479. Tranbaugh RF, Dimitrova KR, Friedmann P, Geller CM, Harris LJ, Stelzer P, Cohen B, Hoffman DM. Radial artery conduits improve long-term survival after coronary artery bypass grafting. *Ann Thorac Surg.* 2010;90:1165-1172.
480. Tranbaugh RF, Dimitrova KR, Friedmann P, Geller CM, Harris LJ, Stelzer P, Cohen BM, Ko W, DeCastro H, Lucido D, Hoffman DM. Coronary artery bypass grafting using the radial artery: Clinical outcomes, patency, and need for reintervention. *Circulation.* 2012;126:S170-S175.
481. Cao C, Manganas C, Horton M, Bannon P, Munkholm-Larsen S, Ang SC, Yan TD. Angiographic outcomes of radial artery versus saphenous vein in coronary artery bypass graft surgery: A meta-analysis of randomized controlled trials. *J Thorac Cardiovasc Surg.* 2013;146:255-261.
482. Gaudino M, Benedetto U, Fremes S, Biondi-Zoccai G, Sedrakyan A, Puskas JD, Angelini GD, Buxton B, Frati G, Hare DL, Hayward P, Nasso G, Moat N, Peric M, Yoo KJ, Speziale G, Girardi LN, Taggart DP; RADIAL Investigators. Radial-artery or saphenous-vein grafts in coronary-artery bypass surgery. *N Engl J Med.* 2018;378:2069-2077.
483. Lytle BW. Skeletonized internal thoracic artery grafts and wound complications. *J Thorac Cardiovasc Surg.* 2001;121:625-627.
484. Sa MP, Ferraz PE, Escobar RR, Vasconcelos FP, Ferraz AA, Braile DM, Lima RC. Skeletonized versus pedicled internal thoracic artery and risk of sternal wound infection after coronary bypass surgery: Meta-analysis and meta-regression of 4817 patients. *Interact Cardiovasc Thorac Surg.* 2013;16:849-857.
485. Sakic A, Chevchik O, Kilo J, Schistek R, Mueller LC, Ulmer H, Grimm M, Ruttman E. Simple adaptations of surgical technique to critically reduce the risk of postoperative sternal complications in patients receiving bilateral internal thoracic arteries. *Interact Cardiovasc Thorac Surg.* 2013;17:378-382.
486. Wendler O, Hennen B, Markwirth T, Konig J, Tscholl D, Huang Q, Shahangi E, Schafers HJ. T grafts with the right internal thoracic artery to left internal thoracic artery versus the left internal thoracic artery and radial artery: Flow dynamics in the internal thoracic artery main stem. *J Thorac Cardiovasc Surg.* 1999;118:841-848.
487. Kajimoto K, Yamamoto T, Amano A. Coronary artery bypass revascularization using bilateral internal thoracic arteries in diabetic patients: A systematic review and meta-analysis. *Ann Thorac Surg.* 2015;99:1097-1104.

488. Sa MP, Cavalcanti PE, Santos HJ, Soares AF, Miranda RG, Araujo ML, Lima RC. Flow capacity of skeletonized versus pedicled internal thoracic artery in coronary artery bypass graft surgery: Systematic review, meta-analysis and meta-regression. *Eur J Cardiothorac Surg.* 2015;48:25-31.
489. Navia JL, Olivares G, Ehasz P, Gillinov AM, Svensson LG, Brozzi N, Lytle B. Endoscopic radial artery harvesting procedure for coronary artery bypass grafting. *Ann Cardiothorac Surg.* 2013;2:557-564.
490. Cao C, Tian DH, Ang SC, Peeceeyen S, Allan J, Fu B, Yan TD. A meta-analysis of endoscopic versus conventional open radial artery harvesting for coronary artery bypass graft surgery. *Innovations (Phila).* 2014;9:269-275.
491. Gaudino M, Leone A, Lupascu A, Toesca A, Mazza A, Ponziani FR, Flore R, Tondi P, Massetti M. Morphological and functional consequences of transradial coronary angiography on the radial artery: Implications for its use as a bypass conduit. *Eur J Cardiothorac Surg.* 2015;48:370-374.
492. Ouzounian M, Hassan A, Buth KJ, MacPherson C, Ali IM, Hirsch GM, Ali IS. Impact of endoscopic versus open saphenous vein harvest techniques on outcomes after coronary artery bypass grafting. *Ann Thorac Surg.* 2010;89:403-408.
493. Yun KL, Wu Y, Aharonian V, Mansukhani P, Pfeffer TA, Sintek CF, Kochamba GS, Grunkemeier G, Khonsari S. Randomized trial of endoscopic versus open vein harvest for coronary artery bypass grafting: Six-month patency rates. *J Thorac Cardiovasc Surg.* 2005;129:496-503.
494. Chernyavskiy A, Volkov A, Lavrenyuk O, Terekhov I, Kareva Y. Comparative results of endoscopic and open methods of vein harvesting for coronary artery bypass grafting: A prospective randomized parallel-group trial. *J Cardiothorac Surg.* 2015; 10:163.
495. Krishnamoorthy B, Critchley WR, Glover AT, Nair J, Jones MT, Waterworth PD, Fildes JE, Yonan N. A randomized study comparing three groups of vein harvesting methods for coronary artery bypass grafting: endoscopic harvest versus standard bridging and open techniques. *Interact Cardiovasc Thorac Surg.* 2012;15:224-228.
496. Lopes RD, Hafley GE, Allen KB, Ferguson TB, Peterson ED, Harrington RA, Mehta RH, Gibson CM, Mack MJ, Kouchoukos NT, Califf RM, Alexander JH. Endoscopic versus open vein-graft harvesting in coronary-artery bypass surgery. *N Engl J Med.* 2009;361: 235-244.
497. Zenati MA, Shroyer AL, Collins JF, Hattler B, Ota T, Almassi GH, Amidi M, Novitzky D, Grover FL, Sonel AF. Impact of endoscopic versus open saphenous vein harvest technique on late coronary artery bypass grafting patient outcomes in the ROOBY (Randomized On/Off Bypass) Trial. *J Thorac Cardiovasc Surg.* 2011;141:338-434.
498. Andreasen JJ, Vadmann H, Oddershede L, Tilsted HH, Frokjaer JB, Jensen SE. Decreased patency rates following endoscopic vein harvest in coronary artery bypass surgery. *Scand Cardiovasc J.* 2015;49:286-292.
499. Deppe AC, Liakopoulos OJ, Choi YH, Slottosch I, Kuhn EW, Scherner M, Stange S, Wahlers T. Endoscopic vein harvesting for coronary artery bypass grafting: A systematic review with meta-analysis of 27,789 patients. *J Surg Res.* 2013;180:114-124.
500. Williams JB, Peterson ED, Brennan JM, Sedrakyan A, Tavis D, Alexander JH, Lopes RD, Dokholyan RS, Zhao Y, O'Brien SM, Michler RE, Thourani VH, Edwards FH, Duggirala H, Gross T, Marinac-Dabic D, Smith PK. Association between endoscopic vs open vein-graft harvesting and mortality, wound complications, and cardiovascular events in patients undergoing CABG surgery. *JAMA.* 2012;308:475-484.
501. Brown EN, Kon ZN, Tran R, Burris NS, Gu J, Laird P, Brazio PS, Kallam S, Schwartz K, Bechtel L, Joshi A, Zhang S, Poston RS. Strategies to reduce intraluminal clot formation in endoscopically harvested saphenous veins. *J Thorac Cardiovasc Surg.* 2007;134:1259-1265.
502. Khaleel MS, Dorheim TA, Duryee MJ, Durbin HE Jr, Bussey WD, Garvin RP, Klassen LW, Thiele GM, Anderson DR. High-pressure distention of the saphenous vein during preparation results in increased markers of inflammation: A potential mechanism for graft failure. *Ann Thorac Surg.* 2012;93:552-558.
503. Rousou LJ, Taylor KB, Lu XG, Healey N, Crittenden MD, Khuri SF, Thatté HS. Saphenous vein conduits harvested by endoscopic technique exhibit structural and functional damage. *Ann Thorac Surg.* 2009;87:62-70.
504. Johansson BL, Souza DS, Bodin L, Filbey D, Loesch A, Geijer H, Bojo L. Slower progression of atherosclerosis in vein grafts harvested with 0 touch0 technique compared with conventional harvesting technique in coronary artery bypass grafting: An angiographic and intravascular ultrasound study. *Eur J Cardiothorac Surg.* 2010;38:414-419.
505. Souza DS, Dashwood MR, Tsui JC, Filbey D, Bodin L, Johansson B, Borowiec J. Improved patency in vein grafts harvested with surrounding tissue: Results of a randomized study using three harvesting techniques. *Ann Thorac Surg.* 2002;73: 1189-1195.
506. Dreifaldt M, Mannion JD, Bodin L, Olsson H, Zagodzón L, Souza D. The no-touch saphenous vein as the preferred second conduit for coronary artery bypass grafting. *Ann Thorac Surg.* 2013;96: 105-111.
507. Samano N, Geijer H, Liden M, Fremes S, Bodin L, Souza D. The no-touch saphenous vein for coronary artery bypass grafting maintains a patency, after 16 years, comparable to the left internal thoracic artery: A randomized trial. *J Thorac Cardiovasc Surg.* 2015;150:880-888.
508. Emmert MY, Seifert B, Wilhelm M, Grunenfelder J, Falk V, Salzberg SP. Aortic no-touch technique makes the difference in off-pump coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2011;142:1499-1506.
509. Borgermann J, Hakim K, Renner A, Parsa A, Aboud A, Becker T, Masshoff M, Zittermann A, Gummert JF, Kuss O. Clamless off-pump versus conventional coronary artery revascularization: A propensity score analysis of 788 patients. *Circulation.* 2012;126:S176-S182.
510. Misfeld M, Brereton RJ, Sweetman EA, Doig GS. Neurologic complications after off-pump coronary artery bypass grafting with and without aortic manipulation: Meta-analysis of 11,398 cases from 8 studies. *J Thorac Cardiovasc Surg.* 2011;142: e11-e17.
511. Guerrieri Wolf L, Abu-Omar Y, Choudhary BP, Pigott D, Taggart DP. Gaseous and solid cerebral microembolization during proximal aortic anastomoses in off-pump coronary surgery: The effect of an aortic side-biting clamp and two clamless devices. *J Thorac Cardiovasc Surg.* 2007;133:485-493.

512. El Zayat H, Puskas JD, Hwang S, Thourani VH, Lattouf OM, Kilgo P, Halkos ME. Avoiding the clamp during off-pump coronary artery bypass reduces cerebral embolic events: Results of a prospective randomized trial. *Interact Cardiovasc Thorac Surg.* 2012;14:12-16.
513. Kieser TM, Rose S, Kowalewski R, Belenkie I. Transit-time flow predicts outcomes in coronary artery bypass graft patients: A series of 1000 consecutive arterial grafts. *Eur J Cardiothorac Surg.* 2010;38:155-162.
514. Mujanovic E, Kabil E, Bergsland J. Transit time flowmetry in coronary surgery-an important tool in graft verification. *Bosn J Basic Med Sci.* 2007;7:275-8.
515. Jokinen JJ, Werkkala K, Vainikka T, Perakyla T, Simpanen J, Ihlberg L. Clinical value of intra-operative transit-time flow measurement for coronary artery bypass grafting: A prospective angiography-controlled study. *Eur J Cardiothorac Surg.* 2011;39:918-923.
516. Lehnert P, Moller CH, Damgaard S, Gerds TA, Steinbruchel DA. Transit-time flow measurement as a predictor of coronary bypass graft failure at one year angiographic follow-up. *J Card Surg.* 2015;30:47-52.
517. Niclauss L. Techniques and standards in intraoperative graft verification by transit time flow measurement after coronary artery bypass graft surgery: A critical review. *Eur J Cardiothorac Surg.* 2017;51:26-33.
518. Diegeler A, Borgermann J, Kappert U, Breuer M, Boning A, Ursulescu A, Rastan A, Holzhey D, Treede H, Riess FC, Veeckmann P, Asfoor A, Reents W, Zacher M, Hilker M, Group GS. Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. *N Engl J Med.* 2013;368:1189-1198.
519. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes JC, Novick RJ, Vijayanath P, Reddy S, Tao L, Olavegogeoascoechea PA, Airan B, Sulling TA, Whitlock RP, Ou Y, Ng J, Chrolavicius S, Yusuf S, CORONARY Investigators. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *N Engl J Med.* 2012;366:1489-1497.
520. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes JC, Novick RJ, Vijayanath P, Reddy SK, Tao L, Olavegogeoascoechea PA, Airan B, Sulling TA, Whitlock RP, Ou Y, Pogue J, Chrolavicius S, Yusuf S, CORONARY Investigators. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. *N Engl J Med.* 2013;368:1179-1188.
521. Hattler B, Messenger JC, Shroyer AL, Collins JF, Haugen SJ, Garcia JA, Baltz JH, Cleveland JC Jr, Novitzky D, Grover FL, Veterans Affairs Randomized On/Off Bypass (ROOBY) Study Group. Off-pump coronary artery bypass surgery is associated with worse arterial and saphenous vein graft patency and less effective revascularization: Results from the Veterans Affairs Randomized On/Off Bypass (ROOBY) trial. *Circulation.* 2012;125:2827-2835.
522. Houliand K, Kjeldsen BJ, Madsen SN, Rasmussen BS, Holme SJ, Nielsen PH, Mortensen PE; DOORS Group. On-pump versus off-pump coronary artery bypass surgery in elderly patients: Results from the Danish on-pump versus off-pump randomization study. *Circulation.* 2012;125:2431-2439.
523. Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E, Lucke JC, Baltz JH, Novitzky D; Veterans Affairs Randomized On/Off Bypass (ROOBY) Study Group. On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med.* 2009;361:1827-1837.
524. Keeling WB, Kilgo PD, Puskas JD, Halkos ME, Lattouf OM, Guyton RA, Thourani VH. Off-pump coronary artery bypass grafting attenuates morbidity and mortality for patients with low and high body mass index. *J Thorac Cardiovasc Surg.* 2013;146:1442-1448.
525. Puskas JD, Thourani VH, Kilgo P, Cooper W, Vassiliades T, Vega JD, Morris C, Chen E, Schmotzer BJ, Guyton RA, Lattouf OM. Off-pump coronary artery bypass disproportionately benefits high-risk patients. *Ann Thorac Surg.* 2009;88:1142-1147.
526. Puskas JD, Williams WH, O'Donnell R, Patterson RE, Sigman SR, Smith AS, Baio KT, Kilgo PD, Guyton RA. Off-pump and on-pump coronary artery bypass grafting are associated with similar graft patency, myocardial ischemia, and freedom from re-intervention: Long-term follow-up of a randomized trial. *Ann Thorac Surg.* 2011;91:1836-1842; discussion 1842-1843.
527. Sedrakyan A, Wu AW, Parashar A, Bass EB, Treasure T. Off-pump surgery is associated with reduced occurrence of stroke and other morbidity as compared with traditional coronary artery bypass grafting: A meta-analysis of systematically reviewed trials. *Stroke.* 2006;37:2759-2769.
528. Altarabsheh SE, Deo SV, Rababa'h AM, Lim JY, Cho YH, Sharma V, Jung SH, Shin E, Markowitz AH, Park SJ. Off-pump coronary artery bypass reduces early stroke in octogenarians: A meta-analysis of 18,000 patients. *Ann Thorac Surg.* 2015;99:1568-1575.
529. Chawla LS, Zhao Y, Lough FC, Schroeder E, Seneff MG, Brennan JM. Off-pump versus on-pump coronary artery bypass grafting outcomes stratified by preoperative renal function. *J Am Soc Nephrol.* 2012;23:1389-1397.
530. Head SJ, Borgermann J, Osnabrugge RL, Kieser TM, Falk V, Taggart DP, Puskas JD, Gummert JF, Kappetein AP. Coronary artery bypass grafting: Part 2-optimizing outcomes and future prospects. *Eur Heart J.* 2013;34:2873-2886.
531. Diegeler A, Walther T, Metz S, Falk V, Krakor R, Autschbach R, Mohr FW. Comparison of MIDCAP versus conventional CABG surgery regarding pain and quality of life. *Heart Surg Forum.* 1999;2:290-5; discussion 295-296.
532. Groh MA, Sutherland SE, Burton HG III, Johnson AM, Ely SW. Port-access coronary artery bypass grafting: Technique and comparative results. *Ann Thorac Surg.* 1999;68:1506-1508.
533. Lapierre H, Chan V, Sohmer B, Mesana TG, Ruel M. Minimally invasive coronary artery bypass grafting via a small thoracotomy versus off-pump: A case-matched study. *Eur J Cardiothorac Surg.* 2011;40:804-810.
534. Deppe AC, Liakopoulos OJ, Kuhn EW, Slottosch I, Scherner M, Choi YH, Rahmanian PB, Wahlers T. Minimally invasive direct coronary bypass grafting versus percutaneous coronary intervention for single-vessel disease: A meta-analysis of 2885 patients. *Eur J Cardiothorac Surg.* 2015;47:397-406.
535. Wang XW, Qu C, Huang C, Xiang XY, Lu ZQ. Minimally invasive direct coronary bypass compared with percutaneous coronary intervention for left anterior descending artery disease: A meta-analysis. *J Cardiothorac Surg.* 2016;11:125.
536. Gasior M, Zembala MO, Tajstra M, Filipiak K, Gierlotka M, Hrapkowicz T, Hawranek M, Polonski L, Zembala M; POL-MIDES

- (HYBRID) Investigators. Hybrid revascularization for multivessel coronary artery disease. *JACC Cardiovasc Interv.* 2014;7:1277-1283.
537. Bonatti JO, Zimrin D, Lehr EJ, Vesely M, Kon ZN, Wehman B, de Biasi AR, Hofauer B, Weidinger F, Schachner T, Bonaros N, Friedrich G. Hybrid coronary revascularization using robotic totally endoscopic surgery: Perioperative outcomes and 5-year results. *Ann Thorac Surg.* 2012;94:1920-1926.
538. Shen L, Hu S, Wang H, Xiong H, Zheng Z, Li L, Xu B, Yan H, Gao R. One-stop hybrid coronary revascularization versus coronary artery bypass grafting and percutaneous coronary intervention for the treatment of multivessel coronary artery disease: 3-year follow-up results from a single institution. *J Am Coll Cardiol.* 2013;61:2525-2533.
539. Harskamp RE, Bonatti JO, Zhao DX, Puskas JD, de Winter RJ, Alexander JH, Halkos ME. Standardizing definitions for hybrid coronary revascularization. *J Thorac Cardiovasc Surg.* 2014;147:556-560.
540. Zembala M, Tajstra M, Zembala M, Filipiak K, Knapik P, Hrapkiewicz T, Gierlotka M, Hawranek M, Polonski L, Gasior M. Prospective randomised piLOt study evalUating the safety and efficacy of hybrid revascularisation in Multi-vessel coronary artery DisEaSe (POLMIDES) - study design. *Kardiol Pol.* 2011;69:460-466.
541. Tajstra M, Hrapkiewicz T, Hawranek M, Filipiak K, Gierlotka M, Zembala M, Gąsior M, Zembala MO; POL-MIDES Study Investigators. Hybrid coronary revascularization in selected patients with multivessel disease: 5-year clinical outcomes of the prospective randomized pilot study. *JACC Cardiovasc Interv.* 2018;11:847-852.
542. Panoulas VF, Colombo A, Margonato A, Maisano F. Hybrid coronary revascularization: Promising, but yet to take off. *J Am Coll Cardiol.* 2015;65:85-97.
543. Siregar S, Groenwold RH, de Mol BA, Speekenbrink RG, Versteegh MI, Brandon Bravo Bruinsma GJ, Bots ML, van der Graaf Y, van Herwerden LA. Evaluation of cardiac surgery mortality rates: 30-day mortality or longer follow-up? *Eur J Cardiothorac Surg.* 2013;44:875-883.
544. Zhao DF, Edelman JJ, Seco M, Bannon PG, Wilson MK, Byrom MJ, Thourani V, Lamy A, Taggart DP, Puskas JD, Valletly MP. Coronary artery bypass grafting with and without manipulation of the ascending aorta: A network meta-analysis. *J Am Coll Cardiol.* 2017;69:924-936.
545. Moss E, Puskas JD, Thourani VH, Kilgo P, Chen EP, Leshnower BG, Lattouf OM, Guyton RA, Glas KE, Halkos ME. Avoiding aortic clamping during coronary artery bypass grafting reduces postoperative stroke. *J Thorac Cardiovasc Surg.* 2015;149:175-180.
546. Hlatky MA, Boothroyd DB, Reitz BA, Shilane DA, Baker LC, Go AS. Adoption and effectiveness of internal mammary artery grafting in coronary artery bypass surgery among Medicare beneficiaries. *J Am Coll Cardiol.* 2014;63:33-39.
547. Kieser TM, Lewin AM, Graham MM, Martin BJ, Galbraith PD, Rabi DM, Norris CM, Faris PD, Knudtson ML, Ghali WA; APPROACH Investigators. Outcomes associated with bilateral internal thoracic artery grafting: The importance of age. *Ann Thorac Surg.* 2011;92:1269-1275; discussion 1275-1276.
548. Yi G, Shine B, Rehman SM, Altman DG, Taggart DP. Effect of bilateral internal mammary artery grafts on long-term survival: A meta-analysis approach. *Circulation.* 2014;130:539-545.
549. Taggart DP, Altman DG, Flather M, Gerry S, Gray A, Lees B, Benedetto U, ART (Arterial Revascularization Trial) Investigators. Associations between adding a radial artery graft to single and bilateral internal thoracic artery grafts and outcomes: Insights from the Arterial Revascularization Trial. *Circulation.* 2017;136:454-463.
550. Yamasaki M, Deb S, Tsubota H, Moussa F, Kiss A, Cohen EA, Radhakrishnan S, Dubbin J, Ko D, Schwartz L, Fremes SE, Radial Artery Patency Study Investigators. Comparison of radial artery and saphenous vein graft stenosis more than 5 years after coronary artery bypass grafting. *Ann Thorac Surg.* 2016;102:712-719.
551. Benedetto U, Amrani M, Raja SG, Harefield Cardiac Outcomes Research Group. Guidance for the use of bilateral internal thoracic arteries according to survival benefit across age groups. *J Thorac Cardiovasc Surg.* 2014;148:2706-2711.
552. Desai ND, Cohen EA, Naylor CD, Fremes SE, Radial Artery Patency Study Investigators. A randomized comparison of radial-artery and saphenous-vein coronary bypass grafts. *N Engl J Med.* 2004;351:2302-2309.
553. Gaudino M, Tondi P, Benedetto U, Milazzo V, Flore R, Glieda F, Ponziani FR, Luciani N, Girardi LN, Crea F, Massetti M. Radial artery as a coronary artery bypass conduit: 20-year results. *J Am Coll Cardiol.* 2016;68:603-610.
554. Dacey LJ, Braxton JH Jr, Kramer RS, Schmoker JD, Charlesworth DC, Helm RE, Frumiento C, Sardella GL, Clough RA, Jones SR, Malenka DJ, Olmstead EM, Ross CS, O'Connor GT, Likosky DS; Northern New England Cardiovascular Disease Study Group. Long-term outcomes of endoscopic vein harvesting after coronary artery bypass grafting. *Circulation.* 2011;123:147-153.
555. Sen O, Gonca S, Solakoglu S, Dalcik H, Dalcik C, Ozkara A. Comparison of conventional and no-touch techniques in harvesting saphenous vein for coronary artery bypass grafting in view of endothelial damage. *Heart Surg Forum.* 2013;16:E177-E183.
556. Kim YH, Oh HC, Choi JW, Hwang HY, Kim KB. No-touch saphenous vein harvesting may improve further the patency of saphenous vein composite grafts: Early outcomes and 1-year angiographic results. *Ann Thorac Surg.* 2017;103:1489-1497.
557. Benedetto U, Lau C, Caputo M, Kim L, Feldman DN, Ohmes LB, Di Franco A, Soletti G, Angelini GD, Girardi LN, Gaudino M. Comparison of outcomes for off-pump versus on-pump coronary artery bypass grafting in low-volume and high-volume centers and by low-volume and high-volume surgeons. *Am J Cardiol.* 2018;121:552-557.
558. Lapar DJ, Mery CM, Kozower BD, Kern JA, Kron IL, Stukenborg GJ, Ailawadi G. The effect of surgeon volume on mortality for off-pump coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2012;143:854-863.
559. Afilalo J, Rasti M, Ohayon SM, Shimony A, Eisenberg MJ. Off-pump vs. on-pump coronary artery bypass surgery: An updated meta-analysis and meta-regression of randomized trials. *Eur Heart J.* 2012;33:1257-1267.
560. Lemma MG, Coscioni E, Tritto FP, Centofanti P, Fondacone C, Salica A, Rossi A, De Santo T, Di Benedetto G, Piazza L, Rinaldi M, Schinosa AL, De Paulis R, Contino M, Genoni M. On-pump versus off-pump coronary artery bypass surgery in high-risk patients: Operative results of a prospective randomized trial (on-off study). *J Thorac Cardiovasc Surg.* 2012;143:625-631.

