ESC European Society of Cardiology

European Heart Journal (2020) **00**, 1–35
doi:10.1093/eurheartj/ehaa575

**ESC GUIDELINES**

# 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: *supplementary data*

## The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

**Authors/Task Force Members: Jean-Philippe Collet * (Chairperson) (France), Holger Thiele * (Chairperson) (Germany), Emanuele Barbato (Italy), Olivier Barthélémy (France), Johann Bauersachs (Germany), Deepak L. Bhatt (United States of America), Paul Dendale (Belgium), Maria Dorobantu (Romania), Thor Edvardsen (Norway), Thierry Folliguet (France), Chris P. Gale (United Kingdom), Martine Gilard (France), Alexander Jobs (Germany), Peter Jüni (Canada), Ekaterini Lambrinou (Cyprus), Basil S. Lewis (Israel), Julinda Mehilli (Germany), Emanuele Meliga (Italy), Béla Merkely (Hungary), Christian Mueller (Switzerland), Marco Roffi (Switzerland), Frans H. Rutten (Netherlands), Dirk Sibbing (Germany), George C.M. Siontis (Switzerland)**

* Corresponding authors: Jean-Philippe Collet, Sorbonne Université, ACTION Study Group, INSERM UMRS 1166, Institut de Cardiologie, Hôpital Pitié-Salpêtrière (Assistance Publique- Hôpitaux de Paris) (AP-HP), 83, boulevard de l'Hôpital, 75013 Paris, France. Tel + 33 01 42 16 29 62, E-mail: jean-philippe.collet@aphp.fr
Holger Thiele, Department of Internal Medicine/Cardiology, Heart Center Leipzig at University of Leipzig, Strümpellstr. 39, 04289 Leipzig, Germany. Tel: +49 341 865 1428, Fax: +49 341 865 1461, E-mail: holger.thiele@medizin.uni-leipzig.de

**ESC entities having participated in the development of this document:**

**Associations**: Association for Acute CardioVascular Care (ACVC), Association of Cardiovascular Nursing & Allied Professions (ACNAP), European Association of Cardiovascular Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).

**Councils**: Council for Cardiology Practice.

**Working Groups**: Cardiovascular Pharmacotherapy, Cardiovascular Surgery, Coronary Pathophysiology and Microcirculation, Thrombosis.

**Document Reviewers: Adnan Kastrati (CPG Review Coordinator) (Germany), Mamas A. Mamas (CPG Review Coordinator) (United Kingdom), Victor Aboyans (France), Dominick J. Angiolillo (United States of America), Hector Bueno (Spain), Raffaele Bugiardini (Italy), Robert A. Byrne (Ireland), Silvia Castelletti (Italy), Alaide Chieffo (Italy), Veronique Cornelissen (Belgium), Filippo Crea (Italy), Victoria Delgado (Netherlands), Heinz Drexel (Austria), Marek Gierlotka (Poland), Sigrun Halvorsen (Norway), Kristina Hermann Haugaa (Norway), Ewa A. Jankowska (Poland), Hugo A. Katus (Germany), Tim Kinnaird (United Kingdom), Jolanda Kluin (Netherlands), Vijay Kunadian (United Kingdom), Ulf Landmesser (Germany), Christophe Leclercq (France), Maddalena Lettino (Italy), Leena Meinila (Finland), Darren Mylotte (Ireland), Gjin Ndrepepa (Germany), Elmir Omerovic (Sweden), Roberto F. E. Pedretti (Italy), Steffen E. Petersen (United Kingdom), Anna Sonia Petronio (Italy), Gianluca Pontone (Italy), Bogdan A. Popescu (Romania), Tatjana Potpara (Serbia), Kausik K. Ray (United Kingdom), Flavio Luciano Ribichini (Italy), Dimitrios J. Richter (Greece), Evgeny Shlyakhto (Russian Federation), Iain A. Simpson (United Kingdom), Miguel Sousa-Uva (Portugal), Robert F. Storey (United Kingdom), Rhian M. Touyz (United Kingdom), Marco Valgimigli (Switzerland), Pascal Vranckx (Belgium), Robert W. Yeh (United States of America)**

**The disclosure forms of all experts involved in the development of these guidelines are available on the ESC website www.escardio.org/guidelines**

**Keywords** Acute cardiac care • acute coronary syndrome • angioplasty • anticoagulation • antiplatelet • apixaban • aspirin • atherothrombosis • betablockers • bleedings • bivalirudin • bypass surgery • cangrelor • chest pain unit • clopidogrel • dabigatran • diabetes • dual antithrombotic therapy • early invasive strategy • edoxaban • enoxaparin • European Society of Cardiology • fondaparinux • glycoprotein IIb/IIIa inhibitors • guidelines • heparin • high-sensitivity troponin – minoca • myocardial ischaemia • myocardial infarction • nitrates • non-ST-elevation myocardial infarction • platelet inhibition • prasugrel • recommendations • revascularisation • rhythm monitoring • rivaroxaban • stent • ticagrelor • triple therapy • unstable angina

# 1 Supplementary data

# Table of contents

## List of tables



## List of figures



# Abbreviations and Acronyms

| | |
|---|---|
| ABOARD | Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention |
| AβYSS | Beta Blocker Interruption After Uncomplicated Myocardial Infarction |
| ACC | American College of Cardiology |
| ACE | angiotensin-converting enzyme |
| ACS | acute coronary syndromes |
| ACUITY | Acute Catheterization and Urgent Intervention Triage strategY |
| AF | atrial fibrillation |
| AHA | American Heart Association |
| AMI | acute myocardial infarction |
| ARR | absolute risk reduction |
| AUGUSTUS | Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation |
| b.i.d. | twice daily (latin: bis in die) |
| BMI | body mass index |
| CABG | coronary artery bypass graft(ing) |
| CAD | coronary artery disease |
| CCS | chronic coronary syndrome |
| $CHA_2DS_2$-VASc | Cardiac failure, Hypertension, Age ≥75 (2 points), Diabetes, Stroke (2 points)-Vascular disease, Age 65–74, Sex category |
| CI | confidence interval |
| CK-MB | creatine kinase myocardial band |
| CMR | cardiac magnetic resonance |
| CPC | cerebral performance category |
| CRUSADE | Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines |
| CS | cardiogenic shock |
| CVD | cardiovascular disease |
| DANAMI 3-PRIMULTI | Primary PCI in Patients With ST-Elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization |
| DAPT | dual antiplatelet therapy |
| DAT | dual antithrombotic therapy |
| DEFINE-FLAIR | Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation |
| DEFINE REAL | REal-life information for the utilization of instantaneous wave-free ratio |
| EARLY | Early or Delayed Revascularization for Intermediate- and High-Risk Non-ST-Segment Elevation Acute Coronary Syndromes? |
| ECG | electrocardiogram |
| ECLS | extracorporeal life support |
| ECLS-SHOCK | Extracorporeal Life Support in Cardiogenic Shock |
| ECMO | extracorporeal membrane oxygenation |
| ECMO-CS | ExtraCorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock |
| ELISA | Early or Late Intervention in unStable Angina |
| ENTRUST-AF PCI | EdoxabaN TRreatment versUS VKA in paTients with AF undergoing PCI |