561. Rosenblum JM, Harskamp RE, Hoedemaker N, Walker P, Liberman HA, de Winter RJ, Vassiliades TA, Puskas JD, Halkos ME. Hybrid coronary revascularization versus coronary artery bypass surgery with bilateral or single internal mammary artery grafts. *J Thorac Cardiovasc Surg.* 2016;151:1081-1099.
562. Harskamp RE, Brennan JM, Xian Y, Halkos ME, Puskas JD, Thourani VH, Gammie JS, Taylor BS, de Winter RJ, Kim S, O'Brien S, Peterson ED, Gaca JG. Practice patterns and clinical outcomes after hybrid coronary revascularization in the United States: An analysis from the society of thoracic surgeons adult cardiac database. *Circulation.* 2014;130:872-879.
563. Puskas JD, Halkos ME, DeRose JJ, Bagiella E, Miller MA, Overbey J, Bonatti J, Srinivas VS, Vesely M, Sutter F, Lynch J, Kirkwood K, Shapiro TA, Boudoulas KD, Crestanello J, Gehrig T, Smith P, Ragosta M, Hoff SJ, Zhao D, Gelijns AC, Szeto WY, Weisz G, Argenziano M, Vassiliades T, Liberman H, Matthai W, Ascheim DD. Hybrid coronary revascularization for the treatment of multivessel coronary artery disease: A multicenter observational study. *J Am Coll Cardiol.* 2016;68:356-365.
564. Brophy JM, Belisle P, Joseph L. Evidence for use of coronary stents. A hierarchical bayesian meta-analysis. *Ann Intern Med.* 2003;138:7777-7786.
565. Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ, Berger PB, Iakovou I, Dangas G, Waksman R, Antoniucci D, Sartori S, Krucoff MW, Hermiller JB, Shawl F, Gibson CM, Chieffo A, Alu M, Moliterno DJ, Colombo A, Pocock S. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. *Lancet.* 2013;382:1714-1722.
566. Silber S, Kirtane AJ, Belardi JA, Liu M, Brar S, Rothman M, Windecker S. Lack of association between dual antiplatelet therapy use and stent thrombosis between 1 and 12 months following resolute zotarolimus-eluting stent implantation. *Eur Heart J.* 2014;35:1949-1956.
567. Kastrati A, Mehilli J, Dirschinger J, Dotzer F, Schuhlen H, Neumann FJ, Fleckenstein M, Pfafferott C, Seyfarth M, Schomig A. Intracoronary stenting and angiographic results: Strut thickness effect on restenosis outcome (ISAR-STEREO) trial. *Circulation.* 2001;103:2816-2821.
568. Pache J, Kastrati A, Mehilli J, Schuhlen H, Dotzer F, Hausleiter J, Fleckenstein M, Neumann FJ, Sattelberger U, Schmitt C, Muller M, Dirschinger J, Schomig A. Intracoronary stenting and angiographic results: Strut thickness effect on restenosis outcome (ISAR-STEREO-2) trial. *J Am Coll Cardiol.* 2003;41:1283-1288.
569. Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H, Menichelli M, Sabate M, Suttorp MJ, Baumgart D, Seyfarth M, Pfisterer ME, Schomig A. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med.* 2007;356:1030-1039.
570. Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med.* 2007;356:998-1008.
571. Raber L, Magro M, Stefanini GG, Kalesan B, van Domburg RT, Onuma Y, Wenaweser P, Daemen J, Meier B, Juni P, Serruys PW, Windecker S. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: A prospective cohort study. *Circulation.* 2012;125:1110-1121.
572. Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, Doostzadeh J, Cao S, Simonton CA, Sudhir K, Lansky AJ, Cutlip DE, Kereiakes DJ; SPIRIT IV Investigators. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med.* 2010;362:1663-1674.
573. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbaek H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med.* 2010;363:136-146.
574. Christiansen EH, Jensen LO, Thayssen P, Tilsted HH, Krusell LR, Hansen KN, Kaltoft A, Maeng M, Kristensen SD, Botker HE, Terkelsen CJ, Villadsen AB, Ravkilde J, Aaroe J, Madsen M, Thuesen L, Lassen JF; Scandinavian Organization for Randomized Trials with Clinical Outcome (SORT OUT) V Investigators. Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V): A randomised non-inferiority trial. *Lancet.* 2013;381:661-669.
575. Byrne RA, Kastrati A, Kufner S, Massberg S, Birkmeier KA, Laugwitz KL, Schulz S, Pache J, Fusaro M, Seyfarth M, Schomig A, Mehilli J, Intracoronary S, Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Investigators. Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: The Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Trial. *Eur Heart J.* 2009;30:2441-2449.
576. Smits PC, Hofma S, Togni M, Vazquez N, Valdes M, Voudris V, Slagboom T, Goy JJ, Vuillomenet A, Serra A, Nouche RT, den Heijer P, van der Ent M. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): A randomised, controlled, non-inferiority trial. *Lancet.* 2013;381:651-660.
577. Massberg S, Byrne RA, Kastrati A, Schulz S, Pache J, Hausleiter J, Ibrahim T, Fusaro M, Ott I, Schomig A, Laugwitz KL, Mehilli J; Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucoel-Eluting Versus Zotarolimus-Eluting Stents (ISAR-TEST 5) Investigators. Polymer-free sirolimus- and probuocol-eluting versus new generation zotarolimus-eluting stents in coronary artery disease: the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucoel-Eluting versus Zotarolimus-eluting Stents (ISAR-TEST 5) trial. *Circulation.* 2011;124:624-632.
578. Byrne RA, Serruys PW, Baumbach A, Escaned J, Fajadet J, James S, Joner M, Oktay S, Juni P, Kastrati A, Sianos G, Stefanini GG, Wijns W, Windecker S. Report of a European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions task force on the evaluation of coronary stents in Europe: Executive summary. *Eur Heart J.* 2015; 36:2608-2620.
579. Bona KH, Mannsverk J, Wiseth R, Aaberge L, Myreng Y, Nygard O, Nilsen DW, Klow NE, Uchto M, Trovik T, Bendz B,

- Stavnes S, Bjornerheim R, Larsen AI, Slette M, Steigen T, Jakobsen OJ, Bleie O, Fossum E, Hanssen TA, Dahl-Eriksen O, Njolstad I, Rasmussen K, Wilsgaard T, Nordrehaug JE; NORSTENT Investigators. Drug-eluting or bare-metal stents for coronary artery disease. *N Engl J Med*. 2016;375:1242-1252.
580. Palmerini T, Benedetto U, Biondi-Zoccai G, Della Riva D, Bacchi-Reggiani L, Smits PC, Vlachojannis GJ, Jensen LO, Christiansen EH, Berencsi K, Valgimigli M, Orlandi C, Petrou M, Rapezzi C, Stone GW. Long-term safety of drug-eluting and bare-metal stents: Evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol*. 2015;65:2496-2507.
581. Varenne O, Cook S, Sideris G, Kedev S, Cuisset T, Carrie D, Hovasse T, Garot P, El Mahmoud R, Spaulding C, Helft G, Diaz Fernandez JF, Brugaletta S, Pinar-Bermudez E, Mauri Ferre J, Commeau P, Teiger E, Bogaerts K, Sabate M, Morice MC, Sinnaeve PR; SENIOR Investigators. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): A randomised single-blind trial. *Lancet*. 2018;391:41-50.
582. Kang SH, Park KW, Kang DY, Lim WH, Park KT, Han JK, Kang HJ, Koo BK, Oh BH, Park YB, Kandzari DE, Cohen DJ, Hwang SS, Kim HS. Biodegradable-polymer drug-eluting stents vs. bare metal stents vs. durable-polymer drug-eluting stents: A systematic review and Bayesian approach network meta-analysis. *Eur Heart J*. 2014;35:1147-1158.
583. Pilgrim T, Heg D, Roffi M, Tuller D, Muller O, Vuillomenet A, Cook S, Weilenmann D, Kaiser C, Jamshidi P, Fahrni T, Moschovitis A, Noble S, Eberli FR, Wenaweser P, Juni P, Windecker S. Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): A randomised, single-blind, non-inferiority trial. *Lancet*. 2014;384:2111-2122.
584. Kaiser C, Galati S, Jeger R, Gilgen N, Skov Jensen J, Naber C, Alber H, Wanitschek M, Eberli F, Kurz DJ, Pedrazzini G, Moccetti T, Rickli H, Weilenmann D, Vuillomenet A, Steiner M, Von Felten S, Vogt DR, Wadt Hansen K, Rickenbacher P, Conen D, Muller C, Buser P, Hoffmann A, Pfisterer M BASKET-PROVE II Study Group. Long-term efficacy and safety of biodegradable-polymer biolimus-eluting stents: Main results of the Basel Stent Kosten-Effektivitats Trial-PROspective Validation Examination II (BASKET-PROVE II), a randomized, controlled noninferiority 2-year outcome trial. *Circulation*. 2015;131:74-81.
585. Raungaard B, Jensen LO, Tilsted HH, Christiansen EH, Maeng M, Terkelsen CJ, Krusell LR, Kaltoft A, Kristensen SD, Botker HE, Thuesen L, Aaroe J, Jensen SE, Villadsen AB, Thayssen P, Veien KT, Hansen KN, Junker A, Madsen M, Ravkilde J, Lassen JF, Scandinavian Organization for Randomized Trials with Clinical Outcome (SORT OUT). Zotarolimus-eluting durable-polymer-coated stent versus a biolimus-eluting biodegradable-polymer-coated stent in unselected patients undergoing percutaneous coronary intervention (SORT OUT VI): A randomised non-inferiority trial. *Lancet*. 2015;385:1527-1535.
586. von Birgelen C, Kok MM, van der Heijden LC, Danse PW, Schotborgh CE, Scholte M, Gin R, Somi S, van Houwelingen KG, Stoel MG, de Man F, Louwerenburg JHW, Hartmann M, Zocca P, Linssen GCM, van der Palen J, Doggen CJM, Lowik MM. Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease (BIO-RESORT): A three-arm, randomised, non-inferiority trial. *Lancet*. 2016;388:2607-2617.
587. Kereiakes DJ, Meredith IT, Windecker S, Lee Jobe R, Mehta SR, Sarembock IJ, Feldman RL, Stein B, Dubois C, Grady T, Saito S, Kimura T, Christen T, Allocco DJ, Dawkins KD. Efficacy and safety of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent: The EVOLVE II Randomized Trial. *Circ Cardiovasc Interv*. 2015;8:e002372.
588. Natsuaki M, Kozuma K, Morimoto T, Kadota K, Muramatsu T, Nakagawa Y, Akasaka T, Igarashi K, Tanabe K, Morino Y, Ishikawa T, Nishikawa H, Awata M, Abe M, Okada H, Takatsu Y, Ogata N, Kimura K, Urasawa K, Tarutani Y, Shiode N, Kimura T; NEXT Investigators. Biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent: A randomized, controlled, noninferiority trial. *J Am Coll Cardiol*. 2013;62:181-190.
589. Saito S, Valdes-Chavarri M, Richardt G, Moreno R, Iniguez Romo A, Barbato E, Carrie D, Ando K, Merkely B, Kornowski R, Eltchaninoff H, James S, Wijns W; CENTURY II Investigators. A randomized, prospective, intercontinental evaluation of a bioresorbable polymer sirolimus-eluting coronary stent system: The CENTURY II (Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients with Coronary Artery Disease) trial. *Eur Heart J*. 2014;35:2021-2031.
590. Kandzari DE, Mauri L, Koolen JJ, Massaro JM, Doros G, Garcia-Garcia HM, Bennett J, Roguin A, Gharib EG, Cutlip DE, Waksman R; BIOFLOW Investigators V. Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): A randomised trial. *Lancet*. 2017;390:1843-1852.
591. Kufner S, Sorges J, Mehilli J, Cassese S, Repp J, Wiebe J, Lohaus R, Lahmann A, Rheude T, Ibrahim T, Massberg S, Laugwitz KL, Kastrati A, Byrne RA; ISAR-TEST-5 Investigators. Randomized trial of polymer-free sirolimus- and probucol-eluting stents versus durable polymer zotarolimus-eluting stents: 5-year results of the ISAR-TEST-5 trial. *JACC Cardiovasc Interv*. 2016;9:784-792.
592. Kufner S, Byrne RA, Valeskini M, Schulz S, Ibrahim T, Hoppmann P, Schneider S, Laugwitz KL, Schunkert H, Kastrati A; Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST 4) Investigators. Five-year outcomes from a trial of three limus-eluting stents with different polymer coatings in patients with coronary artery disease: Final results from the ISAR-TEST 4 randomised trial. *EuroIntervention*. 2016;11:1372-1379.
593. Vlachojannis GJ, Smits PC, Hofma SH, Togni M, Vazquez N, Valdes M, Voudris V, Slagboom T, Goy JJ, den Heijer P, van der Ent M. Biodegradable polymer biolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with coronary artery disease: Final 5-year report from the COMPARE II Trial (abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent). *JACC Cardiovasc Interv*. 2017;10:1215-1221.
594. Vlachojannis GJ, Puricel S, Natsuaki M, Morimoto T, Smits PC, Kimura T. Biolimus-eluting versus everolimus-eluting stents in coronary artery disease: a pooled analysis from the NEXT

- (NOBORI biolimus-eluting versus XIENCE/PROMUS everolimus-eluting stent) and COMPARE II (Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent) randomised trials. *EuroIntervention*. 2017;12:1970-1977.
595. Wiebe J, Nef HM, Hamm CW. Current status of bioresorbable scaffolds in the treatment of coronary artery disease. *J Am Coll Cardiol*. 2014;64:2541-2551.
596. Sorrentino S, Giustino G, Mehran R, Kini AS, Sharma SK, Faggioni M, Farhan S, Vogel B, Indolfi C, Dangas GD. Everolimus-eluting bioresorbable scaffolds versus everolimus-eluting metallic stents. *J Am Coll Cardiol*. 2017;69:3055-3066.
597. Montone RA, Niccoli G, De Marco F, Minelli S, D'Ascenzo F, Testa L, Bedogni F, Crea F. Temporal trends in adverse events after everolimus-eluting bioresorbable vascular scaffold versus everolimus-eluting metallic stent implantation: A meta-analysis of randomized controlled trials. *Circulation*. 2017;135:2145-2154.
598. Bondesson P, Lagerqvist B, James SK, Olivecrona GK, Venetsanos D, Harnek J. Comparison of two drug-eluting balloons: A report from the SCAAR registry. *EuroIntervention*. 2012;8:444-449.
599. Latib A, Colombo A, Castriota F, Micari A, Cremonesi A, De Felice F, Marchese A, Tespili M, Presbitero P, Sgueglia GA, Buffoli F, Tamburino C, Varbella F, Menozzi A. A randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels: The BELLO (Balloon Elution and Late Loss Optimization) study. *J Am Coll Cardiol*. 2012;60:2473-2480.
600. Cortese B, Micheli A, Picchi A, Coppolaro A, Bandinelli L, Severi S, Limbruno U. Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomised clinical trial. The PICCOLETO study. *Heart*. 2010;96:1291-1296.
601. Stella PR, Belkacemi A, Dubois C, Nathoe H, Dens J, Naber C, Adriaenssens T, van Belle E, Doevendans P, Agostoni P. A multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug-eluting stent in bifurcation lesions treated with a single-stenting technique: Six-month angiographic and 12-month clinical results of the drug-eluting balloon in bifurcations trial. *Catheter Cardiovasc Interv*. 2012;80:1138-1146.
602. Abdel-Wahab M, Richardt G, Joachim Buttner H Toelg, R Geist, V Meinertz, T Schofer, J King, L Neumann, FJ Khattab, AA. High-speed rotational atherectomy before paclitaxel-eluting stent implantation in complex calcified coronary lesions: The randomized ROTAXUS (Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease) trial. *JACC Cardiovasc Interv*. 2013;6:10-19.
603. Parise H, Maehara A, Stone GW, Leon MB, Mintz GS. Meta-analysis of randomized studies comparing intravascular ultrasound versus angiographic guidance of percutaneous coronary intervention in pre-drug-eluting stent era. *Am J Cardiol*. 2011;107:374-382.
604. Lodi-Junqueira L, de Sousa MR, da Paixao LC, Kelles SM, Amaral CF, Ribeiro AL. Does intravascular ultrasound provide clinical benefits for percutaneous coronary intervention with bare-metal stent implantation? A meta-analysis of randomized controlled trials. *Syst Rev*. 2012;1:42.
605. Nerlekar N, Cheshire CJ, Verma KP, Ihdahid AR, McCormick LM, Cameron JD, Bennett MR, Malaiapan Y, Meredith IT, Brown AJ. Intravascular ultrasound guidance improves clinical outcomes during implantation of both first- and second-generation drug-eluting stents: A meta-analysis. *EuroIntervention*. 2017;12:1632-1642.
606. Buccheri S, Franchina G, Romano S, Puglisi S, Venuti G, D'Arrigo P, Francaviglia B, Scalia M, Condorelli A, Barbanti M, Capranzano P, Tamburino C, Capodanno D. Clinical outcomes following intravascular imaging-guided versus coronary angiography-guided percutaneous coronary intervention with stent implantation: A systematic review and Bayesian network meta-analysis of 31 studies and 17,882 patients. *JACC Cardiovasc Interv*. 2017;10:2488-2498.
607. Prati F, Di Vito L, Biondi-Zoccai G, Occhipinti M, La Manna A, Tamburino C, Burzotta F, Trani C, Porto I, Ramazzotti V, Imola F, Manzoli A, Materia L, Cremonesi A, Albertucci M. Angiography alone versus angiography plus optical coherence tomography to guide decision-making during percutaneous coronary intervention: The Centro per la Lotta contro l'Infarto-Optimization of Percutaneous Coronary Intervention (CLI-OPCI) study. *EuroIntervention*. 2012;8:823-829.
608. Wijns W, Shite J, Jones MR, Lee SW, Price MJ, Fabbiochi F, Barbato E, Akasaka T, Bezerra H, Holmes D. Optical coherence tomography imaging during percutaneous coronary intervention impacts physician decision-making: ILUMIEN I study. *Eur Heart J*. 2015;36:3346-3355.
609. Prati F, Guagliumi G, Mintz GS, Costa M, Regar E, Akasaka T, Barlis P, Tearney GJ, Jang IK, Arbustini E, Bezerra HG, Ozaki Y, Bruining N, Dudek D, Radu M, Erglis A, Motreff P, Alfonso F, Toutouzias K, Gonzalo N, Tamburino C, Adriaenssens T, Pinto F, Serruys PW, Di Mario C; Expert's OCT Review Document. Expert review document part 2: Methodology, terminology and clinical applications of optical coherence tomography for the assessment of interventional procedures. *Eur Heart J*. 2012;33:2513-2520.
610. Radu MD, Raber L, Heo J, Gogas BD, Jorgensen E, Kelbaek H, Muramatsu T, Farooq V, Helqvist S, Garcia-Garcia HM, Windecker S, Saunamaki K, Serruys PW. Natural history of optical coherence tomography-detected non-flow-limiting edge dissections following drug-eluting stent implantation. *EuroIntervention*. 2014;9:1085-1094.
611. Ali ZA, Maehara A, Genereux P, Shlofmitz RA, Fabbiochi F, Nazif TM, Guagliumi G, Meraj PM, Alfonso F, Samady H, Akasaka T, Carlson EB, Leeser MA, Matsumura M, Ozan MO, Mintz GS, Ben-Yehuda O, Stone GW; ILUMIEN III: OPTIMIZE PCI Investigators. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): A randomised controlled trial. *Lancet*. 2016;388:2618-2628.
612. Meneveau N, Souteyrand G, Motreff P, Caussin C, Amabile N, Ohlmann P, Morel O, Lefrancois Y, Descotes-Genon V, Silvain J, Braik N, Chopard R, Chatot M, Ecartot F, Tauzin H, Van Belle E, Belle L, Schiele F. Optical coherence tomography to optimize results of percutaneous coronary intervention in patients with non-ST-elevation acute coronary syndrome: Results of the multicenter, randomized DOCTORS study (Does Optical Coherence Tomography Optimize Results of Stenting). *Circulation*. 2016;134:906-917.

613. Taniwaki M, Radu MD, Zaugg S, Amabile N, Garcia-Garcia HM, Yamaji K, Jorgensen E, Kelbaek H, Pilgrim T, Caussin C, Zanchin T, Veugeois A, Abildgaard U, Juni P, Cook S, Koskinas KC, Windecker S, Raber L. Mechanisms of very late drug-eluting stent thrombosis assessed by optical coherence tomography. *Circulation*. 2016;133:650-660.
614. Souteyrand G, Amabile N, Mangin L, Chabin X, Meneveau N, Cayla G, Vanzetto G, Barnay P, Trouillet C, Rioufol G, Range G, Teiger E, Delaunay R, Dubreuil O, Lhermusier T, Mulliez A, Levesque S, Belle L, Caussin C, Motreff P; PESTO Investigators. Mechanisms of stent thrombosis analysed by optical coherence tomography: Insights from the national PESTO French registry. *Eur Heart J*. 2016;37:1208-1216.
615. Kang SJ, Mintz GS, Akasaka T, Park DW, Lee JY, Kim WJ, Lee SW, Kim YH, Whan Lee C, Park SW, Park SJ. Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. *Circulation*. 2011;123:2954-2963.
616. Malle C, Tada T, Steigerwald K, Ughi GJ, Schuster T, Nakano M, Massberg S, Jehle J, Guagliumi G, Kastrati A, Virmani R, Byrne RA, Joner M. Tissue characterization after drug-eluting stent implantation using optical coherence tomography. *Arterioscler Thromb Vasc Biol*. 2013;33:1376-1383.
617. Gao XF, Zhang YJ, Tian NL, Wu W, Li MH, Bourantas CV, Jiang XM, Wang ZM, Li B, Mao WX, Zhang JJ, Chen SL. Stenting strategy for coronary artery bifurcation with drug-eluting stents: A meta-analysis of nine randomised trials and systematic review. *EuroIntervention*. 2014;10:561-569.
618. Behan MW, Holm NR, de Belder AJ, Cockburn J, Erglis A, Curzen NP, Niemela M, Oldroyd KG, Kervinen K, Kumsars I, Gunnes P, Stables RH, Maeng M, Ravkilde J, Jensen JS, Christiansen EH, Cooter N, Steigen TK, Vikman S, Thuesen L, Lassen JF, Hildick-Smith D. Coronary bifurcation lesions treated with simple or complex stenting: 5-year survival from patient-level pooled analysis of the Nordic Bifurcation Study and the British Bifurcation Coronary Study. *Eur Heart J*. 2016;37:1923-1928.
619. Hildick-Smith D, Behan MW, Lassen JF, Chieffo A, Lefevre T, Stankovic G, Burzotta F, Pan M, Ferenc M, Bennett L, Hovasse T, Spence MJ, Oldroyd K, Brunel P, Carrie D, Baumbach A, Maeng M, Skipper N, Louvard Y. The EBC TWO Study (European Bifurcation Coronary TWO): A randomized comparison of provisional T-stenting versus a systematic 2 stent culotte strategy in large caliber true bifurcations. *Circ Cardiovasc Interv*. 2016;9:e003643.
620. Chen SL, Zhang JJ, Han Y, Kan J, Chen L, Qiu C, Jiang T, Tao L, Zeng H, Li L, Xia Y, Gao C, Santoso T, Paiboon C, Wang Y, Kwan TW, Ye F, Tian N, Liu Z, Lin S, Lu C, Wen S, Hong L, Zhang Q, Sheiban I, Xu Y, Wang L, Rab TS, Li Z, Cheng G, Cui L, Leon MB, Stone GW. Double kissing crush versus provisional stenting for left main distal bifurcation lesions: DKCRUSH-V randomized trial. *J Am Coll Cardiol*. 2017;70:2605-2617.
621. Erglis A, Kumsars I, Niemela M, Kervinen K, Maeng M, Lassen JF, Gunnes P, Stavnes S, Jensen JS, Galloe A, Narbutė I, Sondore D, Makikallio T, Ylitalo K, Christiansen EH, Ravkilde J, Steigen TK, Mannsverk J, Thayssen P, Hansen KN, Syvanne M, Helqvist S, Kjell N, Wiseth R, Aaroe J, Puhakka M, Thuesen L; Nordic PCI Study Group. Randomized comparison of coronary bifurcation stenting with the crush versus the culotte technique using sirolimus eluting stents: The Nordic stent technique study. *Circ Cardiovasc Interv*. 2009;2:27-34.
622. Zheng XW, Zhao DH, Peng HY, Fan Q, Ma Q, Xu ZY, Fan C, Liu LY, Liu JH. Randomized comparison of the crush versus the culotte stenting for coronary artery bifurcation lesions. *Chin Med J (Engl)*. 2016;129:505-510.
623. Chen SL, Xu B, Han YL, Sheiban I, Zhang JJ, Ye F, Kwan TW, Paiboon C, Zhou YJ, Lv SZ, Dangas GD, Xu YW, Wen SY, Hong L, Zhang RY, Wang HC, Jiang TM, Wang Y, Chen F, Yuan ZY, Li WM, Leon MB. Comparison of double kissing crush versus Culotte stenting for unprotected distal left main bifurcation lesions: Results from a multicenter, randomized, prospective DKCRUSH-III study. *J Am Coll Cardiol*. 2013;61:1482-1488.
624. Niemela M, Kervinen K, Erglis A, Holm NR, Maeng M, Christiansen EH, Kumsars I, Jegere S, Dombrovskis A, Gunnes P, Stavnes S, Steigen TK, Trovik T, Eskola M, Vikman S, Romppanen H, Makikallio T, Hansen KN, Thayssen P, Aberg L, Jensen LO, Hervold A, Airaksinen J, Pietila M, Frobert O, Kellerth T, Ravkilde J, Aaroe J, Jensen JS, Helqvist S, Sjogren I, James S, Miettinen H, Lassen JF, Thuesen L; Nordic-Baltic PCI Study Group. Randomized comparison of final kissing balloon dilatation versus no final kissing balloon dilatation in patients with coronary bifurcation lesions treated with main vessel stenting: The Nordic-Baltic Bifurcation Study III. *Circulation*. 2011;123:79-86.
625. Gwon HC, Hahn JY, Koo BK, Song YB, Choi SH, Choi JH, Lee SH, Jeong MH, Kim HS, Seong IW, Yang JY, Rha SW, Jang Y, Yoon JH, Takh SJ, Seung KB, Park SJ. Final kissing ballooning and long-term clinical outcomes in coronary bifurcation lesions treated with 1-stent technique: Results from the COBIS registry. *Heart*. 2012;98:225-231.
626. Genereux P, Kumsars I, Lesiak M, Kini A, Fontos G, Slagboom T, Ungi I, Metzger DC, Wykrzykowska JJ, Stella PR, Bartorelli AL, Fearon WF, Lefevre T, Feldman RL, LaSalle L, Francese DP, Onuma Y, Grundeken MJ, Garcia-Garcia HM, Laak LL, Cutlip DE, Kaplan AV, Serruys PW, Leon MB. A randomized trial of a dedicated bifurcation stent versus provisional stenting in the treatment of coronary bifurcation lesions. *J Am Coll Cardiol*. 2015;65:533-543.
627. Lassen JF, Holm NR, Banning A, Burzotta F, Lefevre T, Chieffo A, Hildick-Smith D, Louvard Y, Stankovic G. Percutaneous coronary intervention for coronary bifurcation disease: 11th consensus document from the European Bifurcation Club. *EuroIntervention*. 2016;12:38-46.
628. Henriques JP, Hoehers LP, Ramunddal T, Laanmets P, Eriksen E, Bax M, Ioanes D, Suttorp MJ, Strauss BH, Barbato E, Nijveldt R, van Rossum AC, Marques KM, Elias J, van Dongen IM, Claessen BE, Tijssen JG, van der Schaaf RJ; EXPLORE Investigators Trial. Percutaneous intervention for concurrent chronic total occlusions in patients with STEMI: The EXPLORE trial. *J Am Coll Cardiol*. 2016;68:1622-1632.
629. Werner GS, Martin-Yuste V, Hildick-Smith D, Boudou N, Sianos G, Gelev V, Rumoroso JR, Erglis A, Christiansen EH, Escaned J, di Mario C, Hovasse T, Teruel L, Bufe A, Lauer B, Bogaerts K, Goicolea J, Spratt JC, Gershlick AH, Galassi AR, Louvard Y; EUROCTO trial investigators. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *Eur Heart J*. doi:10.1093/eurheartj/ehy220. Published online ahead of print 2 May 2018.

630. Christakopoulos GE, Christopoulos G, Carlino M, Jeroudi OM, Roesle M, Rangan BV, Abdullah S, Grodin J, Kumbhani DJ, Vo M, Luna M, Alaswad K, Karpaliotis D, Rinfret S, Garcia S, Banerjee S, Brilakis ES. Meta-analysis of clinical outcomes of patients who underwent percutaneous coronary interventions for chronic total occlusions. *Am J Cardiol.* 2015;115:1367-1375.
631. Brilakis ES, Banerjee S, Karpaliotis D, Lombardi WL, Tsai TT, Shunk KA, Kennedy KF, Spertus JA, Holmes DR Jr, Grantham JA. Procedural outcomes of chronic total occlusion percutaneous coronary intervention: A report from the NCDR (National Cardiovascular Data Registry). *JACC Cardiovasc Interv.* 2015;8:245-253.
632. Maeremans J, Walsh S, Knaapen P, Spratt JC, Avran A, Hanratty CG, Faurie B, Agostoni P, Bressollette E, Kayaert P, Bagnall AJ, Egred M, Smith D, Chase A, McEntegart MB, Smith WH, Harcombe A, Kelly P, Irving J, Smith EJ, Strange JW, Dens J. The hybrid algorithm for treating chronic total occlusions in Europe: The RECHARGE registry. *J Am Coll Cardiol.* 2016;68:1958-1970.
633. Galassi AR, Sianos G, Werner GS, Escaned J, Tomasello SD, Boukhris M, Castaing M, Buttner JH, Bufe A, Kalnins A, Spratt JC, Garbo R, Hildick-Smith D, Elhadad S, Gagnor A, Lauer B, Bryniarski L, Christiansen EH, Thuesen L, Meyer-Gessner M, Goktekin O, Carlino M, Louvard Y, Lefevre T, Lismanis A, Gelev VL, Serra A, Marza F, Di Mario C, Reifart N; Euro CTO Club. Retrograde recanalization of chronic total occlusions in Europe: Procedural, in-hospital, and long-term outcomes from the multicenter ERCTO registry. *J Am Coll Cardiol.* 2015;65:2388-400.
634. Koh JS, Koo BK, Kim JH, Yang HM, Park KW, Kang HJ, Kim HS, Oh BH, Park YB. Relationship between fractional flow reserve and angiographic and intravascular ultrasound parameters in ostial lesions: Major epicardial vessel versus side branch ostial lesions. *JACC Cardiovasc Interv.* 2012;5:409-415.
635. Arnous S, Shakhshir N, Wiper A, Ordoubadi FF, Williams P, Clarke B, Mahadavan V, El-Omar M, Mamas M, Fraser D. Incidence and mechanisms of longitudinal stent deformation associated with Biomatrix, Resolute, Element, and Xience stents: Angiographic and case-by-case review of 1,800 PCIs. *Catheter Cardiovasc Interv.* 2015;86:1002-1011.
636. Szabo S, Abramowitz B, Vaitkus P. New technique of aorto-ostial stent placement. *Am J Cardiol.* 2005;96:212H.
637. Gutierrez-Chico JL, Villanueva-Benito I, Villanueva-Montoto L, Vazquez-Fernandez S, Kleinecke C, Gielen S, Iniguez-Romo A. Szabo technique versus conventional angiographic placement in bifurcations 010-001 of Medina and in aorto-ostial stenting: Angiographic and procedural results. *EuroIntervention.* 2010;5:801-808.
638. Jolly SS, Yusuf S, Cairns J, Niemela K, Xavier D, Widimsky P, Budaj A, Niemela M, Valentin V, Lewis BS, Avezum A, Steg PG, Rao SV, Gao P, Afzal R, Joyner CD, Chrolavicius S, Mehta SR; RIVAL trial group. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): A randomised, parallel group, multicentre trial. *Lancet.* 2011;377:1409-1420.
639. Hamon M, Pristipino C, Di Mario C, Nolan J, Ludwig J, Tubaro M, Sabate M, Mauri-Ferre J, Huber K, Niemela K, Haude M, Wijns W, Dudek D, Fajadet J, Kiemeneij F; European Association of Percutaneous Cardiovascular Interventions; Working Group on Acute Cardiac Care of the European Society of Cardiology; Working Group on Thrombosis on the European Society of Cardiology. Consensus document on the radial approach in percutaneous cardiovascular interventions: Position paper by the European Association of Percutaneous Cardiovascular Interventions and Working Groups on Acute Cardiac Care\*\* and Thrombosis of the European Society of Cardiology. *EuroIntervention.* 2013;8:1242-1251.
640. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, Kimura T, Briguori C, Sabate M, Kim HS, De Waha A, Kedhi E, Smits PC, Kaiser C, Sardella G, Marullo A, Kirtane AJ, Leon MB, Stone GW. Stent thrombosis with drug-eluting and bare-metal stents: Evidence from a comprehensive network meta-analysis. *Lancet.* 2012;379:1393-1402.
641. Ferrante G, Rao SV, Juni P, Da Costa BR, Reimers B, Condorelli G, Anzuini A, Jolly SS, Bertrand OF, Krucoff MW, Windecker S, Valgimigli M. Radial versus femoral access for coronary interventions across the entire spectrum of patients with coronary artery disease: A meta-analysis of randomized trials. *JACC Cardiovasc Interv.* 2016;9:1419-1434.
642. Sabate M, Windecker S, Iniguez A, Okkels-Jensen L, Cequier A, Brugaletta S, Hofma SH, Raber L, Christiansen EH, Suttorp M, Pilgrim T, Anne van Es G, Sotomi Y, Garcia-Garcia HM, Onuma Y, Serruys PW. Everolimus-eluting bioresorbable stent vs. durable polymer everolimus-eluting metallic stent in patients with ST-segment elevation myocardial infarction: Results of the randomized ABSORB ST-segment elevation myocardial infarction-TROFI II trial. *Eur Heart J.* 2016;37:229-240.
643. Cassese S, Byrne RA, Ndrepepa G, Kufner S, Wiebe J, Repp J, Schunkert H, Fusaro M, Kimura T, Kastrati A. Everolimus-eluting bioresorbable vascular scaffolds versus everolimus-eluting metallic stents: A meta-analysis of randomised controlled trials. *Lancet.* 2016;387:537-544.
644. Serruys PW, Chevalier B, Dudek D, Cequier A, Carrie D, Iniguez A, Dominici M, van der Schaaf RJ, Haude M, Wasungu L, Veldhof S, Peng L, Staehr P, Grundeken MJ, Ishibashi Y, Garcia-Garcia HM, Onuma Y. A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischaemic heart disease caused by de-novo native coronary artery lesions (ABSORB II): An interim 1-year analysis of clinical and procedural secondary outcomes from a randomised controlled trial. *Lancet.* 2015;385:43-54.
645. Puricel S, Arroyo D, Corpataux N, Baeriswyl G, Lehmann S, Kallinikou Z, Muller O, Allard L, Stauffer JC, Togni M, Goy JJ, Cook S. Comparison of everolimus- and biolimus-eluting coronary stents with everolimus-eluting bioresorbable vascular scaffolds. *J Am Coll Cardiol.* 2015;65:791-801.
646. Kimura T, Kozuma K, Tanabe K, Nakamura S, Yamane M, Muramatsu T, Saito S, Yajima J, Hagiwara N, Mitsudo K, Popma JJ, Serruys PW, Onuma Y, Ying S, Cao S, Staehr P, Cheong WF, Kusano H, Stone GW; ABSORB Japan Investigators. A randomized trial evaluating everolimus-eluting Absorb bioresorbable scaffolds vs. everolimus-eluting metallic stents in patients with coronary artery disease: ABSORB Japan. *Eur Heart J.* 2015;36:3332-3342.
647. Gao R, Yang Y, Han Y, Huo Y, Chen J, Yu B, Su X, Li L, Kuo HC, Ying SW, Cheong WF, Zhang Y, Su X, Xu B, Popma JJ,

- Stone GW, Investigators AC. Bioresorbable vascular scaffolds versus metallic stents in patients with coronary artery disease: ABSORB China trial. *J Am Coll Cardiol*. 2015;66:2298-2309.
648. Ellis SG, Kereiakes DJ, Metzger DC, Caputo RP, Rizik DG, Teirstein PS, Litt MR, Kini A, Kabour A, Marx SO, Popma JJ, McGreevy R, Zhang Z, Simonton C, Stone GW; ABSORB III Investigators. Everolimus-eluting bioresorbable scaffolds for coronary artery disease. *N Engl J Med*. 2015;373:1905-1915.
649. Wykrzykowska JJ, Kraak RP, Hofma SH, van der Schaaf RJ, Arkenbout EK, AJ IJ, Elias, J, van Dongen, IM, Tijssen, RYG, Koch, KT, Baan, J Jr, Vis MM, de Winter RJ, Piek JJ, Tijssen JGP, Henriques JPS; AIDA Investigators. Bioresorbable scaffolds versus metallic stents in routine PCI. *N Engl J Med*. 2017;376: 2319-2328.
650. Cassese S, Byrne RA, Juni P, Wykrzykowska JJ, Puricel S, Ndrepepa G, Schunkert H, Fusaro M, Cook S, Kimura T, Henriques JPS, Serruys PW, Windecker S, Kastrati A. Midterm clinical outcomes with everolimus-eluting bioresorbable scaffolds versus everolimus-eluting metallic stents for percutaneous coronary interventions: A meta-analysis of randomised trials. *EuroIntervention*. 2018;13:1565-1573.
651. Casella G, Klauss V, Ottani F, Siebert U, Sangiorgio P, Bracchetti D. Impact of intravascular ultrasound-guided stenting on long-term clinical outcome: A meta-analysis of available studies comparing intravascular ultrasound-guided and angiographically guided stenting. *Catheter Cardiovasc Interv*. 2003;59:314-321.
652. Witzencbichler B, Maehara A, Weisz G, Neumann FJ, Rinaldi MJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Brodie BR, Stuckey TD, Mazzaferri EL Jr, Xu K, Parise H, Mehran R, Mintz GS, Stone GW. Relationship between intravascular ultrasound guidance and clinical outcomes after drug-eluting stents: The assessment of dual antiplatelet therapy with drug-eluting stents (ADAPT-DES) study. *Circulation*. 2014;129:463-470.
653. Maehara A, Ben-Yehuda O, Ali Z, Wijns W, Bezerra HG, Shite J, Genereux P, Nichols M, Jenkins P, Witzencbichler B, Mintz GS, Stone GW. Comparison of stent expansion guided by optical coherence tomography versus intravascular ultrasound: The ILUMIEN II study (observational study of optical coherence tomography [OCT] in patients undergoing fractional flow reserve [FFR] and percutaneous coronary intervention). *JACC Cardiovasc Interv*. 2015;8:1704-1714.
654. Maeng M, Holm NR, Erglis A, Kumsars I, Niemela M, Kervinen K, Jensen JS, Galloe A, Steigen TK, Wiseth R, Narbutė I, Gunnes P, Mannsverk J, Meyerdierks O, Rotevatn S, Nikus K, Vikman S, Ravkilde J, James S, Aaroe J, Ylitalo A, Helqvist S, Sjogren I, Thayssen P, Virtanen K, Puhakka M, Airaksinen J, Christiansen EH, Lassen JF, Thuesen L; Nordic-Baltic Percutaneous Coronary Intervention Study Group. Long-term results after simple versus complex stenting of coronary artery bifurcation lesions: Nordic Bifurcation Study 5-year follow-up results. *J Am Coll Cardiol*. 2013;62:30-34.
655. Hildick-Smith D, de Belder AJ, Cooter N, Curzen NP, Clayton TC, Oldroyd KG, Bennett L, Holmberg S, Cotton JM, Glennon PE, Thomas MR, Mccarthy PA, Baumbach A, Mulvihill NT, Henderson RA, Redwood SR, Starkey IR, Stables RH. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: The British Bifurcation Coronary Study: Old, new, and evolving strategies. *Circulation*. 2010;121: 1235-1243.
656. Behan MW, Holm NR, Curzen NP, Erglis A, Stables RH, de Belder AJ, Niemela M, Cooter N, Chew DP, Steigen TK, Oldroyd KG, Jensen JS, Lassen JF, Thuesen L, Hildick-Smith D. Simple or complex stenting for bifurcation coronary lesions: A patient-level pooled-analysis of the Nordic Bifurcation Study and the British Bifurcation Coronary Study. *Circ Cardiovasc Interv*. 2011;4:57-64.
657. Chen SL, Santoso T, Zhang JJ, Ye F, Xu YW, Fu Q, Kan J, Paiboon C, Zhou Y, Ding SQ, Kwan TW. A randomized clinical study comparing double kissing crush with provisional stenting for treatment of coronary bifurcation lesions: Results from the DKCRUSH-II (Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions) trial. *J Am Coll Cardiol*. 2011;57:914-920.
658. Katrītis DG, Siontis GC, Ioannidis JP. Double versus single stenting for coronary bifurcation lesions: A meta-analysis. *Circ Cardiovasc Interv*. 2009;2:409-415.
659. Mehran R, Claessen BE, Godino C, Dangas GD, Obunai K, Kanwal S, Carlino M, Henriques JP, Di Mario C, Kim YH, Park SJ, Stone GW, Leon MB, Moses JW, Colombo A, Multinational Chronic Total Occlusion Registry. Long-term outcome of percutaneous coronary intervention for chronic total occlusions. *JACC Cardiovasc Interv*. 2011;4:952-961.
660. Claessen BE, Dangas GD, Godino C, Lee SW, Obunai K, Carlino M, Suh JW, Leon MB, Di Mario C, Park SJ, Stone GW, Moses JW, Colombo A, Mehran R, Multinational Cto Registry. Long-term clinical outcomes of percutaneous coronary intervention for chronic total occlusions in patients with versus without diabetes mellitus. *Am J Cardiol*. 2011;108:924-931.
661. Jones DA, Weerackody R, Rathod K, Behar J, Gallagher S, Knight CJ, Kapur A, Jain AK, Rothman MT, Thompson CA, Mathur A, Wragg A, Smith EJ. Successful recanalization of chronic total occlusions is associated with improved long-term survival. *JACC Cardiovasc Interv*. 2012;5:380-388.
662. Grantham JA, Jones PG, Cannon L, Spertus JA. Quantifying the early health status benefits of successful chronic total occlusion recanalization: Results from the FlowCardia's Approach to Chronic Total Occlusion Recanalization (FACTOR) Trial. *Circ Cardiovasc Qual Outcomes*. 2010;3:284-290.
663. Joyal D, Afilalo J, Rinfret S. Effectiveness of recanalization of chronic total occlusions: A systematic review and meta-analysis. *Am Heart J*. 2010;160:179-187.
664. Ndrepepa G, Berger PB, Mehilli J, Seyfarth M, Neumann FJ, Schomig A, Kastrati A. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: Appropriateness of including bleeding as a component of a quadruple end point. *J Am Coll Cardiol*. 2008;51:690-697.
665. Schomig A, Neumann FJ, Kastrati A, Schühlen H, Blasini R, Hadamitzky M, Walter H, Zitzmann-Roth EM, Richardt G, Alt E, Schmitt C, Ulm K. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med*. 1996;334:1084-1089.
666. Sibbing D, Kastrati A, Berger PB. Pre-treatment with P2Y12 inhibitors in ACS patients: Who, when, why, and which agent? *Eur Heart J*. 2016;37:1284-1295.
667. Steinhilbl SR, Berger PB, Mann JT III, Fry ET, DeLago A, Wilmer C, Topol EJ; CREDO Investigators. Clopidogrel from the Reduction of Events During Observation. Early and sustained dual

- oral antiplatelet therapy following percutaneous coronary intervention: A randomized controlled trial. *JAMA*. 2002;288:2411-2420.
668. Bellemain-Appaix A, O'Connor SA, Silvain J, Cucherat M, Beygui F, Barthelemy O, Collet JP, Jacq L, Bernasconi F, Montalescot G; ACTION Group. Association of clopidogrel pre-treatment with mortality, cardiovascular events, and major bleeding among patients undergoing percutaneous coronary intervention: A systematic review and meta-analysis. *JAMA*. 2012;308:2507-2516.
669. Lincoff AM, Kleiman NS, Kereiakes DJ, Feit F, Bittl JA, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Rutsch W, Wilcox RG, de Feyter PJ, Vahanian A, Topol EJ; REPLACE-2 Investigators. Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. *JAMA*. 2004;292:696-703.
670. Kastrati A, Neumann FJ, Mehilli J, Byrne RA, Iijima R, Buttner HJ, Khattab AA, Schulz S, Blankenship JC, Pache J, Minners J, Seyfarth M, Graf I, Skelding KA, Dirschinger J, Richardt G, Berger PB, Schomig A; ISAR-REACT 3 Trial Investigators. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N Engl J Med*. 2008;359:688-696.
671. Schulz S, Mehilli J, Neumann FJ, Schuster T, Massberg S, Valina C, Seyfarth M, Pache J, Laugwitz KL, Buttner HJ, Ndrepepa G, Schomig A, Kastrati A, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 3A Trial Investigators. ISAR-REACT 3A: A study of reduced dose of unfractionated heparin in biomarker negative patients undergoing percutaneous coronary intervention. *Eur Heart J*. 2010;31:2482-2491.
672. Montalescot G, White HD, Gallo R, Cohen M, Steg PG, Aylward PE, Bode C, Chiariello M, King SB III, Harrington RA, Desmet WJ, Macaya C, Steinhubl SR; STEEPLE Investigators. Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. *N Engl J Med*. 2006;355:1006-1017.
673. Steg PG, Bhatt DL, Hamm CW, Stone GW, Gibson CM, Mahaffey KW, Leonardi S, Liu T, Skerjanec S, Day JR, Iwaoka RS, Stuckey TD, Gogia HS, Gruberg L, French WJ, White HD, Harrington RA; CHAMPION Investigators. Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: A pooled analysis of patient-level data. *Lancet*. 2013;382:1981-1992.
674. Valgimigli M, Percoco G, Barbieri D, Ferrari F, Guardigli G, Parrinello G, Soukhomovskaia O, Ferrari R. The additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high-risk coronary angioplasty: The ADVANCE Trial. *J Am Coll Cardiol*. 2004;44:14-19.
675. Kastrati A, Mehilli J, Schuhlen H, Dirschinger J, Dotzer F, ten Berg JM, Neumann FJ, Bollwein H, Volmer C, Gawaz M, Berger PB, Schomig A; Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment Study Investigators. A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med*. 2004;350:232-238.
676. Winchester DE, Wen X, Brearley WD, Park KE, Anderson RD, Bavry AA. Efficacy and safety of glycoprotein IIb/IIIa inhibitors during elective coronary revascularization: A meta-analysis of randomized trials performed in the era of stents and thienopyridines. *J Am Coll Cardiol*. 2011;57:1190-1199.
677. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005;293:2126-2130.
678. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfeld J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Kakkar AK, Fox KAA, Parkhomenko AN, Ertl G, Stork S, Keltai M, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusuf S, Yusuf S; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377:1319-1330.
679. Di Sciascio G, Patti G, Pasceri V, Gatto L, Colonna G, Montinaro A; ARMYDA-5 PRELOAD Investigators. Effectiveness of in-laboratory high-dose clopidogrel loading versus routine pre-load in patients undergoing percutaneous coronary intervention: Results of the ARMYDA-5 PRELOAD (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) randomized trial. *J Am Coll Cardiol*. 2010;56:550-557.
680. Widimsky P, Motovska Z, Simek S, Kala P, Pudil R, Holm F, Petr R, Bilkova D, Skalicka H, Kuchynka P, Poloczek M, Miklik R, Maly M, Aschermann M; PRAGUE-8 Trial Investigators. Clopidogrel pre-treatment in stable angina: For all patients >6 h before elective coronary angiography or only for angiographically selected patients a few minutes before PCI? A randomized multicentre trial PRAGUE-8. *Eur Heart J*. 2008;29:1495-1503.
681. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71-86.
682. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ*. 1994;308:81-106.
683. Antithrombotic Trialists C, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: Collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373:1849-1860.
684. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH; CLASSICS Investigators. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation*. 2000;102:624-629.
685. Taniuchi M, Kurz HI, Lasala JM. Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. *Circulation*. 2001;104:539-543.
686. Muller C, Buttner HJ, Petersen J, Roskamm H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and

- aspirin after the placement of coronary-artery stents. *Circulation*. 2000;101:590-593.
687. von Beckerath N, Taubert D, Pogatsa-Murray G, Schödmig E, Kastrati A, Schödmig A. Absorption, metabolism, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel: Results of the ISAR-CHOICE (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) Trial. *Circulation*. 2005;112:2946-2950.
688. Montalescot G, Sideris G, Meuleman C, Bal-dit-Sollier C, Lellouche N, Steg PG, Slama M, Milleron O, Collet JP, Henry P, Beygui F, Drouet L, Investigators AT. A randomized comparison of high clopidogrel loading doses in patients with non-ST-segment elevation acute coronary syndromes: The ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) trial. *J Am Coll Cardiol*. 2006;48:931-938.
689. Silvain J, Beygui F, Barthelemy O, Pollack C Jr, Cohen M, Zeymer U, Huber K, Goldstein P, Cayla G, Collet JP, Vicaut E, Montalescot G. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: Systematic review and meta-analysis. *BMJ*. 2012;344:e553.
690. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fuca G, Kubba M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R; Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) Investigators. Short-versus long-term duration of dual-antiplatelet therapy after coronary stenting: A randomized multicenter trial. *Circulation*. 2012;125:2015-2026.
691. Schulz-Schupke S, Byrne RA, Ten Berg JM, Neumann FJ, Han Y, Adriaenssens T, Tolg R, Seyfarth M, Maeng M, Zrenner B, Jacobshagen C, Mudra H, von Hodenberg E, Wöhrle J, Angiolillo DJ, von Merzljak B, Rifatov N, Kufner S, Morath T, Feuchtenberger A, Ibrahim T, Janssen PW, Valina C, Li Y, Desmet W, Abdel-Wahab M, Tiroch K, Hengstenberg C, Bernlochner I, Fischer M, Schunkert H, Laugwitz KL, Schomig A, Mehilli J, Kastrati A; Intracoronary Stenting and Antithrombotic Regimen: Safety And Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) Trial Investigators. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J*. 2015;36:1252-1263.
692. Han Y, Xu B, Xu K, Guan C, Jing Q, Zheng Q, Li X, Zhao X, Wang H, Zhao X, Li X, Yu P, Zang H, Wang Z, Cao X, Zhang J, Pang W, Li J, Yang Y, Dangas GD. Six versus 12 months of dual antiplatelet therapy after implantation of biodegradable polymer sirolimus-eluting stent: Randomized substudy of the I-LOVE-IT 2 trial. *Circ Cardiovasc Interv*. 2016;9:e003145.
693. Hong SJ, Shin DH, Kim JS, Kim BK, Ko YG, Choi D, Her AY, Kim YH, Jang Y, Hong MK, IVUS-Investigators XPL. 6-month versus 12-month dual-antiplatelet therapy following long everolimus-eluting stent implantation: The IVUS-XPL randomized clinical trial. *JACC Cardiovasc Interv*. 2016;9:1438-1446.
694. Kereiakes DJ, Yeh RW, Massaro JM, Driscoll-Shempp P, Cutlip DE, Steg PG, Gershlick AH, Darius H, Meredith IT, Ormiston J, Tanguay JF, Windecker S, Garratt KN, Kandzari DE, Lee DP, Simon DI, Iancu AC, Trebacz J, Mauri L; Dual Antiplatelet Therapy (DAPT) Study Investigators. Antiplatelet therapy duration following bare metal or drug-eluting coronary stents: The dual antiplatelet therapy randomized clinical trial. *JAMA*. 2015;313:1113-1121.
695. Kim BK, Hong MK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Park BE, Kang WC, Lee SH, Yoon JH, Hong BK, Kwon HM, Jang Y; RESET Investigators. A new strategy for discontinuation of dual antiplatelet therapy: The RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol*. 2012;60:1340-1348.
696. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, King SB III, Negoita M, Liu M, de Paula JE, Mangione JA, Meireles GX, Castello HJ Jr, Nicolela EL Jr, Perin MA, Devito FS, Labrunie A, Salvadori D Jr, Gusmao M, Staico R, Costa JR Jr, de Castro JP, Abizaid AS, Bhatt DL; OPTIMIZE Trial Investigators. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: The OPTIMIZE randomized trial. *JAMA*. 2013;310:2510-2522.
697. Palmerini T, Benedetto U, Bacchi-Reggiani L, Della Riva D, Biondi-Zoccai G, Feres F, Abizaid A, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Genereux P, Bhatt DL, Orlandi C, De Servi S, Petrou M, Rapezzi C, Stone GW. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: A pairwise and Bayesian network meta-analysis of randomised trials. *Lancet*. 2015;385:2371-2382.
698. Giustino G, Baber U, Sartori S, Mehran R, Mastoris I, Kini AS, Sharma SK, Pocock SJ, Dangas GD. Duration of dual antiplatelet therapy after drug-eluting stent implantation: A systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol*. 2015;65:1298-1310.
699. Navarese EP, Andreotti F, Schulze V, Kolodziejczak M, Buffon A, Brouwer M, Costa F, Kowalewski M, Parati G, Lip GY, Kelm M, Valgimigli M. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: Meta-analysis of randomised controlled trials. *BMJ*. 2015;350:h1618.
700. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371:2155-2266.
701. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; TRITON TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001-2015.
702. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045-1057.
703. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin

- in acute coronary syndrome without ST elevation: A meta-analysis. *Lancet*. 2000;355:1936-1942.
704. Cohen M, Mahaffey KW, Pieper K, Pollack CV Jr, Antman EM, Hoekstra J, Goodman SG, Langer A, Col JJ, White HD, Califf RM, Ferguson JJ; SYNERGY Trial Investigators. A subgroup analysis of the impact of prerandomization antithrombin therapy on outcomes in the SYNERGY trial: Enoxaparin versus unfractionated heparin in non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol*. 2006;48:1346-1354.
705. Ferguson JJ, Califf RM, Antman EM, Cohen M, Grines CL, Goodman S, Kereiakes DJ, Langer A, Mahaffey KW, Nessel CC, Armstrong PW, Avezum A, Aylward P, Becker RC, Biasucci L, Borzak S, Col J, Frey MJ, Fry E, Gulba DC, Guneri S, Gurfinkel E, Harrington R, Hochman JS, Kleiman NS, Leon MB, Lopez-Sendon JL, Pepine CJ, Ruzyllo W, Steinhubl SR, Teirstein PS, Toro-Figueroa L, White H; SYNERGY Trial Investigators. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: Primary results of the SYNERGY randomized trial. *JAMA*. 2004;292:45-54.
706. Cavender MA, Sabatine MS. Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: A meta-analysis of randomised controlled trials. *Lancet*. 2014;384:599-606.
707. Cassese S, Byrne RA, Laugwitz KL, Schunkert H, Berger PB, Kastrati A. Bivalirudin versus heparin in patients treated with percutaneous coronary intervention: A meta-analysis of randomised trials. *EuroIntervention*. 2015;11:196-203.
708. Zhang S, Gao W, Li H, Zou M, Sun S, Ba Y, Liu Y, Cheng G. Efficacy and safety of bivalirudin versus heparin in patients undergoing percutaneous coronary intervention: A meta-analysis of randomized controlled trials. *Int J Cardiol*. 2016;209:87-95.
709. Erlinge D, Omerovic E, Frobert O, Linder R, Danielewicz M, Hamid M, Swahn E, Henareh L, Wagner H, Hardhammar P, Sjogren I, Stewart J, Grimfjard P, Jensen J, Aasa M, Robertsson L, Lindroos P, Haupt J, Wikstrom H, Ulvenstam A, Bhiladvala P, Lindvall B, Lundin A, Todt T, Ioanes D, Ramunddal T, Kellerth T, Zagozdzon L, Gotberg M, Andersson J, Angeras O, Ostlund O, Lagerqvist B, Held C, Wallentin L, Schersten F, Eriksson P, Koul S, James S. Bivalirudin versus heparin monotherapy in myocardial infarction. *N Engl J Med*. 2017;377:1132-1142.
710. Nührenberg TG, Hochholzer W, Mashayekhi K, Ferenc M, Neumann FJ. Efficacy and safety of bivalirudin for percutaneous coronary intervention in acute coronary syndromes: A meta-analysis of randomized-controlled trials. *Clin Res Cardiol*. doi:10.1007/s00392-018-1251-1. Published online ahead of print 13 April 2018.
711. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes I, Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJ, Bassand JP, Wallentin L, Joyner C, Fox KA. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med*. 2006;354:1464-1476.
712. Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van de Werf F, de Torbal A, Armstrong PW, Wallentin LC, Wilcox RG, Simes J, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: A meta-analysis of all major randomised clinical trials. *Lancet*. 2002;359:189-198.
713. Giugliano RP, White JA, Bode C, Armstrong PW, Montalescot G, Lewis BS, van 't Hof A, Berdan LG, Lee KL, Strony JT, Hildemann S, Veltri E, Van de Werf F, Braunwald E, Harrington RA, Califf RM, Newby LK; EARLY Investigators ACS. Early versus delayed, provisional eptifibatid in acute coronary syndromes. *N Engl J Med*. 2009;360:2176-2190.
714. Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, White HD, Pocock SJ, Ware JH, Feit F, Colombo A, Aylward PE, Cequier AR, Darius H, Desmet W, Ebrahimi R, Hamon M, Rasmussen LH, Rupprecht HJ, Hoekstra J, Mehran R, Ohman EM; ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med*. 2006;355: 2203-2216.
715. Hahn JY, Song YB, Oh JH, Cho DK, Lee JB, Doh JH, Kim SH, Jeong JO, Bae JH, Kim BO, Cho JH, Suh IW, Kim DI, Park HK, Park JS, Choi WG, Lee WS, Kim J, Choi KH, Park TK, Lee JM, Yang JH, Choi JH, Choi SH, Gwon HC, SMART-DATE Investigators. 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): A randomised, open-label, non-inferiority trial. *Lancet*. 2018;391:1274-1284.
716. Cuisset T, Deharo P, Quilici J, Johnson TW, Deffarges S, Bassez C, Bonnet G, Fourcade L, Mouret JP, Lambert M, Verdier V, Morange PE, Alessi MC, Bonnet JL. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: The TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. *Eur Heart J*. 2017;38:3070-3078.
717. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, Orban M, Hadamitzky M, Merkely B, Kiss RG, Komocsi A, Dezsai CA, Holdt L, Felix SB, Parma R, Klopotoski M, Schwinger RHG, Rieber J, Huber K, Neumann FJ, Koltowski L, Mehilli J, Huczek Z, Massberg S; TROPICAL-ACS Investigators. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): A randomised, open-label, multicentre trial. *Lancet*. 2017;390:1747-1757.
718. Angiolillo DJ, Rollini F, Storey RF, Bhatt DL, James S, Schneider DJ, Sibbing D, So DYF, Trenk D, Alexopoulos D, Gurbel PA, Hochholzer W, De Luca L, Bonello L, Aradi D, Cuisset T, Tantry US, Wang TY, Valgimigli M, Waksman R, Mehran R, Montalescot G, Franchi F, Price MJ. International expert consensus on switching platelet P2Y12 receptor-inhibiting therapies. *Circulation*. 2017;136:1955-1975.
719. Grines CL, Bonow RO, Casey DE Jr, Gardner TJ, Lockhart PB, Moliterno DJ, O'Gara P, Whitlow P; American Heart Association; American College of Cardiology; Society for Cardiovascular Angiography and Interventions; American College of Surgeons; American Dental Association; American College of Physicians. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: A science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Circulation*. 2007;115:813-818.
720. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM, ATLAS ACS 2-TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;366:9-19.

721. Patrono C, Andreotti F, Arnesen H, Badimon L, Baigent C, Collet JP, De Caterina R, Gulba D, Huber K, Husted S, Kristensen SD, Morais J, Neumann FJ, Rasmussen LH, Siegbahn A, Steg PG, Storey RF, Van de Werf F, Verheugt F. Antiplatelet agents for the treatment and prevention of atherothrombosis. *Eur Heart J*. 2011;32:2922-2932.
722. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA, Clopidogrel in Unstable angina to prevent Recurrent Events trial Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: The PCI-CURE study. *Lancet*. 2001;358:527-533.
723. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494-502.
724. Mehta SR, Tanguay JF, Eikelboom JW, Jolly SS, Joyner CD, Granger CB, Faxon DP, Rupprecht HJ, Budaj A, Avezum A, Widimsky P, Steg PG, Bassand JP, Montalescot G, Macaya C, Di Pasquale G, Niemela K, Ajani AE, White HD, Chrolavicius S, Gao P, Fox KA, Yusuf S; CURRENT-OASIS 7 Investigators. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): A randomised factorial trial. *Lancet*. 2010;376(9748):1233-1243.
725. Stone GW, Bertrand ME, Moses JW, Ohman EM, Lincoff AM, Ware JH, Pocock SJ, McLaurin BT, Cox DA, Jafar MZ, Chandna H, Hartmann F, Leisch F, Strasser RH, Desaga M, Stuckey TD, Zelman RB, Lieber IH, Cohen DJ, Mehran R, White HD; ACUITY Investigators. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: The ACUITY Timing trial. *JAMA*. 2007;297:591-602.
726. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *JAMA*. 1996;276:811-815.
727. FUTURA/OASIS-Trial Group 8, Steg PG, Jolly SS, Mehta SR, Afzal R, Xavier D, Rupprecht HJ, Lopez-Sendon JL, Budaj A, Diaz R, Avezum A, Widimsky P, Rao SV, Chrolavicius S, Meeks B, Joyner C, Pogue J, Yusuf S. Low-dose vs standard-dose unfractionated heparin for percutaneous coronary intervention in acute coronary syndromes treated with fondaparinux: The FUTURA/OASIS-8 randomized trial. *JAMA*. 2010;304:1339-1349.
728. Valgimigli M, Frigoli E, Leonardi S, Rothenbuhler M, Gagnor A, Calabro P, Garducci S, Rubartelli P, Briguori C, Ando G, Repetto A, Limbruno U, Garbo R, Sganzerla P, Russo F, Lupi A, Cortese B, Ausiello A, Ierna S, Esposito G, Presbitero P, Santarelli A, Sardella G, Varbella F, Tresoldi S, de Cesare N, Rigattieri S, Zingarelli A, Tosi P, van 't Hof A, Boccuzzi G, Omerovic E, Sabate M, Heg D, Juni P, Vranckx P; MATRIX Investigators. Bivalirudin or unfractionated heparin in acute coronary syndromes. *N Engl J Med*. 2015;373:997-1009.
729. Palmerini T, Della Riva D, Benedetto U, Reggiani LB, Feres F, Abizaid A, Gilard M, Morice M, Valgimigli M, Hong M, Kim B, Jang Y, Kim H, Park KW, Colombo A, Chieffo A, Sangiorgi D, Biondi-Zoccai G, Genereux P, Angelini GD, White, Bhatt DL, Stone GW. Three, six or twelve months of dual antiplatelet therapy after drug-eluting stent implantation in patients with or without acute coronary syndromes: An individual patient data pairwise and network meta-analysis of six randomized trials and 11,473 patients. *Eur Heart J*. 2017;38:1034-1043.
730. Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M; PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: A pooled analysis of individual-patient datasets from clinical trials. *Lancet*. 2017;389:1025-1034.
731. Bonaca MP, Bhatt DL, Steg PG, Storey RF, Cohen M, Im K, Oude Ophuis T, Budaj A, Goto S, Lopez-Sendon J, Diaz R, Dalby A, Van de Werf F, Ardissino D, Montalescot G, Aylward P, Magnani G, Jensen EC, Held P, Braunwald E, Sabatine MS. Ischaemic risk and efficacy of ticagrelor in relation to time from P2Y12 inhibitor withdrawal in patients with prior myocardial infarction: Insights from PEGASUS-TIMI 54. *Eur Heart J*. 2016;37:1133-1142.
732. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS, PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372:1791-1800.
733. Costa F, Adamo M, Ariotti S, Navarese EP, Biondi-Zoccai G, Valgimigli M. Impact of greater than 12-month dual antiplatelet therapy duration on mortality: Drug-specific or a class-effect? A meta-analysis. *Int J Cardiol*. 2015;201:179-181.
734. Hermiller JB, Krucoff MW, Kereiakes DJ, Windecker S, Steg PG, Yeh RW, Cohen DJ, Cutlip DE, Massaro JM, Hsieh WH, Mauri L; DAPT Study Investigators. Benefits and risks of extended dual antiplatelet therapy after everolimus-eluting stents. *JACC Cardiovasc Interv*. 2016;9:138-147.
735. Motovska Z, Hlinomaz O, Miklik R, Hromadka M, Varvarovsky I, Dusek J, Knot J, Jarkovsky J, Kala P, Rokyta R, Tousek F, Kramarikova P, Majtan B, Simek S, Branny M, Mrozek J, Cervinka P, Ostransky J, Widimsky P; PRAGUE-18 Study Group. Prasugrel versus ticagrelor in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: Multicenter randomized PRAGUE-18 study. *Circulation*. 2016;134:1603-1612.
736. Montalescot G, van 't Hof AW, Lapostolle F, Silvain J, Lassen JF, Bolognese L, Cantor WJ, Cequier A, Chettibi M, Goodman SG, Hammett CJ, Huber K, Janzon M, Merkely B, Storey RF, Zeymer U, Stibbe O, Ecollan P, Heutz WM, Swahn E, Collet JP, Willems FF, Baradat C, Licour M, Tsatsaris A, Vicaut E, Hamm CW; ATLANTIC Investigators. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med*. 2014;371:1016-1027.
737. Montalescot G, Zeymer U, Silvain J, Boulanger B, Cohen M, Goldstein P, Ecollan P, Combes X, Huber K, Pollack C Jr,

- Benezet JF, Stibbe O, Filippi E, Teiger E, Cayla G, Elhadad S, Adnet F, Chouihed T, Gallula S, Greffet A, Aout M, Collet JP, Vicaut E; ATOLL Investigators. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: The international randomised open-label ATOLL trial. *Lancet*. 2011;378:693-703.
738. Montalescot G, Barragan P, Wittenberg O, Ecollan P, Elhadad S, Villain P, Boulenc JM, Morice MC, Maillard L, Pansieri M, Choussat R, Pinton P; ADMIRAL Investigators. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med*. 2001;344:1895-1903.
739. Stone GW, Grines CL, Cox DA, Garcia E, Tchong JE, Griffin JJ, Guagliumi G, Stuckey T, Turco M, Carroll JD, Rutherford BD, Lansky AJ; Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Investigators. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med*. 2002;346:957-966.
740. De Luca G, Navarese E, Marino P. Risk profile and benefits from Gp IIb-IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: A meta-regression analysis of randomized trials. *Eur Heart J*. 2009;30:2705-2713.
741. Ellis SG, Tendera M, de Belder MA, van Boven AJ, Widimsky P, Janssens L, Andersen HR, Betriu A, Savonitto S, Adamus J, Peruga JZ, Kosmider M, Katz O, Neunteufl T, Jorgova J, Dorobantu M, Grinfeld L, Armstrong P, Brodie BR, Herrmann HC, Montalescot G, Neumann FJ, Effron MB, Barnathan ES, Topol EJ; FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med*. 2008;358:2205-2217.
742. Van't Hof AW, Ten Berg J, Heestermaans T, Dill T, Funck RC, van Werkum W, Dambrink JH, Suryapranata H, van Houwelingen G, Ottervanger JP, Stella P, Giannitsis E, Hamm C; Ongoing Tirofiban In Myocardial infarction Evaluation 2 Study Group. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): A multi-centre, double-blind, randomised controlled trial. *Lancet*. 2008;372:537-546.
743. Steg PG, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP, Emanuelsson H, Finkelstein A, Husted S, Katus H, Kilham J, Olofsson S, Storey RF, Weaver WD, Wallentin L; PLATO Study Group. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation*. 2010;122:2131-2141.
744. Steg PG, van 't Hof A, Hamm CW, Clemmensen P, Lapostolle F, Coste P, Ten Berg J, Van Grunsven P, Eggink GJ, Nibbe L, Zeymer U, Campo dell'Orto M, Nef H, Steinmetz J, Soulat L, Huber K, Deliargyris EN, Bernstein D, Schuette D, Prats J, Clayton T, Pocock S, Hamon M, Goldstein P; EUROMAX Investigators. Bivalirudin started during emergency transport for primary PCI. *N Engl J Med*. 2013;369:2207-2217.
745. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong SC, Kirtane AJ, Parise H, Mehran R; HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. 2008;358:2218-2230.
746. Shahzad A, Kemp I, Mars C, Wilson K, Roome C, Cooper R, Andron M, Appleby C, Fisher M, Khand A, Kunadian B, Mills JD, Morris JL, Morrison WL, Munir S, Palmer ND, Perry RA, Ramsdale DR, Velavan P, Stables RH; HEAT-PPCI Trial Investigators. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): An open-label, single centre, randomised controlled trial. *Lancet*. 2014;384:1849-1858.
747. Hansson EC, Jideus L, Aberg B, Bjursten H, Dreifaldt M, Holmgren A, Ivert T, Nozohoor S, Barbu M, Svedjeholm R, Jeppsson A. Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: A nationwide study. *Eur Heart J*. 2016;37:189-197.
748. Tomsic A, Schotborgh MA, Manshanden JS, Li WW, de Mol BA. Coronary artery bypass grafting-related bleeding complications in patients treated with dual antiplatelet treatment. *Eur J Cardiothorac Surg*. 2016;50:849-856.
749. Gherli R, Mariscalco G, Dalen M, Onorati F, Perrotti A, Chocron S, Verhoye JP, Gulbins H, Reichart D, Svenarud P, Faggian G, Santarpino G, Fischlein T, Maselli D, Dominici C, Musumeci F, Rubino AS, Mignosa C, De Feo M, Bancone C, Gatti G, Maschietto L, Santini F, Nicolini F, Gherli T, Zanobini M, Kinnunen EM, Ruggieri VG, Rosato S, Biancari F. Safety of preoperative use of ticagrelor with or without aspirin compared with aspirin alone in patients with acute coronary syndromes undergoing coronary artery bypass grafting. *JAMA Cardiol*. 2016;1:921-928.
750. Kwak YL, Kim JC, Choi YS, Yoo KJ, Song Y, Shim JK. Clopidogrel responsiveness regardless of the discontinuation date predicts increased blood loss and transfusion requirement after off-pump coronary artery bypass graft surgery. *J Am Coll Cardiol*. 2010;56:1994-2002.
751. Ranucci M, Baryshnikova E, Soro G, Ballotta A, De Benedetti D, Conti D; Surgical and Clinical Outcome Research (SCORE) Group. Multiple electrode whole-blood aggregometry and bleeding in cardiac surgery patients receiving thienopyridines. *Ann Thorac Surg*. 2011;91:123-129.
752. Ranucci M, Colella D, Baryshnikova E, Di Dedda U; Surgical and Clinical Outcome Research (SCORE) Group. Effect of preoperative P2Y12 and thrombin platelet receptor inhibition on bleeding after cardiac surgery. *Br J Anaesth*. 2014;113:970-976.
753. Lamberts M, Gislason GH, Olesen JB, Kristensen SL, Schjerning Olsen AM, Mikkelsen A, Christensen CB, Lip GY, Kober L, Torp-Pedersen C, Hansen ML. Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention. *J Am Coll Cardiol*. 2013;62:981-989.
754. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermaans AA, Vis MM, Tijssen JG, van 't Hof AW, ten Berg JM; WOEST Study Investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: An open-label, randomised, controlled trial. *Lancet*. 2013;381:1107-1115.
755. Fiedler KA, Maeng M, Mehilli J, Schulz-Schupke S, Byrne RA, Sibbing D, Hoppmann P, Schneider S, Fusaro M, Ott I, Kristensen SD, Ibrahim T, Massberg S, Schunkert H, Laugwitz KL, Kastrati A, Sarafoff N. Duration of triple therapy in patients

- requiring oral anticoagulation after drug-eluting stent implantation: The ISAR-TRIPLE trial. *J Am Coll Cardiol*. 2015;65:1619-1629.
756. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Ianus J, Burton P, van Eickels M, Korjian S, Daaboul Y, Lip GY, Cohen M, Husted S, Peterson ED, Fox KA. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med*. 2016;375:2423-2434.
757. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S, Nordaby M, Kleine E, Harper R, Manassie J, Januzzi JL, Ten Berg JM, Steg PG, Hohnloser SH; DUAL RE-Steering Committee PCI and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017;377:1513-1524.
758. Dans AL, Connolly SJ, Wallentin L, Yang S, Nakamya J, Brueckmann M, Ezekowitz M, Oldgren J, Eikelboom JW, Reilly PA, Yusuf S. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. *Circulation*. 2013;127:634-640.
759. Kopin D, Jones WS, Sherwood MW, Wojdyla DM, Wallentin L, Lewis BS, Verheugt FWA, Vinereanu D, Bahit MC, Halvorsen S, Huber K, Parkhomenko A, Granger CB, Lopes RD, Alexander JH. Percutaneous coronary intervention and antiplatelet therapy in patients with atrial fibrillation receiving apixaban or warfarin: Insights from the ARISTOTLE trial. *Am Heart J*. 2018;197:133-141.
760. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. *Lancet*. 2014;383:955-962.
761. Post PN, Kuijpers M, Ebels T, Zijlstra F. The relation between volume and outcome of coronary interventions: a systematic review and meta-analysis. *Eur Heart J*. 2010;31:1985-1992.
762. Kim LK, Looser P, Feldman DN. Peri- and postoperative care after coronary artery bypass grafting in low versus high volume centers. *J Thorac Cardiovasc Surg*. 2016;152:1205.
763. Gonzalez AA, Dimick JB, Birkmeyer JD, Ghaferi AA. Understanding the volume-outcome effect in cardiovascular surgery: The role of failure to rescue. *JAMA Surg*. 2014;149:119-123.
764. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med*. 2003;349:2117-2127.
765. Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah A, Papadimos TJ, Engoren M, Habib RH. Is hospital procedure volume a reliable marker of quality for coronary artery bypass surgery? A comparison of risk and propensity adjusted operative and midterm outcomes. *Ann Thorac Surg*. 2005;79:1961-199.
766. Kurlansky PA, Argenziano M, Dunton R, Lancey R, Nast E, Stewart A, Williams T, Zapolanski A, Chang H, Tingley J, Smith CR. Quality, not volume, determines outcome of coronary artery bypass surgery in a university-based community hospital network. *J Thorac Cardiovasc Surg*. 2012;143:287-293.
767. Auerbach AD, Hilton JF, Maselli J, Pekow PS, Rothberg MB, Lindenauer PK. Shop for quality or volume? Volume, quality, and outcomes of coronary artery bypass surgery. *Ann Intern Med*. 2009;150:696-704.
768. Pagano D, Kappetein AP, Sousa-Uva M, Beyersdorf F, Klautz R, Mohr F, Falk V; European Association for Cardio-Thoracic Surgery (EACTS) and the EACTS Quality Improvement Programme. EACTS clinical statement: Guidance for the provision of adult cardiac surgery. *Eur J Cardiothorac Surg*. 2016;50:1006-1009.
769. Hannan EL, Wu C, Walford G, King SB, III, Holmes DR, Jr, Ambrose JA, Sharma S, Katz S, Clark LT, Jones RH. Volume-outcome relationships for percutaneous coronary interventions in the stent era. *Circulation*. 2005;112:1171-1179.
770. McGrath PD, Wennberg DE, Dickens JD Jr, Siewers AE, Lucas FL, Malenka DJ, Kellett MA Jr, Ryan TJ Jr. Relation between operator and hospital volume and outcomes following percutaneous coronary interventions in the era of the coronary stent. *JAMA*. 2000;284:3139-3144.
771. Nallamothu BK, Wang Y, Magid DJ, McNamara RL, Herrin J, Bradley EH, Bates ER, Pollack CV Jr, Krumholz HM; National Registry of Myocardial Infarction Investigators. Relation between hospital specialization with primary percutaneous coronary intervention and clinical outcomes in ST-segment elevation myocardial infarction: National Registry of Myocardial Infarction-4 analysis. *Circulation*. 2006;113:222-229.
772. Spaulding C, Morice MC, Lancelin B, El Haddad S, Lepage E, Bataille S, Tresca JP, Mouranche X, Fosse S, Monchi M, de Vernejoul N; CARDIO-ARIF registry Investigators. Is the volume-outcome relation still an issue in the era of PCI with systematic stenting? Results of the greater Paris area PCI registry. *Eur Heart J*. 2006;27:1054-1060.
773. Vakili BA, Kaplan R, Brown DL. Volume-outcome relation for physicians and hospitals performing angioplasty for acute myocardial infarction in New York state. *Circulation*. 2001;104:2171-2176.
774. Canto JG, Every NR, Magid DJ, Rogers WJ, Malmgren JA, Frederick PD, French WJ, Tiefenbrunn AJ, Misra VK, Kiefe CI, Barron HV. The volume of primary angioplasty procedures and survival after acute myocardial infarction. National Registry of Myocardial Infarction 2 Investigators. *N Engl J Med*. 2000;342:1573-1580.
775. Xu B, Redfors B, Yang Y, Qiao S, Wu Y, Chen J, Liu H, Chen J, Xu L, Zhao Y, Guan C, Gao R, Genereux P. Impact of operator experience and volume on outcomes after left main coronary artery percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2016;9:2086-2093.
776. Di Mario C, Di Sciascio G, Dubois-Rande JL, Michels R, Mills P. Curriculum and syllabus for Interventional Cardiology subspecialty training in Europe. *EuroIntervention*. 2006;2:31-6.
777. Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. *J Am Coll Cardiol*. 2016;67:1-12.
778. Clark AM, Hartling L, Vandermeer B, McAlister FA. Meta-analysis: Secondary prevention programs for patients with coronary artery disease. *Ann Intern Med*. 2005;143:659-72.
779. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: A systematic review. *JAMA*. 2003;290:86-97.
780. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J,

- Lamuela-Raventos RM, Serra-Majem L, Pinto X, Basora J, Munoz MA, Sorli JV, Martinez JA, Martinez-Gonzalez MA, PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med*. 2013;368:1279-1290.
781. Cholesterol Treatment Trialists Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhalra N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670-1681.
782. Patrono C, Morais J, Baigent C, Collet JP, Fitzgerald D, Halvorsen S, Rocca B, Siegbahn A, Storey RF, Vilahur G. Antiplatelet agents for the treatment and prevention of coronary atherothrombosis. *J Am Coll Cardiol*. 2017;70:1760-1776.
783. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: A systematic review and meta-analysis. *Lancet*. 2016;387:957-967.
784. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH. Meta-analysis: Glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med*. 2004;141:421-431.
785. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:854-865.
786. Harb SC, Marwick TH. Prognostic value of stress imaging after revascularization: A systematic review of stress echocardiography and stress nuclear imaging. *Am Heart J*. 2014;167:77-85.