| | |
|---|---|
| ESC | European Society of Cardiology |
| EUROSHOCK | Testing the Value of Novel Strategy and Its Cost Efficacy in Order to Improve the Poor Outcomes in Cardiogenic Shock |
| FAME | Fractional flow reserve versus Angiography for Multivessel Evaluation |
| FAMOUS-NSTEMI | Fractional flow reserve versus angiography in guiding management to optimize outcomes in non-ST-elevation myocardial infarction |
| FFR | fractional flow reserve |
| FRISC | FRagmin and Fast Revascularisation during InStability in Coronary artery disease |
| FU | follow-up |
| FXa | factor Xa |
| GINA | Global Initiative for Asthma |
| GOSPEL | Global Secondary Prevention Strategies to Limit Event Recurrence after Myocardial Infarction |
| GP | glycoprotein |
| GRACE | Global Registry of Acute Coronary Events |
| HIT | heparin-induced thrombocytopenia |
| HORIZONS-AMI | Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction |
| HR | hazard ratio |
| HYPO-ECMO | Effects of Induced Moderate HYPOthermia on Mortality in Cardiogenic Shock Patients Rescued by Veno-arterial ExtraCorporeal Membrane Oxygenation |
| IABP | intra-aortic balloon pump |
| ICTUS | Invasive Versus Conservative Treatment in Unstable Coronary Syndromes |
| iFR | instantaneous wave-free ratio |
| iFR-SWEDEHEART | Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome |
| INR | international normalized ratio |
| IQR | interquartile range |
| ISAR-CLOSURE | Instrumental Sealing of ARterial puncture site—CLOSURE device versus manual compression |
| ISAR-COOL | Intracoronary Stenting and Antithrombotic Regimen - Cooling off strategy |
| ISAR-TRIPLE | Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation |
| i.v. | intravenous |
| LAD | left anterior descending |
| LCX | left circumflex |
| LIPSIA-NSTEMI | Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI |
| LV | left ventricular |
| LVEF | left ventricular ejection fraction |
| MACCE | major adverse cardiovascular and cerebrovascular events |
| MACE | major adverse cardiovascular events |
| MATE | Medicine versus Angiography in Thrombolytic Exclusion |
| MATRIX | Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX |
| METs | metabolic equivalents |
| MI | myocardial infarction |
| NOAC | non-vitamin K antagonist oral anticoagulant |
| NS | not significant |
| NSTE-ACS | non-ST-segment elevation acute coronary syndrome |
| NSTEMI | non-ST-segment elevation myocardial infarction |
| OAC | oral anticoagulation/anticoagulant |
| OASIS-5 | Fifth Organization to Assess Strategies for Ischaemic Syndromes |
| OHCA | out-of-hospital cardiac arrest |
| OPTIMA | Optimal timing of coronary intervention in unstable angina |
| OR | odds ratio |
| PCI | percutaneous coronary intervention |
| PIONEER AF-PCI | Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention |
| PLATO | PLATelet inhibition and patient Outcomes |
| POST-IT | Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease |
| PROMs | patient-reported outcome measures |
| R3F | French FFR Registry |
| RCA | right coronary artery |
| RCT | randomized controlled trial |
| REACH | REduction of Atherothrombosis for Continued Health |
| REBOOT-CNIC | TREatment With Beta-blockers After myOcardial Infarction withOut Reduced Ejection fracTion |
| RE-DUAL PCI | Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention |
| REDUCE-SWEDEHEART | Evaluation of Decreased Usage of Betablockers After Myocardial Infarction in the SWEDEHEART Registry |
| REPLACE-2 | Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events 2 |
| REVERSE | Impella CP With VA ECMO for Cardiogenic Shock |

| | |
|---|---|
| RIDDLE-NSTEMI | Randomized Study of Immediate Versus Delayed Invasive Intervention in Patients With Non-ST-Segment Elevation Myocardial Infarction |
| RITA-3 | Third Randomised Intervention Treatment of Angina |
| RR | relative risk/risk ratio |
| RRT | renal replacement therapy |
| SBP | systolic blood pressure |
| SISCA | Comparison of Two Treatment Strategies in Patients With an Acute Coronary Syndrome Without ST Elevation |
| STEMI | ST-segment elevation myocardial infarction |
| SWEDEHEART | Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies |
| SYNTAX | Synergy between PCI with Taxus and cardiac surgery. |
| TACTICS-TIMI | Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction |
| TAT | triple antithrombotic therapy |
| TIMACS | Timing of Intervention in Patients with Acute Coronary Syndromes |
| TIMI | Thrombolysis In Myocardial Infarction |
| TRUCS | Treatment of refractory unstable angina in geographically isolated areas without cardiac surgery. Invasive versus conservative strategy |
| UFH | unfractionated heparin |
| VA-ECMO | veno-arterial extracorporeal membrane oxygenation |
| VANQWISH | Veterans Affairs Non-Q-Wave Myocardial Infarction Strategies In-Hospital |
| VERDICT | Very EaRly vs Deferred Invasive evaluation using Computerized Tomography |
| VINO | Value of first day coronary angiography/ angioplasty In evolving Non ST-segment elevation myocardial infarction. An Open multicenter randomized trial. |
| VKA | vitamin K antagonist |
| WOEST | What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing |

# 2 Introduction

## 2.4 Number and partition of classes of recommendations

The total number of recommendations is 131. Partitions according to class of recommendations and level of evidence are provided in *Supplementary Figure 1*.

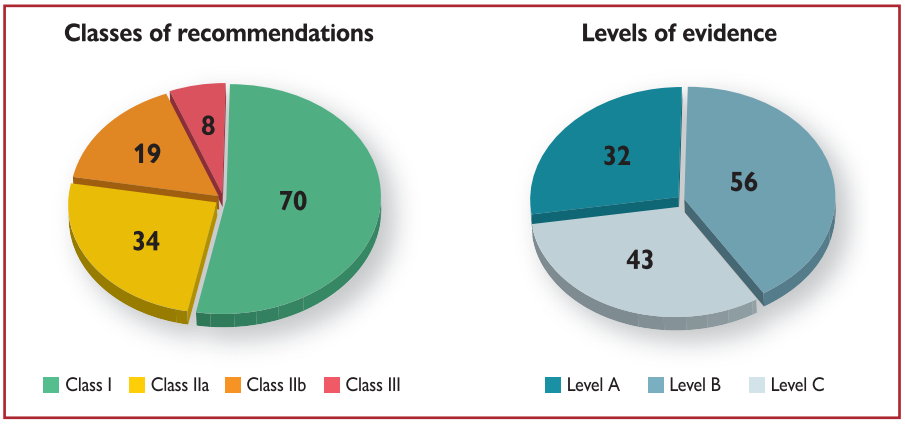
# 3 Diagnosis

## 3.1 Clinical presentation

Acute chest discomfort in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients may have the following presentations:

- Prolonged (>20 min) chest discomfort at rest.
- New-onset (*de novo*) (<3 months) angina (class II or III of the Canadian Cardiovascular Society classification).[1]
- Recent destabilization of previously stable angina with at least Canadian Cardiovascular Society Class III angina characteristics (crescendo angina).
- Post-myocardial infarction (MI) angina.