# 2018 ESC/EACTS Guidelines on myocardial revascularization - Supplementary Data

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

**Developed with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI)**

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## Keywords

Acute coronary syndromes•Antithrombotic therapy•Bare-metal stents•Coronary artery bypass grafting•Coronary artery disease•Drug-eluting stents•Guidelines•Heart Team•Myocardial infarction•Myocardial ischaemia•Myocardial revascularization•Medical therapy•Percutaneous coronary intervention•Recommendation•Revascularization•Risk stratification•Stents•Stable angina•Stable coronary artery disease•ST-segment elevation myocardial infarction•SYNTAX score

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## 1. Supplementary tables and text

**Supplementary Table 1 Revascularization vs. medical therapy: angina, exercise time, and number of medications at early and late follow-up**

Study	Angina		Exercise time		Number of medications	
	Early	Late	Early	Late	Early	Late
ACME <sup>1</sup>	64 vs. 46%* free of angina at 6 months	62 vs. 47%* free of angina at 3 years	11.2 vs. 9.5 min* exercise time duration at 6 months	10.0 vs. 8.5 min* exercise time duration at 3 years	30 vs. 50% on beta-blocker*, 35 vs. 71% on CCB*, and 24 vs. 50% on nitrate* at 6 months	28 vs. 39% on beta-blocker, 47 vs. 72% on CCB*, and 24 vs. 52% on nitrate* at 3 years
RITA-2 <sup>2</sup>	19.4 vs. 35.9%* at 3 months	15.0 vs. 21.4%* at 5 years	37 s in favour of PCI* at 3 months	25 s in favour of PCI* at 3 years	37 vs. 57% on ≥2 drugs at 3 months	31 vs. 45% on ≥2 drugs at 5 years
AVERT <sup>3</sup>	Improvement in angina 54 vs. 41%* at 1.5 years	–	–	–	61 vs. 60% on beta-blocker, 44 vs. 49% on CCB, and 50 vs. 60% on nitrate at 1.5 years	–
TIME <sup>4</sup>	Significant improvement in angina class at 6 months	No differences in angina class at 1 year	–	–	Significant reduction of number of drugs at 6 months	Significant reduction of number of drugs at 1 year
MASS II <sup>5</sup>	21 (PCI) vs. 12 (CABG) vs. 54% (MT) free of angina* at 1 year	41 (PCI) vs. 36 (CABG) vs. 57% (MT) free of angina* at 10 years	–	–	–	–

SWISSI II <sup>6</sup>	–	–	Max workload at bicycle ergometry 169 vs. 148 W* at 4 years	Max workload at bicycle ergometry 173 vs. 136 W* at 10 years	49 vs. 86% on beta-blocker*, 21 vs. 51% on CCB*, and 12 vs. 47% on nitrate* at 4 years	39 vs. 84% on beta-blocker*, 17 vs. 32% on CCB, and 4 vs. 45% on nitrate* at 10 years
COURAGE <sup>7</sup>	56 vs. 47%* free of angina at 6 months	59 vs. 56% free of angina at 3 years	–	–	85 vs. 89% on beta-blocker, 40 vs. 49% on CCB*, and 53 vs. 67% on nitrate* at 1 year	85 vs. 86% on beta-blocker, 42 vs. 52% on CCB*, and 40 vs. 57% on nitrate* at 5 years
FAME II <sup>8</sup>	91 vs. 80%* free of angina (CCS II–IV) at 6 months	94 vs. 88%* free of angina (CCS II–IV) at 2 years	–	–	81% vs. 82% on beta-blocker and 25 vs. 30% on CCB at 6 months	77 vs. 80% on beta-blocker and 30 vs. 32% on CCB* at 2 years
ORBITA <sup>9</sup>	51% vs. 45% improvement by at least 1 CCS class at 6 weeks	–	Difference in increment of 16.6 s in favour of PCI at 6 weeks	–	2.9 anginal medications in both arms at 6 weeks	–

\* $P < 0.05$ .

CABG = coronary artery bypass grafting; CCB = calcium-channel blocker; CCS = Canadian Cardiovascular Society; MT = medical therapy; PCI = percutaneous coronary intervention; W = watts.

Supplementary Table 2 Revascularization vs. medical therapy: study, baseline characteristics, primary endpoint, maximum clinical follow-up

Year of publication	Study	n	Baseline characteristics					Primary endpoint			Maximum clinical follow-up			
			Age (y)	Women (%)	Diabetes (%)	MVD (%)	EF (%)	Definition	Years	Results	Years	Death	MI	Revascularization
<b>CABG vs. MT</b>														
1980	ECSS	768	<65 <sup>b</sup>	0	–	100	>50 <sup>b</sup>	–	–	–	8	11.4 vs. 20.1%*	–	–
1984	VA	686	–	–	–	86	–	–	–	–	18	70 vs. 67%	49 vs. 41%	41 vs. 62% <sup>c</sup>
1984	CASS	780	51	10	9	73	–	–	–	–	10	19.2 vs. 21.8%	–	8.9 vs. 36.9% <sup>d</sup>
2011/2016	STICH	1212	60	12	39	91	27	Death	4.7	36 vs. 41%	9.8	58.9 vs. 66.1%*	–	–
<b>PTCA vs. MT</b>														
1997	RITA-2	1018	–	18	9	40	–	Death or MI	2.7	6.3 vs. 3.3%*	7	8.5 vs. 8.4%	6.3 vs. 4.5% <sup>c</sup>	27.2 vs. 35.4% <sup>c</sup>
1999	AVERT	341	58	16	16	43	61	Cardiac death, cardiac arrest, MI, CVA, revascularization, or hospitalization due to angina	1.5	20.9 vs. 13.4%*	1.5	0.6 vs. 0.6% <sup>a</sup>	2.8 vs. 2.4% <sup>c</sup>	16 vs. 12% <sup>c</sup>
2003	ALKK	300	58	13	16	0	–	MI, revascularization, or rehospitalization for severe angina	1	10 vs. 18%	4.7	4.0 vs. 11.2%*	6.7 vs. 7.9%	17 vs. 24%
2007	SWISSI-II	201	55	12	11	–	57	Cardiac death, MI, or revascularization	10.2	28.1 vs. 63.8%*	10.2	6.3 vs. 21.0%*	11.5 vs. 38.1%*	27.1 vs. 43.8%*
<b>BMS/CABG vs. MT</b>														
2001	TIME	305	80	43	23	79	53	Death, MI, or hospitalization for ACS	0.5	19.0 vs. 49.3%*	1	11.1 vs. 8.1%	–	–



1993	RITA-I	1011	–	19	6	55	–	Death or MI	2.5	9.8 vs. 8.6%	6.5	7.6 vs. 9.0%	10.8 vs. 7.4%	44.3 vs. 10.8%*	1.8 vs. 2.0% (at 2.5 years)
1994	GABI	359	–	20	12	100	–	Angina	1	29 vs. 26%	13	25.0 vs. 21.9%	4.3 vs. 5.6%	82.9 vs. 58.8%*	–
1994	EAST	392	62	26	23	100	61	Death, MI, or a large defect at thallium scan	3	28.8 vs. 27.3%	8	20.7 vs. 17.3%	3.0 vs. 10.3%* (at 3 year)	65.3 vs. 26.5%*	0.5 vs. 1.5% (at 3 years)
1995	CABRI	1054	60	22	12	99	63	Death	1	3.9 vs. 2.7%	4	10.9 vs. 7.4%	4.9 vs. 3.5% (at 1 year)	33.6 vs. 6.5%* (at 1 year)	–
1996	BARI	1829	62	27	25	100	57	Death	5	13.7 vs. 10.7%	10	29.0 vs. 26.5%	–	76.8 vs. 20.3%*	0.2 vs. 0.8% (in hospital)
<b>BMS</b>															
2001	AWESOME	454	67	–	31	82	45	Death	3	20 vs. 21%	3	20 vs. 21%	–	–	–
2001	ERACI II	450	62	21	17	100	–	Death, MI, stroke, or repeat revascularization	0.1	3.6 vs. 12.3%*	5	7.1 vs. 11.5%	2.8 vs. 6.2%	28.4 vs. 7.2%*	0 vs. 0.9% (at 30 days)
2001	ARTS	1205	61	23	17	99	61	Death, MI, stroke, or repeat revascularization	1	26.2 vs. 12.2%*	5	8.0 vs. 7.6%	6.7 vs. 5.6%	30.3 vs. 8.8%*	3.8 vs. 3.5%
2002	SoS	988	61	21	14	100	57	Repeat revascularization	2	21 vs. 6%*	6	10.9 vs. 6.8%*	5 vs. 8% (at 2 years)	21 vs. 6%* (at 2 years)	–
2003	OCTOSTENT	280	60	29	11	29	–	Death, MI, stroke, or repeat revascularization	1	14.5 vs. 8.5%	1	0 vs. 2.8%	4.4 vs. 4.9%	15.2 vs. 4.2%*	0 vs. 0%
2005	Thiele	220	62	25	30	0	63	Cardiac death, MI, or TVR	0.5	31 vs. 15%*	5.6	10 vs. 12%	5 vs. 7%	32 vs. 10%* (TVR)	–

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Age and ejection fraction are reported as means. \*P < 0.05.  
BMS = bare-metal stents; EF = ejection fraction; MI = myocardial infarction; MVD = multivessel coronary artery disease; PTCA = percutaneous transluminal coronary angioplasty; TVR = target vessel revascularization.

**Supplementary Table 4 Scoring systems used in conjunction with myocardial revascularization**

Score	Purpose	URL
<b><i>Outcomes after myocardial revascularization or ACS</i></b>		
EuroSCORE II	Prediction of in-hospital mortality	<a href="http://www.euroscore.org">www.euroscore.org</a>
STS	Prediction of in-hospital or 30-day mortality, and in-hospital morbidity	<a href="http://www.sts.org">www.sts.org</a>
SYNTAX	Prediction of medium- and long-term MACCE after PCI	<a href="http://www.syntaxscore.com">www.syntaxscore.com</a>
SYNTAX II	Prediction of mortality after CABG or PCI	<a href="http://www.syntaxscore.com">www.syntaxscore.com</a>
GRACE	Prediction of death or death/myocardial infarction following ACS	<a href="http://www.gracescore.org">www.gracescore.org</a>
<b><i>DAPT treatment duration</i></b>		
PRECISE-DAPT	To determine short (3–6 months) vs. standard/long (12–24 months) DAPT duration at the time of coronary stenting	<a href="http://www.precisedaptscore.com">www.precisedaptscore.com</a>
DAPT	To determine standard DAPT (12 months) vs. long DAPT (30 months) after 12 months of uneventful DAPT	<a href="http://www.daptstudy.org">www.daptstudy.org</a>
<b><i>Embolic and bleeding risk prediction</i></b>		
CHA <sub>2</sub> DS <sub>2</sub> -VASc	Prediction of stroke risk in patients with atrial fibrillation (relevant in a setting of PCI to determine the indication for OAC)	<a href="http://www.chadsvasc.org">www.chadsvasc.org</a>
HAS-BLED	Prediction of bleeding risk, e.g. in a setting of DAPT and OAC (triple treatment)	<a href="http://www.chadsvasc.org">www.chadsvasc.org</a>
ABC	Prediction of bleeding risk, e.g. in a setting of DAPT and OAC (triple treatment)	<a href="http://www.ucr.uu.se/en/services/abc-risk-calculators">www.ucr.uu.se/en/services/abc-risk-calculators</a>
<b><i>Frailty</i></b>		
Clinical Frailty Score	To assess frailty as a predictor of death and length of hospital stay	<a href="http://geriatricresearch.medicine.dal.ca/clinical_frailty_scale.htm">http://geriatricresearch.medicine.dal.ca/clinical_frailty_scale.htm</a>

ABC = Age, Biomarkers, Clinical History; ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled) – Vascular disease, Age 65–74 and Sex category (Female); DAPT = dual antiplatelet treatment; GRACE = Global Registry of Acute Coronary Events; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol; MACCE = major adverse cardiovascular events; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsequent Dual Anti Platelet Therapy; STS = Society of Thoracic Surgeons; SYNTAX = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

**Supplementary Table 5** Randomized trials on revascularization in diabetic patients

Year of publication	Study	n	Baseline characteristics				Primary endpoint			Max clinical follow-up						
			Age (y)	Women (%)	MVD (%)	EF (%)	Definition	Years	Results	Years	Death	CV death	MI	Revascularization		Stroke
<b>Revascularization vs. MT</b>																© ESC 2018
2009	BARI-2D <sup>10</sup>	2368	62	30	31 <sup>a</sup>	57	Death	5	11.7 vs. 12.2%	5	11.7 vs. 12.2%	5.9 vs. 5.7%	11.5 vs. 14.3%	–	2.6 vs. 2.8%	
<b>CABG vs. MT</b>																
2009	BARI-2D <sup>b 10</sup>	763	63	24	52 <sup>a</sup>	57	Death	5	13.6 vs. 16.4%	5	13.6 vs. 16.4%	8.0 vs. 9.0%	10.0 vs. 17.6%*	–	1.9 vs. 2.6%	
<b>PCI vs. MT</b>																
2009	BARI-2D <sup>b 10</sup>	1605	62	33	20 <sup>a</sup>	57	Death	5	10.8 vs. 10.2%	5	10.8 vs. 10.2%	5.0 vs. 4.2%	12.3 vs. 12.6%	–	2.9 vs. 2.9%	
<b>PCI vs. CABG</b>																
2009	SYNTAX <sup>c 11</sup>	452	65	29	100	–	Death, MI, stroke, or repeat revascularization	1	26.0 vs. 14.2%* Sx-Sc 0-22: 20.3 vs. 18.3%; 23-32: 26.0 vs. 12.9%; ≥33: 32.4 vs. 12.2%*	5	19.5 vs. 12.9%	12.7 vs. 6.5%*	9.0 vs. 5.4%	35.3% vs. 14.6%*	3.0 vs. 4.7%	
2010	CARDia <sup>12</sup> (DES/ BMS vs. CABG)	510	64	26	93	–	Death, MI, or stroke	1	13.0 vs. 10.5%	1	3.2 vs. 3.2%	–	9.8 vs. 5.7%	11.8% vs. 2.0%*	0.4 vs. 2.8%	

2012	FREEDOM <sup>13</sup> (DES vs. CABG)	1900	63	29	100	66	Death, MI, or stroke	3.8	26.6 vs. 18.7%* Sx-Sc 0-22: 23 vs. 17%; 23-32: 27 vs. 18%*; ≥33: 31 vs. 23%	3.8	16.3 vs. 10.9%*	10.9 vs. 6.8%	13.9 vs. 6.0%*	12.6% vs. 4.8%* (at 1 year)	2.4 vs. 5.2%*
2013	VA-CARDS <sup>14</sup> (DES vs. CABG)	207	62	1	–	–	Death or MI	2	25.3 vs. 18.4%	2	21 vs. 5.0%*	10.8 vs. 5.0%	6.2 vs. 15.0%	18.9% vs. 19.5%	1.0 vs. 1.2%

Age and ejection fraction are reported as means. \*P <0.05.

BMS = bare-metal stents; CABG = coronary artery bypass grafting; DES = drug-eluting stents; EF = ejection fraction; MI = myocardial infarction; MVD = multivessel coronary artery disease; MT = medical therapy; PCI = percutaneous coronary interventions; Sx-Sc = SYNTAX score

<sup>a</sup>Three-vessel disease.

<sup>b</sup>Randomization stratified by revascularization modality.

<sup>c</sup>Subgroup analysis.

**Supplementary Table 6 CE-approved new-generation drug-eluting stents recommended for clinical use based on randomized trials with a primary clinical endpoint (in alphabetical order)**

DES	Stent platform	Polymer coating	Drug	References
Based on durable polymer coatings				
Promus element	Platinum–chrome	PBMA and PVDF-HFP	Everolimus	15,16
Resolute	Cobalt–chrome	PBMA, PHMA, PVP, and PVA	Zotarolimus	16–18
Xience	Cobalt–chrome	PBMA and PVDF-HFP	Everolimus	19–21
EluNIR (BioNIR)	Cobalt–chrome	PBMA and TSPCU	Ridaforolimus	22
Based on biodegradable polymer coatings				
Biomatrix	Stainless steel	PDLLA	Biolimus A9	23,24
Nobori	Stainless steel	PDLLA	Biolimus A9	25–27
Orsiro	Cobalt–chrome	PLLA	Sirolimus	28,29
Synergy	Platinum–chrome	PLGA	Everolimus	29
Ultimaster	Stainless steel	PDLLA/PCL	Sirolimus	30
Yukon Choice PC	Stainless steel	PDLLA	Sirolimus	31
Polymer-free				
BioFreedom	Stainless steel	–	Biolimus A9	32
Yukon Choice PF	Stainless steel	–	Sirolimus	33

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DES = drug-eluting stent; PBMA = poly n-butyl methacrylate; PC = polymer-coated; PDLLA = poly(D,L)-lactic acid; PDLLA/PCL = poly (D,L)-lactide-co-caprolactone; PF = polymer-free; PHMA = polyhexyl methacrylate; PLGA = poly(d,l-lactide-co-glycolide); PLLA = poly-L-lactic acid; PVA = polyvinyl acetate; PVDF-HFP = poly(vinylidene fluoridehexafluoropropylene); PVP = polyvinyl pyrrolidone; TSPCU = thermoplastic silicone-polycarbonate-urethane.

**Supplementary Table 7 Overview of CE-marked bioresorbable scaffolds**

Commercial name	Manufacturer	Backbone material	Coating material	Device thickness	Drug release	Drug load	Duration of drug release	Bioresorption in pre-clinical swine models	Year of CE-mark	Year of FDA approval	Year of PMDA (Japan) approval	© ESC 2018
ABSORB BVS I.1	Abbott Vascular	PLLA	PDLLA	156 mm	Everolimus	76–308 1g/stent	3 months	36 months	2011	2016	2016	
DESolve (p DESolve 100/ DESolve Cx/ DESolve NXT)	Elixir Medical	PLLA	PLLA	100–150 mm	Novolimus	NA	3 months	24 months	2014	NA	NA	
ART Pure	ART	PDLLA	NA	170 mm	No drug elution	NA	NA	24 months	2015	NA	NA	
Magmaris	Biotronik	Magnesium alloy	PLLA	150 mm	Sirolimus	1.4 1g/mm <sup>2</sup>	3 months	9 - 12 months	2016	NA	NA	
Fantom	Reva	PTD-PC	PTD-PC	125 mm	Sirolimus	115 mg	NA	<3 years	2017	NA	NA	

BVS = bioresorbable vascular scaffold; FDA = US Food and Drug Administration; NA = not available; PDLLA = poly(D,L)-lactic acid; PLLA = poly-L-lactic acid; PMDA = Pharmaceuticals and Medical Devices Agency; PTD-PC = poly-tyrosine-derived polycarbonate.

**Supplementary Table 8 CE-approved drug-coated balloons (in alphabetical order)**

Device	Carrier	Drug	References	© ESC 2018
Agent	ATBC	Paclitaxel		
Angiosculpt	NDGA	Paclitaxel	–	
Danubio	BTHC	Paclitaxel	–	
Dior II	Shellac	Paclitaxel	34,35	
Elutax	–	Paclitaxel	36	
IN.PACT Falcon	Urea	Paclitaxel	37	
MagicTouch	Phospholipid- based	Sirolimus		
Moxy	Polysorbate	Paclitaxel	38	
Pantera Lux	BTHC	Paclitaxel	39	
Protégé NC	BTHC	Paclitaxel	–	
SeQuent Please	Iopromide	Paclitaxel	40–44	

ATBC = acetyl tributyl citrate; BTHC = butyryl-tri-hexyl citrate; NDGA = nordi-hydroguaiaretic acid.

**Supplementary Table 9 Quality indicators for coronary artery bypass grafting**

Pre-operative	© ESC 2018
Beta-blocker therapy	
Operative technique	
Percentage of internal mammary artery use	
Selection and duration of antibiotic prophylaxis	
Post-operative outcome rates	
Death	
Stroke	
Renal failure requiring dialysis	
Re-exploration for bleeding	
Re-intervention for graft failure	
Prolonged intubation time >24 h	
Deep sternal wound infection requiring sternal reconstruction	
Discharge	
Antiplatelet medication prescription	
High-dose lipid-lowering treatment prescription	
Adherence to guideline-recommended discharge medications depending on clinical setting	
Follow-up	
Readmission rates at 90 days	

30 day and 1 year mortality	
Unplanned repeat revascularization at 1 year	

Reference: <http://www.sts.org/quality-safety/performance-measures> (accessed 4 February 2018).

**Supplementary Table 10**      **Quality Indicators for percutaneous coronary intervention**

<b>Pre-interventional</b>	© ESC 2018
Adherence to guideline-recommended pre-treatment	
<b>Interventional technique</b>	
Procedural success	
Percentage of radial arterial access	
Percentage of drug-eluting stent implantation	
<b>Peri-interventional outcome rates</b>	
Death	
Periprocedural myocardial infarction	
Stroke	
Contrast-induced nephropathy	
Major bleeding (BARC 3 - 5)	
Emergency coronary artery bypass surgery	
<b>Discharge</b>	
Antiplatelet medication prescription	
High-dose lipid lowering treatment prescription	
Adherence to guideline-recommended discharge medications depending on clinical setting	
<b>Follow-up</b>	
Readmission rates	
30 day and 1 year mortality	
Unplanned repeat revascularization at 1 year	
Stent thrombosis according to ARC criteria	
Major bleeding (BARC 3 - 5)	
Composite of all-cause death, any myocardial infarction, and any unplanned repeat revascularization at 1 year	

ARC = Academic Research Consortium; BARC = Bleeding Academic Research Consortium.

**Supplementary Table 11**      **Antithrombotic drug dose adjustment in patients with chronic kidney disease**

	Normal kidney function or stage 1–2 CKD ( $\geq 60$ mL/min/1.73m <sup>2</sup> )	Stage 3 CKD ( $\geq 30$ – 59 mL/min/ 1.73m <sup>2</sup> )	Stage 4 CKD (15– 29 mL/min/1.73m <sup>2</sup> )	Stage 5 CKD (<15 mL/min/1.73m <sup>2</sup> )	© E
<b>ASA</b>	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment	

<b>Clopidogrel</b>	No dose adjustment	No dose adjustment	No dose adjustment	Use only for selected indications (e.g. stent thrombosis prevention)
<b>Prasugrel</b>	No dose adjustment	No dose adjustment	No dose adjustment	Not recommended
<b>Ticagrelor</b>	No dose adjustment	No dose adjustment	No dose adjustment	Not recommended
<b>Cangrelor</b>	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
<b>Enoxaparin</b>	1 mg/kg s.c. twice a day		1 mg/kg s.c. once a day; monitor anti-factor-Xa activity	Not recommended
<b>Unfractionated heparin</b>	<ul style="list-style-type: none"> <li>• Prior to coronary angiography: 60–70 IU/kg i.v. (max 5000 IU) and infusion 12–15 IU/kg/h (max 1000 IU/h), target aPTT 1.5–2.5× control</li> <li>• During PCI: according to ACT or 70–1000 IU/kg i.v. in patients not anticoagulated (50–70 IU/kg if concomitant with GP IIb/IIIa inhibitors)</li> </ul>		No dose adjustment	No dose adjustment
<b>Fondaparinux</b>	2.5 mg s.c. once a day	1.5 mg s.c. once a day	Not recommended if eGFR <20 mL/min/1.73m <sup>2</sup> )	Not recommended
<b>Bivalirudin</b>	Bolus 0.75 mg/kg i.v., infusion 1.75 mg/kg/h	Bolus 0.75 mg/kg i.v., infusion 1.4 mg/kg/h	Not recommended	Not recommended
<b>Abciximab</b>	Bolus 0.25 mg/kg i.v., infusion rate 0.125 g/kg/min (maximum 10 g/min)	No specific recommendations for the use of abciximab, or for dose adjustment in the case of renal failure; careful evaluation of haemorrhagic risk is needed		
<b>Eptifibatide</b>	Bolus 180 g/kg i.v., infusion rate 2 g/kg/ min	No adjustment of bolus, reduce infusion rate to 1 g/kg/min if eGFR <50 mL/min/1.73m <sup>2</sup>	Not recommended	Not recommended
<b>Tirofiban</b>	Bolus 25 g/kg or 10 g/kg i.v., infusion rate 0.15 g/kg/min	No dose adjustment	No adjustment of bolus, reduce infusion rate to 0.05 g/kg/min	Not recommended

aPTT = activated partial thromboplastin time; ACT = activated clotting time; ASA = acetylsalicylic acid (aspirin); CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GP = glycoprotein; i.v. = intravenous; PCI = percutaneous coronary intervention; s.c. = subcutaneous.