Typical chest discomfort is characterized by a retrosternal sensation of pain, pressure, or heaviness ('angina') radiating to the left arm, both arms, the right arm, the neck, or the jaw, which may be intermittent (usually lasting several minutes) or persistent.[2] Additional symptoms – such as sweating, nausea,




**Supplementary Figure 1** Breakdown of the recommendations according to ESC classes of recommendations and levels of evidence.

epigastric pain, dyspnoea, and syncope — may be present. Atypical presentations include isolated epigastric pain, indigestion-like symptoms, and isolated dyspnoea or fatigue. Atypical complaints are more often observed in the older patient, in women, and in patients with diabetes, chronic renal disease, or dementia.[3–5] The exacerbation of symptoms by physical exertion, and their relief at rest, increase the probability of myocardial ischaemia. The relief of symptoms after nitrate administration increases the likelihood of NSTE-ACS, but this is not diagnostic as it is also reported in other causes of acute chest pain.[5] In patients presenting to the emergency department with suspected MI, overall, the diagnostic performance of chest pain characteristics for MI is limited.[5] Older age, male sex, family history of coronary artery disease (CAD), diabetes, hyperlipidaemia, smoking, hypertension, renal dysfunction, previous manifestation of CAD, and peripheral or carotid artery disease increase the likelihood of NSTE-ACS.[6,7] Conditions that may exacerbate or precipitate NSTE-ACS include anaemia, infection, inflammation, fever, hypertensive peak, anger, emotional stress, and metabolic or endocrine (particularly thyroid) disorders.

### 3.2 Physical examination

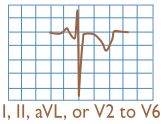
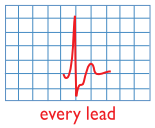
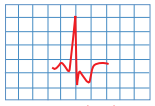
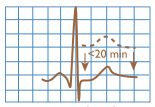
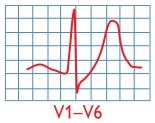
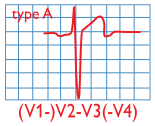
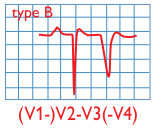
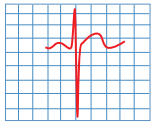
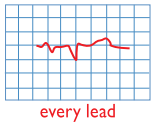
Physical examination is frequently unremarkable in patients with suspected NSTE-ACS.[2] Signs of heart failure or haemodynamic or electrical instability mandate a quick diagnosis and treatment. Cardiac auscultation may reveal a systolic murmur due to ischaemic mitral regurgitation — associated with poor prognosis — or aortic stenosis [mimicking acute coronary syndromes (ACS)][8]. Rarely, a systolic murmur may indicate a mechanical complication (i.e. papillary muscle rupture or ventricular septal defect) of a subacute and possibly undetected MI. Physical examination may identify signs of non-coronary causes of chest pain (e.g. pulmonary embolism, acute aortic syndromes, myopericarditis, aortic stenosis) or extracardiac pathologies (e.g. pneumothorax, pneumonia, or musculoskeletal diseases). In this setting, the presence of chest pain that can be reproduced by exerting pressure on the chest wall has a relatively high negative predictive value for NSTE-ACS.[5] According to the presentation, abdominal disorders (e.g. reflux disease, oesophageal spasm, oesophagitis, gastric ulcer, cholecystitis, or pancreatitis) may also be considered in the differential diagnosis. Differences in blood pressure between the upper and lower limbs or between the arms, irregular pulse, jugular vein distension, heart murmurs, friction rub, and pain reproduced by chest or abdominal palpation are findings suggestive of alternative diagnoses. Pallor, sweating, or tremor may point towards precipitating conditions such as anaemia and thyrotoxicosis.

## 4. Risk assessment and outcomes

### 4.1. Electrocardiogram indicators

The electrocardiogram (ECG) at presentation is a useful tool for risk prediction. Patients with ACS and ST-segment depression on ECG have a worse prognosis than patients with a normal ECG.[9–11] ST-segment depression is not only a qualitative marker, but also a quantitative marker of risk, because the number of leads with ST-segment depression and the magnitude of ST-segment depression (either within a single lead or as sum over all leads) are indicative of the extent of ischaemia and correlate with prognosis.[9,10,12] While the prognostic impact of ST-segment depression (*Supplementary Figure 2*) is indisputable, the evidence regarding the prognostic impact of isolated T-wave inversion is conflicting. T-wave inversion was only independently predictive for an adverse outcome in studies demanding T-wave inversion to occur in ≥5–6 leads,[13–15] while no correlation was found in studies which analysed the prognostic impact of T-wave inversion in fewer leads.[11,16,17] Therefore, the interpretation of the prognostic value of T-wave inversion is hampered due to inconsistent definitions (i.e. occurrence in ≥2 or ≥5 leads). Overall, the prognostic value of T-wave inversion is certainly less than that of ST-segment depression, and T-wave inversion does not alter the prognostic value of associated ST-segment depression.[17] The presence of ST-segment depression >1 mm in ≥6 leads in conjunction with ST-segment elevation in aVR and/or V1, particularly if the patient presents with haemodynamic compromise, suggests multivessel ischaemia or severe left main coronary artery stenosis.[18,19] Transient ST-segment elevation (*Supplementary Figure 2*) identifies patients with a relatively good prognosis and mandates an early, but not an immediate, invasive strategy (see *section 6.1.2.1*).[20–22] Beyond ST-segment deviations and T-wave inversion, additional ECG patterns have been described that may signify severe stenosis or even occlusion of the proximal left anterior descending (LAD) coronary artery. However, these ECG patterns were identified in old, small single-centre series, therefore, their true frequency and diagnostic yield remains unknown (*Supplementary Figure 2*).

Up to a quarter of patients presenting with NSTE-ACS may have a totally occluded vessel on angiography (with decreasing frequency from the right coronary artery [RCA], to the left circumflex [LCX], to LAD distribution), which is associated with increased mortality.[23] Therefore, recognition of ECG patterns in the absence of ST-segment elevation associated with such angiographic finding is of utmost importance. Several ECG patterns that may signify severe CAD have been identified in old, small, single-centre series (*Supplementary Figure 2*). In 1982, de Zwaan *et al.* described an abnormal ST-segment and T-wave morphology now known as part of the Wellens' syndrome (*Supplementary Figure 2 f and g*).[24] In a series of 1260 patients hospitalized for unstable angina during July 1980 and December 1985, 204 (16%) had this ECG pattern.[25] After excluding patients with recent MI and missing data, 180 patients were further analysed. All of these patients had stenosis of ≥50% in the proximal LAD and 18% had a total occlusion. The type A pattern (*Supplementary Figure 2 f*) was present in 25% and the type B pattern (*Supplementary Figure 2 g*) in 75% of patients.[25] In 2008, de Winter *et al.*[26] reported another abnormal ST-segment and T-wave morphology signifying proximal LAD occlusion (*Supplementary Figure 2 e*). This ECG pattern was recognized in 30 of 1532 patients (2%) in their percutaneous coronary intervention (PCI) database.[26] Gerson and McHenry identified resting U wave inversion as a predictor of CAD affecting the left main or LAD (positive predictive value 92%) in patients referred for coronary angiography (*Supplementary Figure 2 h*).[27] Following a study by the Global Registry of Acute Coronary Events (GRACE) ECG substudy and Canadian ACS I registry investigators, low QRS voltage (*Supplementary Figure 2 i*) on admission identifies NSTE-ACS patients at increased risk for in-hospital and 6-month mortality.[28] However, low QRS voltage did not remain

| | ECG pattern | Criteria | Signifying | Figure |
|---|---|---|---|---|
| a | Normal ECG | | No clue |  every lead |
| b | Isolated T-wave inversion | T-wave inversion >1 mm in ≥5 leads considering I, II, aVL, and V2–V6 | Only mildly impaired prognosis |  I, II, aVL, or V2 to V6 |
| c | ST-segment depression | J point depressed by<br>≥0.05 mm in leads V2 and V3 or<br>≥1 mm in all other leads<br><br>followed by a horizontal or downsloping ST-segment for ≥0.08 s in<br>≥1 leads (except aVR) | More severe ischaemia |  every lead<br>  every lead |
| d | Transient ST-segment elevation | ST-segment elevation in ≥2 continuous leads of ≥0.25 mV in men <40 years,<br>≥2 mm in men<br>≥40 years, or ≥0.15 mV in women in leads V2 through V3 and/or<br>≥0.1 mV in other leads lasting <20 min | Only mildly impaired prognosis |  <20 min every lead |
| e | De Winter ST-T | 1–3 mm upsloping ST-segment depression at the J point in leads V1–V6 that continue into tall, positive, and symmetrical T waves | Proximal LAD occlusion/severe stenosis |  V1–V6 |
| f<br>g | Wellens sign | isoelectric or minimally elevated J point (<1 mm)<br>+<br>biphasic T wave in leads V2 and V3 (type A)<br>or<br>symmetric and deeply inverted T waves in leads V2 and V3, occasionally in leads V1, V4, V5, and V6 (type B) | Proximal LAD occlusion/severe stenosis |  type A (V1-)V2-V3(-V4)<br>  type B (V1-)V2-V3(-V4) |
| h | Resting U wave inversion | discrete negative deflection in the T-P segment (negative in comparison to the following P-R segment)<br>no initial positive U wave deflection not obscured by fusion with terminal T wave or following P wave in I, aVL, and V4 through V6 | Occlusion or severe stenosis of the left main artery or LAD |  I, aVL, V4–V6 |
| i | Low QRS voltage | peak to peak QRS complex voltage<br><0.5 mV in all limb leads and<br><1.0 mV in all precordial leads | High risk for in-hospital mortality |  every lead |



**Supplementary Figure 2** Electrocardiogram indicators of risk in patients with non-ST-segment elevation acute coronary syndrome ECG = electrocardiogram; LAD = left anterior descending.

significantly associated with 6-month mortality after adjustment for predictors included in the GRACE risk model predicting 6-month mortality after discharge, which included prior MI and heart failure.[28] Aside from abnormal QRS-ST-T morphologies, atrial fibrillation (AF) is common in the setting of NSTE-ACS and was independently associated with mortality in a Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) analysis.[29]

## 4.3 Clinical scores for risk assessment

Originally, the GRACE risk score was developed to estimate the risk of in-hospital death.[30] In essence, all GRACE risk score models calculated at hospital presentation use the same eight variables [four continuous variables: age, systolic blood pressure (SBP), pulse rate, and serum creatinine; three binary variables: cardiac arrest at admission, elevated cardiac biomarkers, and ST-segment deviation; and one categorical variable: Killip class at presentation] for risk prediction. The

**Supplementary Table 1 Clinical scores for risk assessment**

| Version | Method of calculation | Derivation cohort | Number of variables | Outcome | Model assumption | Model output | c statistics for NSTE-ACS population in derivation cohort |
|---|---|---|---|---|---|---|---|
| 1.0 | Pencil-and-paper calculator | 11 389 patients enrolled from April 1999 to March 2001[30] | 8 | Risk of in-hospital death | Linear association between continuous predictor and risk[30,32,37] | Score is transferred to cumulative risk in percent by means of a nomogram | 0.83[30] |
| | Pencil-and-paper calculator | 15 007 patients enrolled from April 1999 to March 2002[32] | 9 | Risk of death from hospital discharge to 6 months | | | 0.78[32] |
| | Web calculator or iPhone/iPad calculator | 21 688 patients enrolled from April 1999 to September 2005[37] | 8 | Risk of in-hospital death | | | Unknown |
| | | | 8 | Risk of death from hospital admission to 6 months | | | 0.79[37] |
| | | | 8 | Risk of death or MI from hospital admission to 6 months | | | 0.70[37] |
| 2.0 | Web calculator or iPhone/Android application | Unknown | 8 | Risk of in-hospital death | Linear association between continuous predictor and risk | Unknown | Unknown |
| | | Unknown | 8 | Risk of death from hospital admission to 6 months | Linear association between continuous predictor and risk | Score is transferred to cumulative risk in percent by means of a nomogram; risk is adjusted by 80/91 to reflect overall death rates in different populations | Unknown |
| | | 32 037 patients enrolled from January 2002 to December 2007[38] | 8 | Risk of death from hospital admission to 1 year | Non-linear association between predictor and risk[38] | Model estimates are directly used to compute cumulative risk in percent | 0.829[38] |
| | | | 8 | Risk of death or MI from hospital admission to 1 year | | | 0.746[38] |
| | | 1274 patients enrolled in the UK[38,39] | 8 | Risk of death from hospital admission to 3 years | | | 0.782[38] |

MI = myocardial infarction; NSTE-ACS = non-ST-elevation acute coronary syndrome.