## Supplement to chapter 7: revascularization in ST-segment elevation myocardial infarction

### Studies on the revascularization strategy in patients presenting with ST-elevation myocardial infarction and multivessel disease

In the PRAMI (Preventive Angioplasty in Acute Myocardial Infarction) trial ( $n = 465$ ), preventive PCI in the non-IRA with stenosis  $\geq 50\%$  during the index PCI, when compared with PCI limited to the IRA, was associated with a reduced risk of the composite of death, MI, or refractory angina (HR in the preventive PCI group 0.35, 95% CI 0.21–0.58,  $P < 0.001$ ).<sup>45</sup> CvLPRIT (Complete Versus Lesion-Only Primary PCI Trial) randomized 296 STEMI patients with multivessel disease into either in-hospital complete revascularization (simultaneous or staged) or IRA-only revascularization.<sup>46</sup> The primary endpoint—a composite of all-cause death, recurrent MI, HF, and

ischaemia-driven revascularization within 12 months-occurred in 10.0% of the complete revascularization group vs. 21.2% in the IRA-only revascularization group (HR 0.45, 95% CI 0.24–0.84,  $P = 0.009$ ).

The DANAMI-3-PRIMULTI study allocated 627 patients after successful IRA PCI to either no further invasive treatment or complete FFR-guided revascularization of the non-IRA before discharge. The primary endpoint of all-cause mortality, non-fatal MI, and ischaemia-driven revascularization of lesions in the non-IRA at median follow-up of 27 months occurred in 68 (22%) patients who had IRA PCI only and in 40 (13%) patients who had complete revascularization (HR 0.56, 95% CI 0.38–0.83;  $P = 0.004$ ).<sup>47</sup> The benefit was driven by a reduction in repeat revascularization.

The Compare-Acute trial randomized 885 patients with STEMI and multivessel disease undergoing primary PCI to either complete revascularization of the non-IRA (guided by FFR) or no revascularization of the non-IRA.<sup>48</sup> The main finding was a reduction in the primary endpoint incidence (death, MI, revascularization, or stroke) (HR 0.35, 95% CI 0.22–0.55;  $P < 0.001$ ), with multivessel PCI driven mainly by a reduction in the need for revascularization at a later time point by non-IRA FFR-guided revascularization. However, it might also be observed that the overall rate of revascularization was considerably higher in the complete revascularization group.

### Revascularization strategy in patients with myocardial infarction and cardiogenic shock

One-year data from the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial ( $n = 302$ ) showed a significant advantage of early revascularization over medical therapy among patients younger than 75.<sup>49</sup> A subanalysis comparing CABG to PCI revealed similar survival rates between the two subgroups despite the fact that CABG was more often performed in patients with advanced, multivessel disease including LM disease, while patients with one- or two-vessel disease prevailed in the PCI arm.<sup>50</sup>

The SHOCK registry demonstrated that emergency revascularization with PCI or CABG improved long-term survival when compared with initial intensive medical therapy.<sup>51,52</sup> All-cause mortality at 6 months was lower in the group assigned to revascularization than in the medically treated patients (50.3 vs. 63.1%, respectively; RR 0.80, 95% CI 0.65–0.98;  $P < 0.03$ ). The findings of this non-randomized comparison suggest that CABG should be considered in patients with cardiogenic shock who have suitable anatomy, particularly if successful PCI is not feasible. A recent analysis of the Korean Acute Myocardial Infarction Registry (16 620 STEMI patients) suggested that multivessel revascularization at the time of primary PCI was associated with better outcomes in patients with STEMI and cardiogenic shock compared with culprit vessel revascularization only.<sup>53</sup> These studies suggested that multivessel PCI should be considered in STEMI patients with cardiogenic shock.

In the CULPRIT-SHOCK (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock) trial, patients with STEMI or non-ST-segment elevation myocardial infarction (NSTEMI) with cardiogenic shock were randomized to culprit lesion-only PCI or immediate PCI of all obstructive lesions (i.e. those with  $>70\%$  stenosis of the diameter). In the multivessel PCI group, recanalization of chronic total occlusions was performed when possible, and complete revascularization was achieved in 81% of patients. Staged revascularization was performed in 17.7% of the patients in the culprit lesion-only PCI group, and the crossover rate was relatively low (12.5% in the culprit lesion-only PCI group and 9.4% in the multivessel PCI group). The primary endpoint of death or severe renal failure leading to renal replacement therapy was higher with immediate multivessel PCI than with culprit lesion-only PCI. The results were similar for death from any cause (RR 0.84, 95% CI 0.72–0.98,  $P = 0.03$ ) and were consistent across pre-specified subgroups, including subgroups defined according to the presence or absence of a chronic total occlusion.

The CULPRIT-SHOCK trial used modern PCI technique and periprocedural management, and provides clear evidence that a strategy of culprit lesion-only PCI is preferred over initial multivessel PCI for patients with cardiogenic shock. Multivessel PCI should not be performed on a routine basis but may be considered in some patients, e.g. if there is uncertainty in identifying the culprit lesion.

## Supplement to chapter 10: revascularization in patients with chronic kidney disease

### Prevention of contrast-induced nephropathy

The risk of CIN depends on patient-related factors, such as CKD, diabetes mellitus, congestive HF, haemodynamic instability, reduced plasma volume, female sex, advanced age, and anaemia, as well as on the type and volume of contrast administered.<sup>54-55</sup> As compared with high-osmolar contrast agents, low- or iso-osmolar contrast agents reduce the risk of CIN.<sup>56-58</sup> The preference for iso- over low-osmolar contrast agents, suggested

by an initial small study,<sup>66</sup> could not be confirmed subsequently.<sup>69</sup> When the ratio of total contrast volume to GFR exceeds 3.7, the risk of CIN increases significantly.<sup>60,61</sup> Performing diagnostic and interventional procedures separately reduces the total volume exposure to contrast media. On the other hand, 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 if the contrast volume can be maintained at <4 mL/kg.

It is generally recommended that all patients with CKD who undergo catheterization should receive preventive hydration with isotonic saline.<sup>62</sup> Nevertheless, this recommendation is based on limited data on the comparison of isotonic saline with hypotonic saline<sup>63</sup> or with sodium bicarbonate.<sup>64,65</sup> However, no randomized trial until recently had compared intravenous pre-hydration with no prophylaxis. Moreover, the superiority of isotonic saline over sodium bicarbonate seen in the initial studies did not prevail in a recent meta-analysis.<sup>66</sup> Likewise, in the contemporary AMACING (A Maastricht Contrast-Induced Nephropathy Guideline) randomized trial, intravenous 0.9% sodium chloride was directly compared with no prophylaxis in 660 patients with an estimated GFR of 30–59 mL/min/1.73 m<sup>2</sup> undergoing an elective procedure requiring iodinated contrast material.<sup>67</sup> Within 2–6 days after contrast exposure, no prophylaxis was non-inferior to intravenous hydration for the prevention of CIN and cost-saving. These findings need to be interpreted with consideration of the single-centre design of the trial and the relatively small sample size of the low-risk cohort.<sup>67</sup>

Given the known impact of low effective circulating volumes on the risk of CIN, there is still consensus that adequate hydration is needed to prevent CIN. Based on previous experience,<sup>64,65,68</sup> preventive hydration with isotonic saline should be started in patients at increased risk approximately 12 h before angiography and continued for at least 24 h afterwards to reduce the risk of CIN, especially if GFR is <40 mL/min/1.73 m<sup>2</sup>. The optimal duration of the infusion therapy is not fully known. Recently, promising results were obtained by adjusting the infusion rate to central venous pressure.<sup>69</sup> Two targeted hydration regimens starting shortly before catheterization have shown superiority over conventional hydration schemes.<sup>70,71</sup> In the POSEIDON (Prevention of Contrast Renal Injury with Different Hydration Strategies) study, patients with CKD stage 3 were randomly assigned to infusion rates adjusted to LV end-diastolic pressure or to standard infusion rates.<sup>70</sup> CIN occurred less frequently in patients of the targeted hydration group (6.7%) than in the control group (16.3%; RR 0.41, 95% CI 0.22–0.79, *P* = 0.005). Similarly in a high-risk group of patients with CKD, the REMEDIAL II (Renal Insufficiency After Contrast Media Administration II) trial showed that a strategy of controlled hydration with forced diuresis and matched saline infusion using an automated system was superior to the control group [incidence of CIN 11 vs. 20.5%; odds ratio (OR) 0.47, 95% CI 0.24–0.92].<sup>71</sup> The findings of REMEDIAL II were confirmed in a recent meta-analysis including three additional studies.<sup>72</sup> Thus, in specific patient subsets, the targeted hydration regimens represent a valuable alternative to standard hydration.

Apart from adequate hydration, several preventative strategies for CIN have been tested in a number of studies with inconsistent results, as reviewed by several meta-analyses.<sup>66,68,73</sup> In a recent hierarchical Bayesian network meta-analysis of 124 trials and 28 240 patients undergoing cardiac catheterization,<sup>66</sup> only high-dose statins showed an unequivocal beneficial effect that according to another meta-analysis appeared to be independent of the concomitant hydration protocol.<sup>74</sup> Although theophylline, N-acetylcysteine (NAC), sodium bicarbonate, peripheral ischaemic pre-conditioning, and natriuretic peptide also showed some benefit over saline alone in the overall analysis, these findings were highly heterogeneous across studies and did not prevail in sensitivity analyses.<sup>66</sup> None of the apparent benefits were detectable in diabetics and some (theophylline and sodium bicarbonate) were mitigated in patients with CKD stage 3 or 4.<sup>66</sup> The results were confounded by publication bias, the inclusion of trials with lower methodological quality, and suboptimal dosology.<sup>66</sup> More recently, the PRESERVE (Prevention of Serious Adverse Events Following Angiography) trial tested the efficacy of intravenous sodium bicarbonate or oral acetylcysteine in preventing CIN.<sup>75</sup> This randomized controlled trial included 5177 patients at high risk for renal complications who were scheduled for angiography. Using a two-by-two factorial design, PRESERVE did not show any benefit of intravenous sodium bicarbonate over intravenous sodium chloride, or of oral acetylcysteine over placebo, for the prevention of death, need for dialysis, or persistent decline in kidney function at 90 days.

In summary, adequate hydration remains the mainstay of CIN prevention. High-dose statins are also beneficial. Since they are indicated for secondary prevention in patients undergoing coronary revascularization irrespective of the risk of CIN, no specific recommendation for CIN is needed. All other strategies for the prevention of CIN do not have sufficient evidence to justify a recommendation in favour or against.

For patients undergoing CABG, the effectiveness of the implementation of pharmacological preventive measures—such as clonidine, fenoldopam, natriuretic peptides, NAC, or elective pre-operative haemodialysis—remains unproven.

## Supplement to chapter 11: revascularization in patients requiring valve interventions

### Surgical repair of secondary mitral regurgitation in patients undergoing coronary artery bypass grafting

Controversy exists regarding the definition of 'moderate' MR used in the CTSN trial. In the CTSN trial, the integrative approach for the classification of MR, inclusive of an EROA of 0.2–0.39 cm<sup>2</sup>, as described by the American Society of Echocardiography (ASE), was used to define moderate MR. However, both the ASE and European Association for Cardiovascular Imaging Guidelines for valvular regurgitation acknowledge that in ischaemic MR (IMR), an EROA of >0.2 cm<sup>2</sup> and a regurgitant volume of >30 mL indicates a worse prognosis and greater risk of cardiovascular events.<sup>76,77</sup> The 2017 ESC/EACTS Guidelines for the management of valvular heart disease define an EROA of >0.2 cm<sup>2</sup> and a regurgitant volume of >30 mL as the cut-off for severe secondary MR.<sup>78</sup> Furthermore, due to several screening failures in the early phase of the CTSN trial, thought to be due to overly restrictive EROA, the criteria were broadened to include patients with EROA <0.2 cm<sup>2</sup> and other integrative criteria of more than mild MR.<sup>79</sup> In summary therefore, the CTSN trial on moderate IMR included patients with IMR defined by EROA <0.4 cm<sup>2</sup>, and did not demonstrate an improvement in outcomes with surgical correction of secondary MR in combination with CABG compared with CABG alone. While this is not consistent with current Guidelines on the classification of IMR as described above, the main value of the reduced threshold for severe IMR is based on prognostic outcomes of patients with EROA >0.2 cm<sup>2</sup>. The use of this classification in guiding treatment would present challenges with either leaving clinically significant IMR (EROA >0.4 cm<sup>2</sup>) untreated or the over-treatment of patients with EROA <0.4 cm<sup>2</sup>, where the addition of mitral repair has not been shown to improve outcomes.

The dynamic nature of IMR also needs consideration and stress echo may be used to guide treatment, although no robust evidence is available to guide this recommendation. Ultimately, IMR remains a complex area with unanswered questions despite several randomized trials. The present Guidelines express the expert opinion and consensus of the Task Force, and are also in keeping with the valvular heart disease Guidelines. Treatment decisions should be made in the context of the Heart Team taking into account the severity of MR, comorbidities, symptoms, LV and LA size, the viability of revascularized myocardium, completeness of revascularization, tenting area, and coaptation height. Additionally, with the advent of rapidly advancing techniques for transcatheter mitral valve repair/replacement and mitral annuloplasty, a Heart Team discussion on the feasibility of future transcatheter treatment options in patients undergoing myocardial revascularization may be used as a guide to decision-making.

## Supplement to chapter 16: procedural aspects of percutaneous coronary intervention

### Studies on the Absorb bioresorbable vascular scaffold

Primary endpoint results from the ABSORB II (A Bioresorbable Everolimus-Eluting Scaffold Versus a Metallic Everolimus-Eluting Stent II) trial failed to demonstrate superiority of the Absorb BVS (bioresorbable vascular scaffold) vs. conventional DES in terms of vasomotor response to intracoronary nitrate in the stented segment at 3 years.<sup>80</sup> Moreover, the co-primary endpoint late lumen loss was inferior with BVS and there was no difference in terms of patient-reported angina symptoms. There was a significant increase in the device-oriented composite endpoint of cardiac death, target vessel MI, and clinically indicated target lesion revascularization (TLR) with BRS compared with DES (10.4 vs. 4.9%;  $P = 0.043$ ), which was driven by a significant difference in target vessel MI (6 vs. 1%;  $P = 0.011$ ) and in definite or probable device thrombosis (3 vs. 0%;  $P = 0.033$ ). This excess in late adverse clinical events was also seen in the 2 year results of the ABSORB III and ABSORB Japan trial.<sup>81</sup>

ABSORB IV, the largest available trial on BRS, which applied a dedicated technique for BRS implantation, showed inferior procedural outcomes with BRS as compared with EES. The ABSORB IV demonstrated the non-inferiority of BRS as compared with EES for the primary endpoint target lesion failure (a composite of cardiac death, MI, and ischaemia-driven TLR) at 30 days (HR 1.36, 95% CI 0.93–1.97,  $P_{\text{non-inferiority}} = 0.02$ ). Device thrombosis tended to be higher with BRS than EES at 30 days (HR 4.05, 95% CI 0.86–19.07;  $P = 0.06$ ).

The AIDA (Amsterdam Investigator-Initiated Absorb Strategy All-Comers) investigator-initiated trial<sup>82</sup> enrolled relatively unselected patients undergoing intervention in routine practice including patients with ACS. The trial intended to test the non-inferiority of BRS vs. EES at 2 years. However, during follow-up and after full enrolment, the data and safety monitoring board of the trial recommended early reporting due to safety concerns. At the time of reporting, the median duration of follow-up was 707 days. The primary endpoint—a composite of cardiac

death, target vessel MI, or TVR—was similar in both groups (11.7 vs. 10.7%; HR 1.12, 95% CI 0.85–1.48,  $P = 0.43$ ). Definite/probable stent thrombosis was significantly higher in the BRS treatment group (3.5 vs. 0.9%;  $P < 0.001$ ).

Meta-analyses including mid- to long-term follow-up of randomized trials of Absorb BRS vs. conventional DES showed that the risk of adverse events beyond 1 year is also significantly increased with BRS.<sup>83–86</sup>

A recently published individual patient data pooled analysis of 3389 patients from four randomized trials on BRS vs. EES (ABSORB II, ABSORB III, ABSORB China, and ABSORB Japan) showed a higher risk of target lesion failure (a composite of cardiac death, MI, and ischaemia-driven TLR) with BRS as compared with EES at 3 years. This difference was the result of inferior effectiveness (ischaemia-driven TLR; HR 1.46, 95% CI 1.06–2.02) and inferior safety (device thrombosis; HR 3.79, 95% CI 1.72–8.36) with BRS compared with EES at 3 years of follow-up.<sup>83</sup>

## Supplement to chapter 17: antithrombotic treatments

### TRITON-TIMI 38: NSTEMI and STEMI patients

Prasugrel, a third-generation thienopyridine, is a pro-drug that irreversibly inhibits the P2Y<sub>12</sub> receptor on blood platelets. The drug, administered at a 60 mg loading dose and a 5/10 mg maintenance dose, shows fast and predictable platelet inhibition.<sup>87</sup> Prasugrel was tested against clopidogrel in the TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38) study.<sup>88</sup> In the entire trial cohort<sup>88</sup> ( $n = 13\,608$ ) and specifically for the 10\,074 NSTEMI-ACS patients in TRITON-TIMI 38,<sup>88</sup> the primary endpoint was reduced in prasugrel- vs. clopidogrel-treated patients, while TIMI non-CABG major bleeding complications were more common with prasugrel, as were fatal bleeds. Excluding patients with a higher bleeding risk, prasugrel offers significant benefit over clopidogrel with respect to ischaemic events without significantly increasing major bleeding.<sup>88</sup> Especially in diabetic ACS patients, prasugrel showed a net clinical benefit with a substantial reduction in ischaemic events without a significantly increased bleeding risk.<sup>88</sup> Based on an unfavourable risk-benefit profile observed in the TRITON-TIMI 38 study cohort,<sup>88</sup> a maintenance dose of prasugrel is contraindicated in patients with a history of stroke or TIA. Further on, treatment with prasugrel should be used with caution in patients  $\geq 75$  years of age or with a low body weight ( $< 60$  kg). If, after a careful assessment of thrombotic and bleeding risk, treatment is deemed necessary in these patients, a reduced maintenance dose of 5 mg should be prescribed.<sup>81</sup>

In a pre-specified subgroup analysis of STEMI patients ( $n = 3534$ ) in the TRITON-TIMI 38 trial,<sup>82</sup> the benefit of prasugrel was consistent for the primary endpoint and stent thrombosis risk at 15 months. Of note, no significant increase in non-CABG-related major bleeding events was observed and cardiovascular mortality was in favour of prasugrel at 30 days. Thus, for the STEMI group of patients, prasugrel was found to be more effective when compared with clopidogrel, without an apparent excess in bleeding complications.

### PLATO: NSTEMI and STEMI patients

Ticagrelor is a cyclopentyl triazolopyrimidine that reversibly inhibits the P2Y<sub>12</sub> receptor. Along with a PCI procedure, it is administered at a 180 mg loading dose followed by a 90 mg b.i.d. daily maintenance dose. Ticagrelor was tested against clopidogrel in the PLATO (Platelet Inhibition and Patient Outcomes) trial in medically and invasively (PCI or CABG) managed patients.<sup>83</sup> The PLATO study randomly assigned 18\,624 ACS patients to treatment with ticagrelor or clopidogrel and showed a significant improvement in the composite ischaemic endpoint, including a mortality benefit in favour of ticagrelor.<sup>83</sup> Ticagrelor was associated with a higher rate of major non-CABG-related bleeding events, including more fatal intracranial bleeds and fewer fatal bleeds of other types. Within the PLATO study cohort, 11\,080 patients<sup>84</sup> were categorized as NSTEMI-ACS at randomization and 46% of those were treated with PCI. In the NSTEMI cohort, the primary study endpoint of cardiovascular death as well as all-cause death was reduced with ticagrelor. Of note, ticagrelor was associated with an increase in non-CABG major bleeding and with an increased rate of adverse effects including dyspnoea, increased frequency of ventricular pauses, and asymptomatic increases in uric acid in all its major trials.<sup>83–85</sup> These adverse effects, especially the temporary occurrence of dyspnoea, may influence patient compliance, and close surveillance and patient education is required to avoid premature treatment discontinuation. Comparative data coming from randomized comparisons of ticagrelor vs. prasugrel in NSTEMI patients are limited. The ongoing ISAR-REACT 5 trial, enrolling NSTEMI as well as STEMI patients ( $> 4000$ ) with planned invasive management, will provide evidence in this respect.<sup>86</sup>

In the subset of STEMI patients randomized in the PLATO trial,<sup>97</sup> the benefit of ticagrelor over clopidogrel for the primary endpoint was borderline significant but consistent with the overall study results. As for prasugrel, no excess in bleeding events was observed. In a pooled analysis of 48 599 patients, of whom 94% presented with ACS and 84% had PCI, novel P2Y<sub>12</sub> inhibitors, including prasugrel and ticagrelor, have been associated with a mortality benefit and no significant excess of major bleeding among STEMI patients.<sup>98</sup>

### Studies on cangrelor for percutaneous coronary intervention

In two initial clinical trials on clopidogrel-naïve patients, cangrelor was compared with clopidogrel, administered either before PCI in CHAMPION (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition)-PCI ( $n = 8714$ ) or after PCI in CHAMPION-PLATFORM ( $n = 5362$ ). Both studies failed to show a significant benefit with respect to the composite endpoint of death, MI, or ischaemia-driven revascularization at 48 h. Yet, in CHAMPION-PLATFORM, there was a significant reduction in the rate of stent thrombosis from 0.6 to 0.2% (OR 0.31, 95% CI 0.11–0.85;  $P = 0.02$ ), which was not seen in CHAMPION-PCI with upfront administration of clopidogrel. In both trials, there was an increase in AUCITY major bleeding that approached ( $P = 0.06$  in CHAMPION-PCI) or reached ( $P < 0.001$  in CHAMPION-PLATFORM) statistical significance.

A third trial, CHAMPION PHOENIX, was designed that administered clopidogrel after PCI, included stent thrombosis in the primary endpoint, and chose GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) severe bleeding as the primary safety endpoint. In this trial including 11 145 P2Y<sub>12</sub> inhibitor-naïve patients, the primary efficacy endpoint of death, MI, ischaemia-driven revascularization, and stent thrombosis at 48 h was met (4.7% in the cangrelor group and 5.9% in the clopidogrel group; adjusted OR 0.78, 95% CI, 0.66–0.93,  $P = 0.05$ ). There was a significant reduction in stent thrombosis (0.8 vs. 1.4%) that was predominantly driven by intra-procedural stent thrombosis (0.6 vs. 1.0%;  $P = 0.04$ ). A subsequent meta-analysis of all CHAMPION trials revealed a statistically significant 0.7% absolute reduction in death, MI, ischaemia-driven revascularization, and stent thrombosis at 30 days ( $P = 0.008$ ), and a significant 0.5% absolute reduction in death, Q-wave MI, and stent thrombosis ( $P = 0.009$ ), which includes a significant 0.4% absolute reduction in intra-procedural and post-procedural stent thrombosis ( $P = 0.018$ ). These benefits occurred at the expense of a significant increase in AUCITY major bleeding (4.2 vs. 2.8%,  $P < 0.001$ ), which prevailed after the exclusion of major haematomas. There were no significant differences in GUSTO severe or TIMI major bleeding. In the meta-analysis as well as in CHAMPION PHOENIX, the benefit of cangrelor with respect to ischaemic endpoints was independent of the clinical presentation with stable angina, NSTEMI-ACS, or STEMI.

In summary, the available evidence on cangrelor suggests a numerically small benefit with respect to major ischaemic endpoints that is counterbalanced by an increase in relevant bleeding, but not severe bleeding. Moreover, comparison between CHAMPION-PLATFORM and CHAMPION-PCI suggests that the benefit of cangrelor might have been diminished by upstream administration of clopidogrel at the time of PCI. Of note, the drug was never evaluated in a randomized fashion for NSTEMI or STEMI patients when potent P2Y<sub>12</sub> inhibitors were used for oral antiplatelet treatment (either upfront or subsequently). Nevertheless, due to its proven efficacy in preventing intra-procedural and post-procedural stent thrombosis, cangrelor may be considered in P2Y<sub>12</sub> inhibitor-naïve patients, particularly when the risk of PCI is high.

### Studies on bivalirudin vs. unfractionated heparin

A number of large-scale clinical trials have compared bivalirudin vs. UFH (plus GP IIb/IIIa blockade). In the AUCITY (Acute Catheterization and Urgent Intervention Triage strategy) trial,<sup>99</sup> no significant differences were observed for UFH/LMWH plus GP IIb/IIIa inhibitor vs. bivalirudin plus GP IIb/IIIa inhibitor for the composite ischaemia endpoint at 30 days or for major bleeding complications. Bivalirudin alone (with bail-out use of a GP IIb/IIIa inhibitor) was also non-inferior to UFH/LMWH combined with a GP IIb/IIIa inhibitor with respect to the ischaemic endpoint, but it was associated with a significantly lower rate of major bleeding. ISAR-REACT 4 (Intracoronary Stenting and Antithrombotic Regimen Rapid Early Action for Coronary Treatment) compared the outcome of UFH plus abciximab vs. bivalirudin.<sup>100</sup> The primary ischaemic endpoint did not differ between the two groups, while the risk of major bleeding was significantly higher in the UFH plus abciximab group. It must be acknowledged that the above-mentioned evidence in support of bivalirudin is derived from clinical trials where bivalirudin was compared with UFH plus the use of a GP IIb/IIIa inhibitor, a combination that is not used on a routine basis anymore.