**1. Find points for each predictive factor:**

| Killip Class | Points | SBP, mm Hg | Points | Heart Rate, Beats/min | Points | Age, y | Points | Creatinine Level, mg/dL | Points |
|---|---|---|---|---|---|---|---|---|---|
| I | 0 | ≤80 | 58 | ≤50 | 0 | ≤30 | 0 | 0–0.39 | 1 |
| II | 20 | 80–99 | 53 | 50–69 | 3 | 30–39 | 8 | 0.40–0.79 | 4 |
| III | 39 | 100–119 | 43 | 70–89 | 9 | 40–49 | 25 | 0.80–1.19 | 7 |
| IV | 59 | 120–139 | 34 | 90–109 | 15 | 50–59 | 41 | 1.20–1.59 | 10 |
| | | 140–159 | 24 | 110–149 | 24 | 60–69 | 58 | 1.60–1.99 | 13 |
| | | 160–199 | 10 | 150–199 | 38 | 70–79 | 75 | 2.00–3.99 | 21 |
| | | ≥200 | 0 | ≥200 | 46 | 80–89 | 91 | >4.0 | 28 |
| | | | | | | ≥90 | 100 | | |

| Other Risk Factors | Points |
|---|---|
| Cardiac Arrest at Admission | 39 |
| ST-Segment Deviation | 28 |
| Elevated Cardiac Enzyme Levels | 14 |

**2. Sum points for all predictive factors:**

Killip Class + SBP + Heart Rate + Age + Creatinine Level + Cardiac Arrest at Admission + ST-Segment Deviation + Elevated Cardiac Enzyme Levels = Total Points

**3. Look up risk corresponding to total points:**

| Total Points | ≤60 | 70 | 80 | 90 | 100 | 110 | 120 | 130 | 140 | 150 | 160 | 170 | 180 | 190 | 200 | 210 | 220 | 230 | 240 | ≥250 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Probability of In-Hospital Death, % | ≤0.2 | 0.3 | 0.4 | 0.6 | 0.8 | 1.1 | 1.6 | 2.1 | 2.9 | 3.9 | 5.4 | 7.3 | 9.8 | 13 | 18 | 23 | 29 | 36 | 44 | ≥52 |

For example, a patient has Killip class II, SBP of 100 mm Hg, heart rate of 100 beats/min, is 65 years of age, has serum creatinine level of 1 mg/dL, did not have a cardiac arrest at admission but did have ST-segment deviation and elevated enzyme levels.
His score would be: 20 + 53 + 15 + 58 + 7 + 0 + 28 + 14 = 196
This person would have about a 16% risk of having an in-hospital death.

Similarly, a patient with Killip class I, SBP of 80 mm Hg, heart rate of 60 beats/min, is 55 years of age, has serum creatinine level of 0.4 mg/dL, and no risk factors would have the following score:
0 + 58 + 3 + 41 + 1 = 103, which gives approximately a 0.9% risk of having an in-hospital death.

**Supplementary Figure 3** Clinical scores for risk assessment. The figure shows a nomogram for calculation of the GRACE risk score and was adapted by Granger *et al.*[30] SBP = systolic blood pressure.

weighting of these variables, however, differs according to the model version. Continuous variables have to be entered as a range rather than exact numerical values in GRACE risk score calculators (i.e. printable chart, web calculator, and mobile phone application). GRACE risk score calculators then use midpoints of the selected ranges for risk estimation. For the GRACE risk score 2.0, a modified model can be calculated by substituting renal failure and use of diuretics for Killip class or serum creatinine values, respectively, if these are not available.[31] Notably, the variables used by the GRACE risk score to predict post-discharge risk are different.[32] The web calculators provided by the GRACE study group may be accessed via the URL https://www.outcomes-umassmed.org/risk_models_grace_orig.aspx for the GRACE risk score 1.0 and www.outcomes-umassmed.org/grace/acs_risk2/index.html for the GRACE risk score 2.0. The initially developed GRACE risk score for predicting the risk of in-hospital death can be calculated using a paper sheet provided in *Supplementary Figure 3*, which was adapted from the original paper.[30] *Supplementary Table 1* gives an overview of the available GRACE risk score models.

Based on results of a small study, utilization of a high-sensitivity cardiac troponin T assay compared to a conventional assay does not alter the discriminatory ability of the GRACE risk score.[33] Notably, the GRACE risk score model versions 1.0 and 2.0, each derived from populations enrolled more than 10 years ago, likely overestimate risk, but discrimination into low and high risk remains good.[34–36]

# 5. Pharmacological treatments

### 5.2.1 Supportive pharmacological treatment

Relief of chest pain for comfort reasons, but also to decrease sympathetic activation, is essential in NSTE-ACS patients. Opioids [e.g.

intravenous (i.v.) morphine] are the most commonly used analgesics in this setting. However, it has to be kept in mind that morphine use is associated with a slower uptake and a delayed onset of antiplatelet action, which may lead to an early treatment failure in susceptible individuals.[40] In general, oxygen administration is indicated in hypoxic patients with oxygen saturation <90% or in patients with respiratory distress. Interestingly, prior studies have suggested that hyperoxia may be harmful in some patients, presumably due to increased myocardial injury.[41] Therefore, routine oxygen administration is not recommended in cases of oxygen saturation >90%. Anxiety is a natural response to chest pain and a mild tranquillizer (usually a benzodiazepine) should be considered in anxious patients.

#### 5.2.2 Nitrates and beta-blockers

Intravenous nitrates are more effective than sublingual nitrates for symptom relief and resolution of ST depressions in the ECG. During blood pressure monitoring, the dose should be titrated upwards until symptoms are relieved, and in hypertensive patients until blood pressure is normalized, unless side effects (notably headache or hypotension) occur. Beyond symptom control, there is no indication for nitrate treatment. In patients with a recent intake of a phosphodiesterase 5 inhibitor (i.e. within 24 h for sildenafil or vardenafil and 48 h for tadalafil), nitrates should not be administered due to the risk of severe hypotension. Beta-blockers reduce myocardial oxygen consumption by lowering heart rate, blood pressure, and myocardial contractility. Sublingual or i.v. nitrates and early initiation of beta-blocker treatment are recommended in patients with ongoing ischaemic symptoms and without contraindications to the respective drug class. It is recommended to continue chronic beta-blocker therapy unless the patient is in Killip class III or higher. Only a small minority of patients included in randomized controlled trials (RCTs) of early beta-blocker treatment had non-ST-segment elevation MI (NSTEMI),[42] therefore no conclusions can be drawn from randomized trials. However, an observational registry study of 21 822 NSTEMI patients[42] found that, in patients at risk of developing cardiogenic shock (CS) (i.e. at least two characteristics of age >70 years, heart rate >110 beats/min, and/or SBP <120 mmHg), the composite of shock or death was significantly increased in patients receiving beta-blockers very early in the emergency department compared to patients treated later, but within 24 h of hospital admission. Therefore, early administration of beta-blockers should be avoided in these patients, particularly if the ventricular function is unknown. Beta-blockers should not be administered in patients with symptoms possibly related to coronary vasospasm or cocaine use, as they might favour spasm by leaving alpha-mediated vasoconstriction unopposed by beta-mediated vasodilation.