In the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial in 3602 STEMI patients,<sup>101</sup> bivalirudin was superior to UFH with respect to the two primary endpoints of net adverse clinical events, which included a significant survival benefit. In contrast to that, the risk of stent thrombosis was higher during the first 24 h in the bivalirudin group. In a background of potent antiplatelet agents (approximately 50% utilization of prasugrel or ticagrelor) including pre-treatment and a high rate of radial access (47%), the open-label EUROMAX (European Ambulance Acute Coronary Syndrome Angiography) trial

compared a strategy of pre-hospital bivalirudin vs. UFH or LMWH with optional use (69%) of GP IIb/IIIa inhibitors in 2218 STEMI patients.<sup>102</sup> The primary endpoint of death or non-CABG major bleeding at 30 days was significantly reduced by pre-hospital administration of bivalirudin compared with UFH plus optional GP IIb/IIIa inhibitors. Mortality rates were similar and a lower risk of major bleeding (mainly driven by blood transfusion) was observed for bivalirudin. Again, the risk of stent thrombosis was higher in the bivalirudin group. Further data on bivalirudin vs. UFH was generated in the single-centre HEAT-PPCI (How Effective are Antithrombotic Therapies in primary PCI) study,<sup>103</sup> a randomized trial comparing bivalirudin and UFH in 1829 STEMI patients undergoing primary PCI. Of note, HEAT-PPCI is characterized by contemporary practice including the restriction of GP IIb/IIIa inhibitors to bail-out situations (<10% patients) only, frequent (>90%) use of potent P2Y<sub>12</sub> inhibitors, and a radial approach with preferred DES implantation in STEMI. The primary endpoint was significantly higher in the bivalirudin compared with the UFH group, which includes a substantially higher risk of stent thrombosis for bivalirudin vs. UFH but no significant difference in mortality. For major bleeding events, no significant differences were observed either. The BRAVE (Bavarian Reperfusion Alternatives Evaluation) 4 trial examined the hypothesis of whether a strategy of prasugrel plus bivalirudin ( $n = 269$ ) was superior compared with a strategy of clopidogrel plus UFH ( $n = 275$ ) in primary PCI STEMI patients.<sup>104</sup>

While it has to be acknowledged that the trial was terminated prematurely, the investigators were unable to show any significant differences in net clinical outcome between prasugrel plus bivalirudin and clopidogrel plus UFH.

More data on the comparison of bivalirudin vs. UFH alone and with very limited use (<1%) of GP IIb/IIIa inhibitors in the study arms comes from the MATRIX trial,<sup>105</sup> where 7213 ACS patients with planned PCI were enrolled. Patients in the bivalirudin group were also randomized to post-PCI bivalirudin infusion or not. The primary outcomes, 30 day MACE and net adverse clinical events (a composite of major bleeding or MACE), were not significantly lower with bivalirudin than with heparin (10.3 vs. 10.9%,  $P = 0.44$ , and 11.2 vs. 12.4%,  $P = 0.12$ , respectively). Concerning secondary endpoints, bivalirudin compared with heparin was associated with a lower rate of death from any cause (1.7 vs. 2.3%,  $P = 0.04$ ), a higher rate of definite stent thrombosis (1.0 vs. 0.6%,  $P = 0.048$ ), and a lower rate of major bleeding (1.4 vs. 2.5%,  $P < 0.001$ ). Of note, a post-PCI bivalirudin infusion, as compared with no infusion, did not affect outcome.

Recently, the VALIDATE-SWEDEHEART study,<sup>106</sup> a randomized, registry-based, open-label clinical trial, enrolled 6006 patients with STEMI or NSTEMI-ACS who were undergoing PCI by predominantly radial access and receiving treatment with a potent P2Y<sub>12</sub> inhibitor (ticagrelor, prasugrel, or cangrelor) without the planned use of GP IIb/IIIa inhibitors. The primary endpoint—the 180 day composite incidence of death from any cause, MI, or major bleeding—was reached in 12.3% of the patients in the bivalirudin group and 12.8% in the heparin group ( $P = 0.54$ ). There were no significant differences in any component of the primary endpoint or in stent thrombosis. Thus, the study demonstrated similar risk patterns for both ischaemia and bleeding when comparing the two drugs.

Summarizing currently available evidence on the comparison between bivalirudin and heparin for PCI in ACS, a recent study-level meta-analysis identified 12 randomized trials with 33 844 patients included.<sup>107</sup> The 30 day incidences of MACE and all-cause mortality were not significantly different between bivalirudin and heparin (OR 1.06, 95% CI 0.96–1.17,  $P = 0.24$  and OR 0.95, 95% CI 0.76–1.20,  $P = 0.68$ , respectively). There were trends for an increased risk of stent thrombosis (OR 1.24, 95% CI 0.99–1.56;  $P = 0.06$ ) and for a decreased risk of major bleeding (OR 0.68, 95% CI 0.41–1.11;  $P = 0.07$ ) with bivalirudin as compared with heparin. Except for bleeding risk, the findings were consistent irrespective of balanced use of GP IIb/IIIa inhibitors in both arms or preferential use in the heparin arms. Concerning the bleeding risk, there was a significant heterogeneity between trials stratified by use of GP IIb/IIIa inhibitors ( $P < 0.01$ ), with a significant reduction of bleeding risk only in trials with preferential GP IIb/IIIa inhibitor use in the heparin arms (OR 0.53, 95% CI 0.41–0.68,  $P < 0.0001$ ). In the subsets with STEMI or NSTEMI-ACS, the findings were also largely consistent with the overall analysis. There was only a trend towards a lower risk of death with bivalirudin in the subgroup of patients presenting with STEMI (OR 0.84, 95% CI 0.70–1.01,  $P = 0.06$ ) with  $P = 0.07$  for heterogeneity. Yet, no firm conclusion could be drawn from this finding given the inconclusive  $P$ -values, the absent effect in the overall analysis, and the fact that the STEMI subset comprised a higher proportion of trials with predominant use of GP IIb/IIIa inhibitors in the UFH arm than the studies in NSTEMI-ACS. In summary, the available evidence from randomized trials does not favour bivalirudin use over heparin as the anticoagulant of choice for PCI in ACS.

### Revascularization in patients with renal failure

Renal dysfunction is present in 30–40% of patients with CAD and the extent of CKD is strongly related to the risk of in-hospital adverse outcomes.<sup>108–110</sup> Creatinine clearance should be calculated with the Cockcroft–Gault formula to comply with drug labelling and avoid overdosing with antithrombotics leading to increased bleeding risk.<sup>111,112</sup> In patients referred for acute PCI, the first dose of an antithrombotic drug does not usually add to the risk of bleeding in the case of CKD. Repeated infusion or intake might lead to drug accumulation and an increase in 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 ([Supplementary Table 11](#)).

## Monitoring of antiplatelet drugs (platelet function testing and genotyping)

There is a potential value of antiplatelet treatment monitoring on a prognostic level, and on the level of testing for modifying and individualizing treatment. Based on the results of a collaborative meta-analysis that represents the largest dataset available to date ( $n = 20\,389$  patients), platelet reactivity assessment during P2Y<sub>12</sub> inhibitor treatment identifies PCI-treated patients with a high on-treatment platelet reactivity who are at higher risk for mortality and stent thrombosis, and patients with a low on-treatment platelet reactivity who are at an elevated risk for major bleeding.<sup>113</sup> This dataset and study data from the ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) trial,<sup>114</sup> representing the largest prospective registry in this field, showed that platelet function (PF) testing provides relevant prognostic information on the outcome of PCI-treated patients.

Prior randomized trials [GRAVITAS (Gauging Responsiveness with A VerifyNow assay-Impact on Thrombosis And Safety), TRIGGER-PCI (Testing platelet Reactivity In patients underGOing elective stent placement on clopidogrel to Guide alternative thERapy with pRasugrel), and ARCTIC (Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting)], testing the hypothesis of the clinical benefit of PF monitoring to adjust therapy, have so far failed to demonstrate clinical benefit with PF monitoring.<sup>115-117</sup> These initial trials had a common approach of escalating treatment based on testing results obtained during or early after PCI. A further study, the ANTARCTIC (Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome) trial, addressed some limitations of prior studies and specifically focused on elderly ACS patients. This study also provided neutral results and utilized a standard treatment with a reduced dose of 5 mg prasugrel,<sup>118</sup> aiming to treat patients towards a therapeutic window of platelet inhibition.

A pure DAPT de-escalation strategy with a stage-adapted treatment approach was investigated in the randomized TROPICAL-ACS (Testing responsiveness to platelet inhibition on chronic antiplatelet treatment for acute coronary syndromes) trial.<sup>119</sup> In that trial, the primary endpoint was met and a strategy of PF testing-guided DAPT de-escalation (early switch from prasugrel to clopidogrel) was found to be non-inferior and safe in terms of ischaemic risk when compared with potent platelet inhibition for 12 months after ACS-PCI. Thus, a guided de-escalation of P2Y<sub>12</sub> inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) may be considered as an alternative treatment strategy in ACS patients, and especially for patients deemed unsuitable for 12 months potent platelet inhibition.

The influence of genetic variants on the response to antiplatelet agents, especially clopidogrel, has been well established in patients with ACS and planned PCI.<sup>120</sup> Rapidly obtained genetic information on the 2C19 genotype can help in reaching the optimal window of P2Y<sub>12</sub> inhibition according to the cytochrome P2C19 profile,<sup>121,122</sup> but no randomized trial has ever demonstrated any clinical benefit of such an approach. A number of clinical trials in this field are ongoing.

In summary, neither PF testing nor genetic testing can be recommended on a routine basis for tailoring and escalating DAPT after stenting in all PCI-treated patients. Testing may be considered to: (i) de-escalate DAPT treatment, (ii) test the compliance to treatment, or (iii) obtain prognostic information on the individual patient for the time period after PCI.

## 2. References for material in supplementary appendix

1. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. *Veterans Affairs ACME Investigators. N Engl J Med* 1992;**326**:10–16.
2. Henderson RA, Pocock SJ, Clayton TC, Knight R, Fox KA, Julian DG, Chamberlain DA, Second Randomized Intervention Treatment of Angina (RITA-2) Trial Participants. Seven-year outcome in the RITA-2 trial: Coronary angioplasty versus medical therapy. *J Am Coll Cardiol* 2003;**42**:1161–1170.
3. Pitt B, Waters D, Brown WV, van Boven AJ, Schwartz L, Title LM, Eisenberg D, Shurzinske L, McCormick LS. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. *Atorvastatin versus Revascularization Treatment Investigators. N Engl J Med* 1999;**341**:70–76.
4. Pfisterer M, Buser P, Osswald S, Allemann U, Amann W, Angehrn W, Eeckhout E, Erne P, Estlinbaum W, Kuster G, Moccetti T, Naegeli B, Rickenbacher P; Trial of Invasive versus Medical therapy in Elderly patients (TIME) Investigators. Outcome of elderly patients with chronic

symptomatic coronary artery disease with an invasive vs optimized medical treatment strategy: One-year results of the randomized TIME trial. *JAMA* 2003;**289**:1117–1123.

5. Hueb W, Lopes N, Gersh BJ, Soares PR, Ribeiro EE, Pereira AC, Favarato D, Rocha AS, Hueb AC, Ramires JA. Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): A randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 2010;**122**:949–957.

6. Erne P, Schoenenberger AW, Burckhardt D, Zuber M, Kiowski W, Buser PT, Dubach P, Resink TJ, Pfisterer M. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: The SWISSI II randomized controlled trial. *JAMA* 2007;**297**:1985–1991.

7. Weintraub WS, Spertus JA, Kolm P, Maron DJ, Zhang Z, Jurkovic Z, Zhang W, Hartigan PM, Lewis C, Veledar E, Bowen J, Dunbar SB, Deaton C, Kaufman S, O'Rourke RA, Goeree R, Barnett PG, Teo KK, Boden WE; COURAGE Trial Research Group, Mancini GB. Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med* 2008;**359**:677–687.

8. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Juni P, Fearon WF; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;**367**:991–1001.

9. Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, Keeble T, Mielewicz M, Kaprielian R, Malik IS, Nijjer SS, Petraco R, Cook C, Ahmad Y, Howard J, Baker C, Sharp A, Gerber R, Talwar S, Assomull R, Mayet J, Wensel R, Collier D, Shun-Shin M, Thom SA, Davies JE, Francis DP, investigators O. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet* 2018;**391**:31–40.

10. BARI 2D Study Group, Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, Orchard TJ, Chaitman BR, Genuth SM, Goldberg SH, Hlatky MA, Jones TL, Molitch ME, Nesto RW, Sako EY, Sobel BE. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;**360**:2503–2515.

11. Kappetein AP, Head SJ, Morice MC, Banning AP, Serruys PW, Mohr FW, Dawkins KD, Mack MJ; SYNTAX Investigators. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *Eur J Cardiothorac Surg* 2013;**43**:1006–1013.

12. Kapur A, Hall RJ, Malik IS, Qureshi AC, Butts J, de Belder M, Baumbach A, Angelini G, de Belder A, Oldroyd KG, Flather M, Roughton M, Nihoyannopoulos P, Bagger JP, Morgan K, Beatt KJ. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. *J Am Coll Cardiol* 2010;**55**:432–440.

13. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S III, Bertrand M, Fuster V; FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012;**367**:2375–2384.

14. Kamalesh M, Sharp TG, Tang XC, Shunk K, Ward HB, Walsh J, King S III, Colling C, Moritz T, Stroupe K, Reda D; CARDS Investigators VA. Percutaneous coronary intervention versus coronary bypass surgery in United States veterans with diabetes. *J Am Coll Cardiol* 2013;**61**:808–816.

15. Stone GW, Teirstein PS, Meredith IT, Farah B, Dubois CL, Feldman RL, Dens J, Hagiwara N, Allocco DJ, Dawkins KD; PLATINUM Trial Investigators. A prospective, randomized evaluation of a novel everolimus-eluting coronary stent: The PLATINUM (a Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of Up to Two de Novo Coronary Artery Lesions) trial. *J Am Coll Cardiol* 2011;**57**:1700–1708.

16. von Birgelen C, Sen H, Lam MK, Danse PW, Jessurun GA, Hautvast RW, van Houwelingen GK, Schramm AR, Gin RM, Louwerenburg JW, de Man FH, Stoel MG, Lowik MM, Linssen GC, Said SA, Nienhuis MB, Verhorst PM, Basalus MW, Doggen CJ, Tandjung K. Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients requiring a percutaneous coronary intervention (DUTCH PEERS): A randomised, single-blind, multicentre, non-inferiority trial. *Lancet* 2013;**383**:413–423.

17. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbaek H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med* 2010;**363**:136–146.

18. von Birgelen C, Basalus MW, Tandjung K, van Houwelingen KG, Stoel MG, Louwerenburg JH, Linssen GC, Said SA, Kleijne MA, Sen H, Lowik MM, van der Palen J, Verhorst PM, de Man FH. A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: The TWENTE trial. *J Am Coll Cardiol* 2012;**59**:1350–1361.
19. Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, Doostzadeh J, Cao S, Simonton CA, Sudhir K, Lansky AJ, Cutlip DE, Kereiakes DJ. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med* 2010;**362**:1663–1674.
20. Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goedhart D, Smits PC. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): A randomised trial. *Lancet* 2010;**375**:201–209.
21. Sabate M, Cequier A, Iniguez A, Serra A, Hernandez-Antolin R, Mainar V, Valgimigli M, Tsepili M, den Heijer P, Bethencourt A, Vazquez N, Gomez-Hospital JA, Baz JA, Martin-Yuste V, van Geuns RJ, Alfonso F, Bordes P, Tebaldi M, Masotti M, Silvestro A, Backx B, Brugaletta S, van Es GA, Serruys PW. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet* 2012;**380**:1482–1490.
22. Kandzari DE, Smits PC, Love MP, Ben-Yehuda O, Banai S, Robinson SD, Jonas M, Kornowski R, Bagur R, Iniguez A, Danenberg H, Feldman R, Jauhar R, Chandna H, Parikh M, Perlman GY, Balcells M, Markham P, Ozan MO, Genereux P, Edelman ER, Leon MB, Stone GW. Randomized comparison of ridaforolimus- and zotarolimus-eluting coronary stents in patients with coronary artery disease: Primary results from the BIONICS Trial (BioNIR ridaforolimus-eluting coronary stent system in coronary stenosis). *Circulation* 2017;**136**:1304–1314.
23. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): A randomised non-inferiority trial. *Lancet* 2008;**372**:1163–1173.
24. Raber L, Kelbaek H, Ostojic M, Baumbach A, Heg D, Tuller D, von Birgelen C, Roffi M, Moschovitis A, Khattab AA, Wenaweser P, Bonvini R, Pedrazzini G, Kornowski R, Weber K, Trelle S, Luscher TF, Taniwaki M, Matter CM, Meier B, Juni P, Windecker S; COMFORTABLE AMI Investigators. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: The COMFORTABLE AMI randomized trial. *JAMA* 2012;**308**:777–787.
25. Smits PC, Hofma S, Togni M, Vazquez N, Valdes M, Voudris V, Slagboom T, Goy JJ, Vuillomenet A, Serra A, Nouche RT, den Heijer P, van der Ent M. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): A randomised, controlled, non-inferiority trial. *Lancet* 2013;**381**:651–660.
26. Natsuaki M, Kozuma K, Morimoto T, Kadota K, Muramatsu T, Nakagawa Y, Akasaka T, Igarashi K, Tanabe K, Morino Y, Ishikawa T, Nishikawa H, Awata M, Abe M, Okada H, Takatsu Y, Ogata N, Kimura K, Urasawa K, Tarutani Y, Shiode N, Kimura T; NEXT Investigators. Biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent: A randomized, controlled, noninferiority trial. *J Am Coll Cardiol* 2013;**62**:181–190.
27. Christiansen EH, Jensen LO, Thayssen P, Tilsted HH, Krusell LR, Hansen KN, Kaltoft A, Maeng M, Kristensen SD, Botker HE, Terkelsen CJ, Villadsen AB, Ravkilde J, Aaroe J, Madsen M, Thuesen L, Lassen JF; Scandinavian Organization for Randomized Trials with Clinical Outcome V (SORT OUT V) Investigators. Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V): A randomised non-inferiority trial. *Lancet* 2013;**381**:661–669.
28. Pilgrim T, Heg D, Roffi M, Tuller D, Muller O, Vuillomenet A, Cook S, Weilenmann D, Kaiser C, Jamshidi P, Fahrni T, Moschovitis A, Noble S, Eberli FR, Wenaweser P, Juni P, Windecker S. Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): A randomised, single-blind, non-inferiority trial. *Lancet* 2014;**384**:2111–2122.
29. von Birgelen C, Kok MM, van der Heijden LC, Danse PW, Schotborgh CE, Scholte M, Gin RM, Somi S, van Houwelingen KG, Stoel MG, de Man FH, Louwerenburg JH, Hartmann M, Zocca P, Linssen GC, van der Palen J, Doggen CJ, Lowik MM. Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease (BIO-RESORT): A three-arm, randomised, non-inferiority trial. *Lancet* 2016;**388**:2607–2617.
30. Saito S, Valdes-Chavarrí M, Richardt G, Moreno R, Iniguez Romo A, Barbato E, Carrie D, Ando K, Merkely B, Kornowski R, Eltchaninoff H, James S, Wijns W; CENTURY II Investigators. A randomized, prospective, intercontinental evaluation of a bioresorbable polymer sirolimus-eluting coronary stent system: The CENTURY II (Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients with Coronary Artery Disease) trial. *Eur Heart J* 2014;**35**:2021–2031.

31. Byrne RA, Kastrati A, Kufner S, Massberg S, Birkmeier KA, Laugwitz KL, Schulz S, Pache J, Fusaro M, Seyfarth M, Schomig A, Mehilli J. Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: The Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Trial. *Eur Heart J* 2009;**30**:2441–2449.
32. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrie D, Naber C, Lipiecki J, Richardt G, Iniguez A, Brunel P, Valdes-Chavarri M, Garot P, Talwar S, Berland J, Abdellaoui M, Eberli F, Oldroyd K, Zambahari R, Gregson J, Greene S, Stoll HP, Morice MC; LEADERS FREE Investigators. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med* 2015;**373**:2038–2047.
33. Kufner S, Sorges J, Mehilli J, Cassese S, Repp J, Wiebe J, Lohaus R, Lahmann A, Rheude T, Ibrahim T, Massberg S, Laugwitz KL, Kastrati A, Byrne RA; ISAR-TEST-5 Trial Investigators. Randomized trial of polymer-free sirolimus- and probucol-eluting stents versus durable polymer zotarolimus-eluting stents: 5-year results of the ISAR-TEST-5 trial. *JACC Cardiovasc Interv* 2016;**9**:784–792.
34. Stella PR, Belkacemi A, Waksman R, Stahnke S, Torguson R, von Strandmann RP, Agostoni P, Sangiorgi G, Silber S; Valentine Investigators. The Valentines Trial: Results of the first one week worldwide multicentre enrolment trial, evaluating the real world usage of the second generation DIOR paclitaxel drug-eluting balloon for in-stent restenosis treatment. *EuroIntervention* 2011;**7**:705–710.
35. Waksman R, Serra A, Loh JP, Malik FT, Torguson R, Stahnke S, von Strandmann RP, Rodriguez AE. Drug-coated balloons for de novo coronary lesions: Results from the Valentines II trial. *EuroIntervention* 2013;**9**:613–619.
36. Bondesson P, Lagerqvist B, James SK, Olivecrona GK, Venetsanos D, Harnek J. Comparison of two drug-eluting balloons: A report from the SCAAR registry. *EuroIntervention* 2012;**8**:444–449.
37. Latib A, Colombo A, Castriota F, Micari A, Cremonesi A, De Felice F, Marchese A, Tespili M, Presbitero P, Sgueglia GA, Buffoli F, Tamburino C, Varbella F, Menozzi A. A randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels: The BELLO (Balloon Elution and Late Loss Optimization) study. *J Am Coll Cardiol* 2012;**60**:2473–2480.
38. Gutierrez-Chico JL, van Geuns RJ, Koch KT, Koolen JJ, Duckers H, Regar E, Serruys PW. Paclitaxel-coated balloon in combination with bare metal stent for treatment of de novo coronary lesions: An optical coherence tomography first-in-human randomised trial, balloon first vs. stent first. *EuroIntervention* 2011;**7**:711–722.
39. Hehrlein C, Dietz U, Kubica J, Jorgensen E, Hoffmann E, Naber C, Lesiak M, Schneider H, Wiemer M, Tolg R, Richardt G. Twelve-month results of a paclitaxel releasing balloon in patients presenting with in-stent restenosis First-in-Man (PEPPER) trial. *Cardiovasc Revasc Med* 2012;**13**:260–264.
40. Scheller B, Hehrlein C, Bocksch W, Rutsch W, Haghi D, Dietz U, Bohm M, Speck U. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med* 2006;**355**:2113–2124.
41. Unverdorben M, Vallbracht C, Cremers B, Heuer H, Hengstenberg C, Maikowski C, Werner GS, Antoni D, Kleber FX, Bocksch W, Leschke M, Ackermann H, Boxberger M, Speck U, Degenhardt R, Scheller B. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation* 2009;**119**:2986–2994.
42. Habara S, Mitsudo K, Kadota K, Goto T, Fujii S, Yamamoto H, Katoh H, Oka N, Fuku Y, Hosogi S, Hirono A, Maruo T, Tanaka H, Shigemoto Y, Hasegawa D, Tasaka H, Kusunose M, Otsuru S, Okamoto Y, Saito N, Tsujimoto Y, Eguchi H, Miyake K, Yoshino M. Effectiveness of paclitaxel-eluting balloon catheter in patients with sirolimus-eluting stent restenosis. *JACC Cardiovasc Interv* 2011;**4**:149–154.
43. Rittger H, Brachmann J, Sinha AM, Waliszewski M, Ohlow M, Brugger A, Thiele H, Birkemeyer R, Kurowski V, Breithardt OA, Schmidt M, Zimmermann S, Lonke S, von Cranach M, Nguyen TV, Daniel WG, Wohrle J. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: The PEPCAD-DES study. *J Am Coll Cardiol* 2012;**59**:1377–1382.
44. Byrne RA, Neumann FJ, Mehilli J, Piniack S, Wolff B, Tiroch K, Schulz S, Fusaro M, Ott I, Ibrahim T, Hausleiter J, Valina C, Pache J, Laugwitz KL, Massberg S, Kastrati A; ISAR-DESIRE 3 Investigators. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): A randomised, open-label trial. *Lancet* 2013;**381**:461–467.
45. Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, Berry C, Oldroyd KG; PRAMI Investigators. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013;**369**:1115–1123.

46. Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, Blackman DJ, Dalby M, Fairbrother KL, Banya W, Wang D, Flather M, Hetherington SL, Kelion AD, Talwar S, Gunning M, Hall R, Swanton H, McCann GP. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: The CvLPRIT trial. *J Am Coll Cardiol* 2015;**65**:963–972.
47. Engstrom T, Kelbaek H, Helqvist S, Hofsten DE, Klovgaard L, Holmvang L, Jorgensen E, Pedersen F, Saunamaki K, Clemmensen P, De Backer O, Ravkilde J, Tilsted HH, Villadsen AB, Aaroe J, Jensen SE, Raungaard B, Kober L; DANAMI-3-PRIMULTI Investigators. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI): An open-label, randomised controlled trial. *Lancet* 2015;**386**:665–671.
48. Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Ong PJ, Hambrecht R, Angeras O, Richardt G, Omerovic E; Compare-Acute Investigators. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med* 2017;**376**:1234–1244.
49. Hochman JS, Sleeper LA, White HD, Dzavik V, Wong SC, Menon V, Webb JG, Steingart R, Picard MH, Menegus MA, Boland J, Sanborn T, Buller CE, Modur S, Forman R, Desvigne-Nickens P, Jacobs AK, Slater JN, LeJemtel TH; SHOCK Investigators. One-year survival following early revascularization for cardiogenic shock. *JAMA* 2001;**285**:190–192.
50. White HD, Assmann SF, Sanborn TA, Jacobs AK, Webb JG, Sleeper LA, Wong CK, Stewart JT, Aylward PE, Wong SC, Hochman JS. Comparison of percutaneous coronary intervention and coronary artery bypass grafting after acute myocardial infarction complicated by cardiogenic shock: Results from the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial. *Circulation* 2005;**112**:1992–2001.
51. Webb JG, Lowe AM, Sanborn TA, White HD, Sleeper LA, Carere RG, Buller CE, Wong SC, Boland J, Dzavik V, Porway M, Pate G, Bergman G, Hochman JS; SHOCK Investigators. Percutaneous coronary intervention for cardiogenic shock in the SHOCK trial. *J Am Coll Cardiol* 2003;**42**:1380–1386.
52. Dzavik V, Sleeper LA, Cocke TP, Moscucci M, Saucedo J, Hosat S, Jiang X, Slater J, LeJemtel T, Hochman JS; SHOCK Investigators. Early revascularization is associated with improved survival in elderly patients with acute myocardial infarction complicated by cardiogenic shock: A report from the SHOCK Trial Registry. *Eur Heart J* 2003;**24**:828–837.
53. Park JS, Cha KS, Lee DS, Shin D, Lee HW, Oh JH, Kim JS, Choi JH, Park YH, Lee HC, Kim JH, Chun KJ, Hong TJ, Jeong MH, Ahn Y, Chae SC, Kim YJ; Korean Acute Myocardial Infarction Registry Investigators. Culprit or multivessel revascularisation in ST-elevation myocardial infarction with cardiogenic shock. *Heart* 2015;**101**:1225–1232.
54. Ohno Y, Maekawa Y, Miyata H, Inoue S, Ishikawa S, Sueyoshi K, Noma S, Kawamura A, Kohsaka S, Fukuda K. Impact of periprocedural bleeding on incidence of contrast-induced acute kidney injury in patients treated with percutaneous coronary intervention. *J Am Coll Cardiol* 2013;**62**:1260–1266.
55. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: Development and initial validation. *J Am Coll Cardiol* 2004;**44**:1393–1399.
56. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med* 2003;**348**:491–499.
57. Jo SH, Youn TJ, Koo BK, Park JS, Kang HJ, Cho YS, Chung WY, Joo GW, Chae IH, Choi DJ, Oh BH, Lee MM, Park YB, Kim HS. Renal toxicity evaluation and comparison between visipaque (iodixanol) and hexabrix (ioxaglate) in patients with renal insufficiency undergoing coronary angiography: The RECOVER study: A randomized controlled trial. *J Am Coll Cardiol* 2006;**48**:924–930.
58. Solomon RJ, Natarajan MK, Doucet S, Sharma SK, Staniloae CS, Katholi RE, Gelormini JL, Labinaz M, Moreyra AE. Cardiac Angiography in Renally Impaired Patients (CARE) study: A randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease. *Circulation* 2007;**115**:3189–3196.
59. Pandya B, Chaloub J, Parikh V, Gaddam S, Spagnola J, El-Sayegh S, Bogin M, Kandov R, Lafferty J, Bangalore S. Contrast media use in patients with chronic kidney disease undergoing coronary angiography: A systematic review and meta-analysis of randomized trials. *Int J Cardiol* 2017;**228**:137–144.

60. Marenzi G, Assanelli E, Campodonico J, Lauri G, Marana I, De Metrio M, Moltrasio M, Grazi M, Rubino M, Veglia F, Fabbiocchi F, Bartorelli AL. Contrast volume during primary percutaneous coronary intervention and subsequent contrast-induced nephropathy and mortality. *Ann Intern Med* 2009;**150**:170–177.
61. Laskey WK, Jenkins C, Selzer F, Marroquin OC, Wilensky RL, Glaser R, Cohen HA, Holmes DR Jr. Volume-to-creatinine clearance ratio: A pharmacokinetically based risk factor for prediction of early creatinine increase after percutaneous coronary intervention. *J Am Coll Cardiol* 2007;**50**:584–590.
62. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS 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 European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;**35**:2541–2619.
63. Mueller C, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, Marsch S, Roskamm H. Prevention of contrast media-associated nephropathy: Randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med* 2002;**162**:329–336.
64. Brar SS, Shen AY, Jorgensen MB, Kotlewski A, Aharonian VJ, Desai N, Ree M, Shah AI, Burchette RJ. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: A randomized trial. *JAMA* 2008;**300**:1038–1046.
65. Merten GJ, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, Bersin RM, Van Moore A, Simonton CA III, Rittase RA, Norton HJ, Kennedy TP. Prevention of contrast-induced nephropathy with sodium bicarbonate: A randomized controlled trial. *JAMA* 2004;**291**:2328–34.
66. Giacoppo D, Gargiulo G, Buccheri S, Aruta P, Byrne RA, Cassese S, Dangas G, Kastrati A, Mehran R, Tamburino C, Capodanno D. Preventive strategies for contrast-induced acute kidney injury in patients undergoing percutaneous coronary procedures: Evidence from a hierarchical Bayesian network meta-analysis of 124 trials and 28 240 patients. *Circ Cardiovasc Interv* 2017;**10**:e004383.
67. Nijssen EC, Rennenberg RJ, Nelemans PJ, Essers BA, Janssen MM, Vermeeren MA, Ommen VV, Wildberger JE. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): A prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. *Lancet* 2017;**389**:1312–1322.
68. Ali-Hassan-Sayegh S, Mirhosseini SJ, Ghodrati-pour Z, Sarrafan-Chaharsoughi Z, Rahimizadeh E, Karimi-Bondarabadi AA, Haddad F, Shahidzadeh A, Mahdavi P, Dehghan AM, Tahernejad M, Shahidzadeh A, Dehghan H, Ghanei A, Lotfaliani M, Weymann A, Zerious M, Popov AF, Sabashnikov A. Strategies preventing contrast-induced nephropathy after coronary angiography: A comprehensive meta-analysis and systematic review of 125 randomized controlled trials. *Angiology* 2017;**68**:389–413.
69. Qian G, Fu Z, Guo J, Cao F, Chen Y. Prevention of contrast-induced nephropathy by central venous pressure-guided fluid administration in chronic kidney disease and congestive heart failure patients. *JACC Cardiovasc Interv* 2016;**9**:89–96.
70. Brar SS, Aharonian V, Mansukhani P, Moore N, Shen AY, Jorgensen M, Dua A, Short L, Kane K. Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: The POSEIDON randomised controlled trial. *Lancet* 2014;**383**:1814–1823.
71. Briguori C, Visconti G, Focaccio A, Airoldi F, Valgimigli M, Sangiorgi GM, Golia B, Ricciardelli B, Condorelli G. Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard System in high-risk patients for contrast-induced acute kidney injury. *Circulation* 2011;**124**:1260–1269.
72. Putzu A, Boscolo Berto M, Belletti A, Pasotti E, Cassina T, Moccetti T, Pedrazzini G. Prevention of contrast-induced acute kidney injury by furosemide with matched hydration in patients undergoing interventional procedures: A systematic review and meta-analysis of randomized trials. *JACC Cardiovasc Interv* 2017;**10**:355–363.
73. Subramaniam RM, Suarez-Cuervo C, Wilson RF, Turban S, Zhang A, Sherrod C, Aboagye J, Eng J, Choi MJ, Hutfless S, Bass EB. Effectiveness of prevention strategies for contrast-induced nephropathy: A systematic review and meta-analysis. *Ann Intern Med* 2016;**164**:406–416.
74. Thompson K, Razi R, Lee MS, Shen A, Stone GW, Hiremath S, Mehran R, Brar SS. Statin use prior to angiography for the prevention of contrast-induced acute kidney injury: A meta-analysis of 19 randomised trials. *EuroIntervention* 2016;**12**:366–374.

75. Weisbord SD, Gallagher M, Jneid H, Garcia S, Cass A, Thwin SS, Conner TA, Chertow GM, Bhatt DL, Shunk K, Parikh CR, McFalls EO, Brophy M, Ferguson R, Wu H, Androsenko M, Myles J, Kaufman J, Palevsky PM; PRESERVE Trial Group. Outcomes after angiography with sodium bicarbonate and acetylcysteine. *N Engl J Med* 2018;**378**:603–614.
76. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, Badano L, Zamorano JL; Scientific Document Committee of the European Association of Cardiovascular Imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: An executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;**14**:611–644.
77. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, Little SH, Shah DJ, Sherman S, Thavendiranathan P, Thomas JD, Weissman NJ. Recommendations for noninvasive evaluation of native valvular regurgitation: A report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;**30**:303–371.
78. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Munoz D, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–2791.
79. Smith PK, Michler RE, Woo YJ, Alexander JH, Puskas JD, Parides MK, Hahn RT, Williams JB, Dent JM, Ferguson TB Jr, Moquete E, Rose EA, Page P, Jeffries NO, O'Gara PT, Ascheim DD. Design, rationale, and initiation of the Surgical Interventions for Moderate Ischemic Mitral Regurgitation Trial: A report from the Cardiothoracic Surgical Trials Network. *J Thorac Cardiovasc Surg* 2012;**143**:111–117, 117 e1.
80. Serruys PW, Chevalier B, Sotomi Y, Cequier A, Carrie D, Piek JJ, Van Boven AJ, Dominici M, Dudek D, McClean D, Helqvist S, Haude M, Reith S, de Sousa Almeida M, Campo G, Iniguez A, Sabate M, Windecker S, Onuma Y. Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): A 3 year, randomised, controlled, single-blind, multicentre clinical trial. *Lancet* 2016;**388**:2479–2491.
81. Onuma Y, Sotomi Y, Shiomi H, Ozaki Y, Namiki A, Yasuda S, Ueno T, Ando K, Furuya J, Igarashi K, Kozuma K, Tanabe K, Kusano H, Rapoza R, Popma JJ, Stone GW, Simonton C, Serruys PW, Kimura T. Two-year clinical, angiographic, and serial optical coherence tomographic follow-up after implantation of an everolimus-eluting bioresorbable scaffold and an everolimus-eluting metallic stent: Insights from the randomised ABSORB Japan trial. *EuroIntervention* 2016;**12**:1090–1101.
82. Wykrzykowska JJ, Kraak RP, Hofma SH, van der Schaaf RJ, Arkenbout EK, AJ IJ, Elias J, van Dongen IM, Tijssen RYG, Koch KT, Baan J Jr, Vis MM, de Winter RJ, Piek JJ, Tijssen JGP, Henriques JPS; AIDA Investigators. Bioresorbable scaffolds versus metallic stents in routine PCI. *N Engl J Med* 2017;**376**:2319–2328.
83. Ali ZA, Serruys PW, Kimura T, Gao R, Ellis SG, Kereiakes DJ, Onuma Y, Simonton C, Zhang Z, Stone GW. 2-year outcomes with the Absorb bioresorbable scaffold for treatment of coronary artery disease: A systematic review and meta-analysis of seven randomised trials with an individual patient data substudy. *Lancet* 2017;**390**:760–772.
84. Cassese S, Byrne RA, Juni P, Wykrzykowska JJ, Puricel S, Ndrepepa G, Schunkert H, Fusaro M, Cook S, Kimura T, Henriques JPS, Serruys PW, Windecker S, Kastrati A. Mid-term clinical outcomes with everolimus-eluting bioresorbable scaffolds versus everolimus-eluting metallic stents for percutaneous coronary interventions: A meta-analysis of randomized trials. *EuroIntervention* 2018;**13**:1565–1573.
85. Sorrentino S, Giustino G, Mehran R, Kini AS, Sharma SK, Faggioni M, Farhan S, Vogel B, Indolfi C, Dangas GD. Everolimus-eluting bioresorbable scaffolds versus everolimus-eluting metallic stents. *J Am Coll Cardiol* 2017;**69**:3055–3066.
86. Montone RA, Niccoli G, De Marco F, Minelli S, D'Ascenzo F, Testa L, Bedogni F, Crea F. Temporal trends in adverse events after everolimus-eluting bioresorbable vascular scaffold versus everolimus-eluting metallic stent implantation: A meta-analysis of randomized controlled trials. *Circulation* 2017;**135**:2145–2154.
87. Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, Neumann FJ, Michelson AD, Angiolillo DJ, Hod H, Montalescot G, Miller DL, Jakubowski JA, Cairns R, Murphy SA, McCabe CH, Antman EM, Braunwald E; PRINCIPLE-TIMI 44 Investigators. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation* 2007;**116**:2923–2932.
88. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;**357**:2001–2015.

89. De Servi S, Goedicke J, Schirmer A, Widimsky P. Clinical outcomes for prasugrel versus clopidogrel in patients with unstable angina or non-ST-elevation myocardial infarction: An analysis from the TRITON-TIMI 38 trial. *Eur Heart J Acute Cardiovasc Care* 2014;**3**:363–372.
90. Wiviott SD, Braunwald E, Angiolillo DJ, Meisel S, Dalby AJ, Verheugt FW, Goodman SG, Corbalan R, Purdy DA, Murphy SA, McCabe CH, Antman EM; TRITON-TIMI 38 Investigators. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. *Circulation* 2008;**118**:1626–1636.
91. Erlinge D, Ten Berg J, Foley D, Angiolillo DJ, Wagner H, Brown PB, Zhou C, Luo J, Jakubowski JA, Moser B, Small DS, Bergmeijer T, James S, Winters KJ. Reduction in platelet reactivity with prasugrel 5 mg in low-body-weight patients is noninferior to prasugrel 10 mg in higher-body-weight patients: Results from the FEATHER trial. *J Am Coll Cardiol* 2012;**60**:2032–2040.
92. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, Antman EM; TRITON-TIMI 38 Investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): Double-blind, randomised controlled trial. *Lancet* 2009;**373**:723–731.
93. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–1057.
94. Lindholm D, Varenhorst C, Cannon CP, Harrington RA, Himmelmann A, Maya J, Husted S, Steg PG, Cornel JH, Storey RF, Stevens SR, Wallentin L, James SK. Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: Results from the PLATO trial. *Eur Heart J* 2014;**35**:2083–2093.
95. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;**372**:1791–1800.
96. Schulz S, Angiolillo DJ, Antoniucci D, Bernlochner I, Hamm C, Jaitner J, Laugwitz KL, Mayer K, von Merzljak B, Morath T, Neumann FJ, Richardt G, Ruf J, Schomig G, Schuhlen H, Schunkert H, Kastrati A; Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 Trial Investigators. Randomized comparison of ticagrelor versus prasugrel in patients with acute coronary syndrome and planned invasive strategy-design and rationale of the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial. *J Cardiovasc Transl Res* 2014;**7**:91–100.
97. Steg PG, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP, Emanuelsson H, Finkelstein A HS, Katus H, Kilhamn J, Olofsson S, Storey RF, Weaver WD, Wallentin L; PLATO Study Group. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation* 2010;**122**:2131–2141.
98. Bellemain-Appaix A, Brieger D, Beygui F, Silvain J, Pena A, Cayla G, Barthélémy O, Collet JP, Montalescot G. New P2Y12 inhibitors versus clopidogrel in percutaneous coronary intervention: A meta-analysis. *J Am Coll Cardiol* 2010;**56**:1542–1551.
99. Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, White HD, Pocock SJ, Ware JH, Feit F, Colombo A, Aylward PE, Cequier AR, Darius H, Desmet W, Ebrahimi R, Hamon M, Rasmussen LH, Rupprecht HJ, Hoekstra J, Mehran R, Ohman EM; ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;**355**:2203–2216.
100. Kastrati A, Neumann F-J, Schulz S, Massberg S, Byrne RA, Ferenc M, Laugwitz K-L, Pache J, Ott I, Hausleiter J, Seyfarth M, Gick M, Antoniucci D, Schömig A, Berger PB, Mehilli J. Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. *N Engl J Med* 2011;**365**:1980–1989.
101. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong SC, Kirtane AJ, Parise H, Mehran R; HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008;**358**:2218–2230.
102. Steg PG, van 't Hof A, Hamm CW, Clemmensen P, Lapostolle F, Coste P, Ten Berg J, Van Grunsven P, Eggink GJ, Nibbe L, Zeymer U, Campo dell'Orto M, Nef H, Steinmetz J, Soulat L, Huber K, Deliargyris EN, Bernstein D, Schuette D, Prats J, Clayton T, Pocock S, Hamon M, Goldstein P; EUROMAX Investigators. Bivalirudin started during emergency transport for primary PCI. *N Engl J Med* 2013;**369**:2207–2217.

103. Shahzad A, Kemp I, Mars C, Wilson K, Roome C, Cooper R, Andron M, Appleby C, Fisher M, Khand A, Kunadian B, Mills JD, Morris JL, Morrison WL, Munir S, Palmer ND, Perry RA, Ramsdale DR, Velavan P, Stables RH; HEAT-PPCI Trial Investigators. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): An open-label, single centre, randomised controlled trial. *Lancet* 2014;**384**:1849–1858.
104. Schulz S, Richardt G, Laugwitz KL, Morath T, Neudecker J, Hoppmann P, Mehran R, Gershlick AH, Tolg R, Anette Fiedler K, Abdel-Wahab M, Kufner S, Schneider S, Schunkert H, Ibrahim T, Mehilli J, Kastrati A; Bavarian Reperfusion Alternatives Evaluation Investigators. Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. *Eur Heart J* 2014;**35**:2285–2294.
105. Valgimigli M, Frigoli E, Leonardi S, Rothenbuhler M, Gagnor A, Calabro P, Garducci S, Rubartelli P, Briguori C, Ando G, Repetto A, Limbruno U, Garbo R, Sganzerla P, Russo F, Lupi A, Cortese B, Ausiello A, Ierna S, Esposito G, Presbitero P, Santarelli A, Sardella G, Varbella F, Tresoldi S, de Cesare N, Rigattieri S, Zingarelli A, Tosi P, van 't Hof A, Boccuzzi G, Omerovic E, Sabate M, Heg D, Juni P, Vranckx P, for the MATRIX Investigators. Bivalirudin or unfractionated heparin in acute coronary syndromes. *N Engl J Med* 2015;**373**:997–1009.
106. Erlinge D, Omerovic E, Frobert O, Linder R, Danielewicz M, Hamid M, Swahn E, Henareh L, Wagner H, Hardhammar P, Sjogren I, Stewart J, Grimfjard P, Jensen J, Aasa M, Robertsson L, Lindroos P, Haupt J, Wikstrom H, Ulvenstam A, Bhiladvala P, Lindvall B, Lundin A, Todt T, Ioanes D, Ramunddal T, Kellerth T, Zagozdzon L, Gotberg M, Andersson J, Angeras O, Ostlund O, Lagerqvist B, Held C, Wallentin L, Schersten F, Eriksson P, Koul S, James S. Bivalirudin versus heparin monotherapy in myocardial infarction. *N Engl J Med* 2017;**377**:1132–1142.
107. Nühnenberg TG, Hochholzer W, Mashayekhi K, Ferenc M, Neumann FJ. Efficacy and safety of bivalirudin for percutaneous coronary intervention in acute coronary syndromes: A meta-analysis of randomized-controlled trials. *Clin Res Cardiol*;doi: 10.1007/s00392-018-1251-1. Published online ahead of print 13 April 2018.
108. Moscucci M, Fox KA, Cannon CP, Klein W, Lopez-Sendon J, Montalescot G, White K, Goldberg RJ. Predictors of major bleeding in acute coronary syndromes: The Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2003;**24**:1815–1823.
109. Latif F, Kleiman NS, Cohen DJ, Pencina MJ, Yen CH, Cutlip DE, Moliterno DJ, Nassif D, Lopez JJ, Saucedo JF; EVENT Investigators. In-hospital and 1-year outcomes among percutaneous coronary intervention patients with chronic kidney disease in the era of drug-eluting stents: A report from the EVENT (Evaluation of Drug Eluting Stents and Ischemic Events) registry. *JACC Cardiovasc Interv* 2009;**2**:37–45.
110. Mehran R, Nikolsky E, Lansky AJ, Kirtane AJ, Kim YH, Feit F, Manoukian S, Moses JW, Ebrahimi R, Ohman EM, White HD, Pocock SJ, Dangas GD, Stone GW. Impact of chronic kidney disease on early (30-day) and late (1-year) outcomes of patients with acute coronary syndromes treated with alternative antithrombotic treatment strategies: An ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) substudy. *JACC Cardiovasc Interv* 2009;**2**:748–757.
111. Alexander KP, Chen AY, Roe MT, Newby LK, Gibson CM, Allen-LaPointe NM, Pollack C, Gibler WB, Ohman EM, Peterson ED; CRUSADE Investigators. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. *JAMA* 2005;**294**:3108–3116.
112. Steg PG, Huber K, Andreotti F, Arnesen H, Atar D, Badimon L, Bassand JP, De Caterina R, Eikelboom JA, Gulba D, Hamon M, Helft G, Fox KA, Kristensen SD, Rao SV, Verheugt FW, Widimsky P, Zeymer U, Collet JP. Bleeding in acute coronary syndromes and percutaneous coronary interventions: Position paper by the Working Group on Thrombosis of the European Society of Cardiology. *Eur Heart J* 2011;**32**:1854–1864.
113. Aradi D, Kirtane A, Bonello L, Gurbel PA, Tantry US, Huber K, Freynhofer MK, ten Berg J, Janssen P, Angiolillo DJ, Siller-Matula JM, Marcucci R, Patti G, Mangiacapra F, Valgimigli M, Morel O, Palmerini T, Price MJ, Cuisset T, Kastrati A, Stone GW, Sibbing D. Bleeding and stent thrombosis on P2Y12-inhibitors: Collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. *Eur Heart J* 2015;**36**:1762–1771.
114. Stone GW, Witzensichler B, Weisz G, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Gurbel PA, Xu K, Parise H, Kirtane AJ, Brodie BR, Mehran R, Stuckey TD; ADAPT-DES Investigators. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): A prospective multicentre registry study. *Lancet* 2013;**382**:614–623.
115. Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, Puri S, Robbins M, Garratt KN, Bertrand OF, Stillabower ME, Aragon JR, Kandzari DE, Stinis CT, Lee MS, Manoukian SV, Cannon CP, Schork NJ, Topol EJ; GRAVITAS Investigators. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: The GRAVITAS randomized trial. *JAMA* 2011;**305**:1097–1105.

116. Trenk D, Stone GW, Gawaz M, Kastrati A, Angiolillo DJ, Muller U, Richardt G, Jakubowski JA, Neumann FJ. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: Results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) study. *J Am Coll Cardiol* 2012;**59**:2159–2164.
117. Collet JP, Cuisset T, Range G, Cayla G, Elhadad S, Pouillot C, Henry P, Motreff P, Carrie D, Boueri Z, Belle L, Van Belle E, Rousseau H, Aubry P, Monsegu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Barthelemy O, Beygui F, Silvain J, Vicaut E, Montalescot G; ARCTIC Investigators. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med* 2012;**367**:2100–2109.
118. Cayla G, Cuisset T, Silvain J, Leclercq F, Manzo-Silberman S, Saint-Etienne C, Delarche N, Bellemain-Appaix A, Range G, El Mahmoud R, Carrie D, Belle L, Souteyrand G, Aubry P, Sabouret P, du Fretay XH, Beygui F, Bonnet JL, Lattuca B, Pouillot C, Varenne O, Boueri Z, Van Belle E, Henry P, Motreff P, Elhadad S, Salem JE, Abtan J, Rousseau H, Collet JP, Vicaut E, Montalescot G; ANTARCTIC Investigators. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): An open-label, blinded-endpoint, randomised controlled superiority trial. *Lancet* 2016;**388**:2015–2022.
119. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, Orban M, Hadamitzky M, Merkely B, Kiss RG, Komocsi A, Dezsi CA, Holdt L, Felix SB, Parma R, Klopotoski M, Schwinger RHG, Rieber J, Huber K, Neumann FJ, Koltowski L, Mehilli J, Huczek Z, Massberg S; TROPICAL-ACS Investigators. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): A randomised, open-label, multicentre trial. *Lancet* 2017;**390**:1747–1757.
120. Mega JL, Simon T, Collet JP, Anderson JL, Antman EM, Bliden K, Cannon CP, Danchin N, Giusti B, Gurbel P, Horne BD, Hulot JS, Kastrati A, Montalescot G, Neumann FJ, Shen L, Sibbing D, Steg PG, Trenk D, Wiviott SD, Sabatine MS. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: A meta-analysis. *JAMA* 2010;**304**:1821–1830.
121. Roberts JD, Wells GA, Le May MR, Labinaz M, Glover C, Froeschl M, Dick A, Marquis JF, O'Brien E, Goncalves S, Druce I, Stewart A, Gollub MH, So DY. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): A prospective, randomised, proof-of-concept trial. *Lancet* 2012;**379**:1705–1711.
122. Collet JP, Kerneis M, Hulot JS, O'Connor SA, Silvain J, Mansencal N, Brugier D, Abtan J, Barthelemy O, Vignalou JB, Payot L, Rousseau H, Vicaut E, Montalescot G; GAMMA Investigators. Point-of-care genetic profiling and/or platelet function testing in acute coronary syndrome. *Thromb Haemost* 2016;**115**: 382–391.