#### 5.3.1 Patients with atrial fibrillation without mechanical prosthetic heart valves or moderate-to-severe mitral stenosis undergoing percutaneous coronary intervention or managed medically

Single antiplatelet therapy with clopidogrel was first evaluated in the What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing (WOEST) trial, where 573 patients were randomized to dual antithrombotic therapy (DAT) with an oral anticoagulant (OAC) and clopidogrel (75 mg/day) or to triple antithrombotic therapy (TAT) with OAC, clopidogrel, and aspirin 80 mg/day.[43] Treatment was continued for 1 month after bare-metal stent (35% of patients) and for 1 year after drug-eluting stent placement (65% of patients).[43] PCI was performed on vitamin K antagonist (VKA) in half of the patients and one-third of them presented with NSTE-ACS. Femoral access was used in the majority of patients (74%). The primary endpoint of any Thrombolysis In Myocardial Infarction (TIMI) bleeding was significantly reduced in the DAT vs. TAT arm [19.5 vs. 44.9%, hazard ratio (HR) 0.36, 95% confidence interval (CI) 0.26–0.50, $P<0.001$], while no significant differences in major bleeds were observed. The rates of MI, stroke, target vessel revascularization, or stent thrombosis did not differ significantly, but all-cause mortality was lower in the DAT group (2.5 vs. 6.4%, $P=0.027$) at 1 year.

In the Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (ISAR-TRIPLE) trial, 614 patients (one-third with ACS) undergoing stenting and requiring OAC were randomly assigned to either 6-week or 6-month clopidogrel therapy in addition to aspirin and VKA.[44] The primary endpoint of death, MI, stent thrombosis, ischaemic stroke, or TIMI major bleeding at 9 months did not differ between the 6-week and 6-month TAT groups (9.8 vs. 8.8%, HR 1.14, 95% CI 0.68–1.91, $P=0.63$); the same was true for the combined incidence of death, MI, stent thrombosis, and ischaemic stroke (4.0 vs. 4.3%, HR 0.93, 95% CI 0.43–2.05, $P=0.87$). Furthermore, no difference in TIMI major bleeding (5.3 vs. 4.0%, HR 1.35, 95% CI 0.64–2.84, $P=0.44$) was observed. Importantly, 10% of patients in the WOEST trial and 7% in the ISAR-TRIPLE trial had prosthetic heart valves. The subgroup analysis of WOEST showed that patients with prosthetic heart valves on DAT derived a similar benefit as the general population.

In the Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI) trial, 2124 patients with AF [51–53% with ACS (12–14% with ST-segment elevation MI (STEMI)] recently treated with stenting were randomized to rivaroxaban 15 mg once daily plus a $P2Y_{12}$ receptor inhibitor for 12 months (group 1), rivaroxaban 2.5 mg bis in die [b.i.d. (twice a day)] plus dual antiplatelet therapy (DAPT) for 1, 6, or 12 months (group 2), or standard therapy with a VKA plus DAPT for 1, 6, or 12 months (group 3).[45] The $P2Y_{12}$ receptor inhibitor was clopidogrel in 93–96% of patients and DAPT was continued up to 12 months in 49% of patients. The primary endpoint of clinically significant bleeds was lower in the two groups receiving rivaroxaban than in the group receiving standard therapy [16.8% in group 1, 18.0% in group 2, and 26.7% in group 3; HR (group 1 vs. group 3) 0.59, 95% CI 0.47–0.76, $P<0.001$; HR (group 2 vs. group 3) 0.63, 95% CI 0.50–0.80, $P<0.001$]. In ACS patients, the trend toward a reduced rate of clinically significant bleeds was stronger in patients in group 2 than in group 1. The rates of death from cardiovascular causes, MI, or stroke were similar in the three groups. However, all-cause death or rehospitalization was significantly reduced at 1 year in the two groups who received rivaroxaban vs. the group who received standard therapy [34.9% in group 1, 31.9% in group 2, and 41.9% in group 3; HR (group 1 vs. group 3) 0.79, 95% CI 0.66–0.94, $P=0.008$; HR (group 2 vs. group 3) 0.75, 95% CI 0.62–0.90, $P=0.002$].[46]

In the Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL PCI) trial, 2725 patients [50% with ACS (2% with STEMI)] recently treated with stenting were included.[47] Patients were randomized to TAT with VKA plus a $P2Y_{12}$ receptor inhibitor and aspirin (for 1–3 months) or DAT with dabigatran (110 mg or 150 mg b.i.d.) plus a $P2Y_{12}$ receptor inhibitor (no aspirin). The $P2Y_{12}$ receptor inhibitors used were clopidogrel and ticagrelor (in 87 and 13% of patients, respectively). The primary endpoint of major or clinically relevant non-major bleeding was 15.4% in the 110 mg DAT group compared with 26.9% in the TAT group (HR 0.52, 95% CI 0.42–0.63, $P<0.001$ for non-inferiority, $P<0.001$ for superiority), and 20.2% in the 150 mg DAT group compared with 25.7% in the corresponding TAT group. The trial also tested for the non-inferiority of DAT with dabigatran (both doses combined) to TAT with respect to the incidence of a composite efficacy endpoint of thromboembolic events (MI, stroke, or systemic embolism), death, or unplanned revascularization. The incidence of the composite efficacy endpoint was 13.7% in the two DAT groups combined compared with 13.4% in the TAT group (HR 1.04, 95% CI 0.84–1.29, $P=0.005$ for non-inferiority). However, the RE-DUAL PCI trial was underpowered for individual ischaemic endpoints, such as stent thrombosis, which occurred twice as often in the 110 mg DAT group compared with TAT.

The Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation (AUGUSTUS) trial randomized 4614 patients with AF recently treated with PCI or presenting with ACS to either apixaban (5 mg b.i.d.) or VKA [international normalized ratio [INR] 2–3).[48] The trial had a two-by-two factorial design, with a $P2Y_{12}$ receptor inhibitor administered to all patients up to 6 months, while patients allotted to the apixaban or VKA group were further randomized to either aspirin or placebo. The primary outcome of major or clinically relevant non-major bleeding was found in 10.5% of the patients receiving apixaban, compared to 14.7% of those receiving a VKA (HR 0.69, 95% CI 0.58–0.81, $P<0.001$ for both non-inferiority and superiority), and in 16.1% of patients receiving aspirin, compared with 9.0% of those receiving placebo (HR 1.89, 95% CI 1.59–2.24, $P<0.001$). Secondary outcomes included death or hospitalization and a composite of ischaemic events. Patients in the apixaban group had a lower incidence of death or hospitalization than those in the VKA group (23.5 vs. 27.4%, HR 0.83, 95% CI 0.74–0.93, $P=0.002$) that was mostly driven by reduced hospitalization, and a similar incidence of ischaemic events. Patients in the aspirin group had an incidence of death or hospitalization similar to the placebo group.

The EdoxabaN TRreatment versUS VKA in paTients with AF undergoing PCI (ENTRUST-AF PCI) trial randomized 1506 patients with AF successfully treated with PCI (with at least 25% presenting with ACS) to either edoxaban 60 mg daily plus a $P2Y_{12}$ receptor inhibitor or VKA plus DAPT with a $P2Y_{12}$ receptor inhibitor and aspirin (for 1–12 months).[49] The primary endpoint was major or clinically relevant non-major bleeding. The study showed non-inferiority for the primary endpoint but, in contrast to the other trials, no superiority for the DAT strategy with edoxaban.[50]

The individual trials were all powered to address the safety of the tested strategy but were too small to reliably assess differences in individual ischaemic endpoints. A recent meta-analysis of the WOEST, ISAR-TRIPLE, PIONEER AF-PCI, and RE-DUAL PCI trials has demonstrated that DAT is associated with a 47% reduction in TIMI major or minor bleeding (4.3 vs. 9.0%, HR 0.53, 95% credible interval 0.36–0.85, I2 = 42.9%) compared with TAT. In addition, there was no difference in trial-defined major adverse cardiovascular events (MACE) (10.4 vs. 10.0%, HR 0.85, 95% credible interval 0.48–1.29, I2 = 58.4%) or in the individual outcomes of all-cause mortality, cardiac death, MI, stent thrombosis, or stroke between the two arms.[51] In a more recent meta-analysis (including ENTRUST-AF PCI), all four non-VKA OAC (NOAC)-based RCTs comparing DAT vs. TAT in AF patients undergoing PCI, encompassing 10 234 patients (DAT = 5496; TAT = 4738), were included.[52] The primary safety endpoint [International Society on Thrombosis and Haemostasis major or clinically relevant non-major bleeding] was significantly lower with DAT vs. TAT [risk ratio (RR) 0.66, 95% CI 0.56–0.78, $P<0.0001$], which was consistent across all available bleeding definitions. This benefit was counterbalanced by a significant increase in stent thrombosis (RR 1.59, 95% CI 1.01–2.50, $P=0.04$). There were no significant differences in all-cause and cardiovascular death, stroke, and MACE.[52] This translates into an absolute reduction in major bleeding events of 2% compared to an absolute increase of stent thromboses of 0.4% without an effect on overall MACE. However, an AUGUSTUS subanalysis indicated that the stent thrombosis rate was highest within the first 30 days, with a similar timing of occurrence as for bleeds.[53]

The indication for OAC should be reassessed and treatment continued only if a compelling indication exists (e.g. paroxysmal, persistent, or permanent AF with a $CHA_2DS_2$-VASc score $\geq 2$; mechanical heart valve; or recent, or a history of, recurrent deep venous thrombosis or pulmonary embolism). Although it has been tested in a minority of patients, in the absence of safety and efficacy data, the use of prasugrel or ticagrelor as part of TAT should be avoided. The dose intensity of OAC should be carefully monitored with a target INR of 2.0–2.5 in patients treated with VKA (with the exception of individuals with mechanical prosthetic valves in the mitral position). In patients treated with NOACs, the lowest tested dose for stroke prevention should be applied.

## 5.4 Management of acute bleeding events

### 5.4.1 General supportive measures

Recommendations for the resuscitation of patients in early haemorrhagic shock or with ongoing bleeding events have evolved over time.[54] During active bleeding, management has shifted away from the traditional approach of rapid bolus fluid administration, in an effort to normalize arterial pressure, towards acceptance of a lower than normal arterial pressure (i.e. deliberate hypotension). Advantages of this strategy include reduced bleeding episodes, more rapid haemostasis, and a better preservation of native coagulation.[54] Disadvantages are a delay in reperfusion of ischaemic tissue and a prolonged state of shock. However, questions remain about a safe duration of deliberate hypotension and about the risk–benefit ratio in high-risk patients, such as those with underlying cardiac or vascular disorders, who are more likely to be vulnerable to ischaemic injury related to hypotension.[54]

#### 5.4.2 Bleeding events on antiplatelet agents

Since there are no antidotes to oral platelet inhibitors, treatment options in patients with ongoing bleeding events while on antiplatelet therapy are limited. Even though platelet transfusion has been used extensively to improve platelet function in this setting, few investigations have assessed its efficacy.[55,56] Furthermore, there have been no studies in CAD patients. While aspirin-inhibited platelet aggregation can be restored after transfusion of 2–5 units of platelets, it is more difficult to restore adenosine diphosphate-dependent platelet function.[57] In prasugrel- or clopidogrel-treated patients, platelet transfusions may be effective in restoring platelet function 4–6 h after the last drug intake.[58] In patients on ticagrelor, it may take ≥24 h for drug clearance to allow transfused platelets to restore haemostatic competence. Recently, an antidote against ticagrelor has been developed, which has been shown to rapidly reverse the antiplatelet effect of ticagrelor in preclinical studies, translating into a gradual normalization of adenosine diphosphate-induced platelet aggregation.[59,60]

#### 5.4.3 Bleeding events on vitamin K antagonists

The antithrombotic effect of VKA requires a reduction of prothrombin (factor II), which has a relatively long half-life (approximately 60–72 h), compared with 6–24 h for other vitamin K-dependent factors. Warfarin therapy requires approximately 2.5 days for an INR between 6.0 and 10.0 to decline to 4.0.[61] While acenocoumarol has a short half-life, and the time required for an effective decline of the INR may be <1 day for most patients, the longer half-life compared with warfarin or phenprocoumon will result in a far slower decline.[62,63] Finally, the half-life of fluindione is similar to that of warfarin, and thus a similar decline in the INR values should be expected. The risk of bleeding events increases significantly when the INR exceeds 4.5. Four RCTs have compared vitamin K1 with placebo in patients with an INR of 4.5–10 in the absence of ongoing bleeding.[62,64–66] While patients receiving vitamin K1 reversed supratherapeutic INRs more rapidly, there was no evidence of benefit for clinically relevant outcomes, including major bleeds or thromboembolism. Vitamin K1 administration may be considered in the absence of ongoing haemorrhage in patients with an INR >10, as the risk of bleeds may be substantial. In the presence of a major or life-threatening bleed on a VKA, a combination of vitamin K1 with a rapid reversal agent (i.e. prothrombin complex concentrate, fresh frozen plasma, or recombinant activated factor VII) should be considered. Fresh frozen plasma remains the most widely used coagulation factor replacement product for urgent reversal of coumarin-based anticoagulation.[67] However, non-activated prothrombin complex concentrates are probably more effective than plasma in correcting INR values, do not require a crossmatch, are virally inactivated, do not pose a risk of volume overload, and can be infused in 15–30 min.[68] Overall, prothrombin complex concentrates may be associated with less thrombotic risk than recombinant activated factor VII, and the latter should only be used if prothrombin complex concentrates are not available.[68] Vitamin K1 should be added to the rapid reversal agent(s) as a slow i.v. infusion of 5–10 mg because of its more rapid onset compared with oral administration.[68] To minimize the risk of anaphylactoid reactions, vitamin K1 should be mixed in a minimum of 50 mL of i.v. fluid and administered, using an infusion pump, over a minimum of 20 min.

#### 5.4.4 Bleeding events on non-vitamin K antagonist oral anticoagulants

After cessation of NOACs, improvement in haemostasis is to be expected within 12–24 h. In patients with reduced renal function, a longer washout period should be expected, especially after dabigatran administration. For patients with ongoing dabigatran-associated life-threatening bleeds, especially in the presence of reduced renal function, adequate diuresis should be maintained, and dialysis may be considered. However, the setup of dialysis in this setting is challenging and experience is limited.[69] Intracerebral haemorrhage or bleeding involving a critical organ, such as the eye, warrants immediate attempts to neutralize the anticoagulant effect of the NOAC. The first-line reversal agent to consider is the specific dabigatran antidote idarucizumab,[70] which has been effectively tested in an uncontrolled phase III trial at a dose of 5 g i.v. in patients with uncontrollable overt bleeds or in patients requiring surgery.[71] Prothrombin complex concentrates or activated prothrombin complex concentrates (i.e. with the addition of activated factor VII) can be considered as second-line treatments, in case of idarucizumab unavailability.[70,72] Based on studies with prothrombin complex concentrates in preclinical models and in healthy volunteers, an initial dose of 25 U/kg is suggested, with repeat dosing if clinically indicated. Activated prothrombin complex concentrates (50 IE/kg, with a maximum of 200 IE/kg/day) may be considered if available. Although product information for some of the NOACs mentions the use of fresh frozen plasma to help control bleeding, it seems unlikely that this treatment may counteract drug effects.[68] Thus, plasma should be administered only for major or life-threatening bleeds with additional dilutional coagulopathy. Both vitamin K1 and protamine have no role in the management of NOAC-associated bleeds.

With patients treated with factor Xa (FXa) inhibitors (apixaban, edoxaban, rivaroxaban), prothrombin complex concentrate should be the first-line treatment.[70] A specific antidote for FXa inhibitors, the andexanet alfa, has been tested in patients with acute major bleeding associated with FXa inhibitors. At a dose of 400 mg bolus, followed by 480 mg infusion over 2 h, andexanet alfa significantly reduced anti-FXa activity, with effective haemostasis occurring in 79% of patients.[73,74]

#### 5.4.5 Non-access-related bleeding events

Non-access-related bleeding events in patients with ACS undergoing PCI represent roughly 40–60% of all bleeds.[75–78] A pooled analysis of the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events 2 (REPLACE-2), Acute Catheterization and Urgent Intervention Triage strategY (ACUITY), and Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trials, including 17 393 PCI patients, showed that the HR for 1-year mortality of a non-access site bleed was approximately two-fold higher than that of an access site bleed (HR 3.94, 95% CI 3.07–5.15, $P<0.001$ vs. HR 1.82, 95% CI 1.17–2.83, $P=0.008$, respectively).[76,77] According to data collected from the PLATelet inhibition and patient Outcomes (PLATO) trial, the most common locations of non-access-related major bleeds were, in decreasing order of frequency, the gastrointestinal tract, nose, urinary tract, subcutaneous dermal, and intracranial, representing together three-quarters of all non-access bleeding events.[75] Overall, non-access-site

bleeding complications display a clear and significant association with all-cause mortality, or the composite of death or MI, and are associated with a greater hazard of mortality compared with access-site events.

### 5.4.6 Bleeding events related to percutaneous coronary intervention

Depending on the complexity of the treated population, as well as the definition used to classify bleeds, the reported incidence of periprocedural bleeding complications ranges between 1.3 and 12.4%.[79–84] Among different definitions used to classify the severity of bleeding complications, the Bleeding Academic Research Consortium criteria offer a balanced combination of laboratory and clinical parameters, as well as a detailed hierarchical system of quantification of the severity of bleeding events that correlates strongly with the risk of death.[85,86] A pooled analysis of seven RCTs, including a total of 14 180 patients (with both stable CAD and NSTE-ACS), has shown that periprocedural bleeds are associated with a five-fold increase in 30-day mortality.[87,88] Bleeding was the strongest predictor of early mortality, whereas the increased risk of late mortality was mostly mediated by cardiovascular risk factors clustered in patients suffering a bleeding event.[88] Different from periprocedural MI, periprocedural bleeds increase the risk of death and ischaemic events even beyond 3 years after PCI in NSTEMI patients.[80,88] These findings, together with the identification of a variety of non-modifiable independent predictors of periprocedural bleeds, such as female sex, advanced age, renal insufficiency, or a history of bleeding, suggest that major periprocedural bleeds might be a marker of patients at higher risk for mortality rather than a trigger of adverse events.[80,89,90] Access site bleeding complications comprise approximately 40–60% of periprocedural bleeds.[77,91,92] In a pooled patient-level analysis of seven RCTs, 1-year mortality of patients with access site bleeds was reported to be significantly higher compared with patients without periprocedural bleeds [4.5 and 2.5%, respectively, odds ratio (OR) 2.03, 95% CI 1.49–2.77).[92] Modifications of the periprocedural antithrombotic regimen have been efficacious in reducing periprocedural bleeds.[93] The radial approach for coronary angiography and PCI has been shown to be superior to the femoral one in patients with ACS. Accordingly, the Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX) trial showed a significant reduction in major bleeds, as well as all-cause mortality, in patients allocated to the radial compared with the femoral approach.[94] In the randomized Instrumental Sealing of ARterial puncture site–CLOSURE device versus manual compression (ISAR-CLOSURE) trial in 4524 patients undergoing diagnostic catheterization, the incidence of vascular site complications including bleeds was 6.9% after the use of vascular closure devices and 7.9% after manual compression.[95] Except for a significantly shorter time to haemostasis, no benefit was observed with vascular closure devices.[95] Even in the context of intensified antithrombotic therapy in ACS, the use of vascular closure devices was not associated with a reduction in bleeding complications.[91] Therefore, routine use of vascular closure devices with the goal of reducing periprocedural bleeding complications cannot be recommended. Strategies to reduce bleeding complications related to PCI are summarized in *Table 12* (*section 5.3.1* of the main text).

### 5.4.7 Bleeding events related to coronary artery bypass surgery

Reported bleeding rates during coronary artery bypass grafting (CABG) in NSTE-ACS patients range from 64 to 80%, depending on the definition used and the time elapsed between DAPT discontinuation and surgery.[96,97] Bleeding events, as well as blood transfusions during CABG, have been associated with increased rates of morbidity and mortality.[98,99] Several risk factors for CABG-associated bleeding events have been identified, including antithrombotic therapy, preoperative anaemia, female sex, older age, small body size, renal or hepatic dysfunction, urgent or emergent procedures, redo surgery, and hereditary or acquired platelet dysfunction.[100,101] Timing of DAPT cessation in NSTE-ACS patients undergoing CABG is detailed elsewhere.[102] 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%.[103,104] Severe CABG-associated bleeds in patients on DAPT should be managed with platelet concentrates. Recombinant factor VIIa should only be used for rescue therapy in patients with uncontrollable bleeding events in whom other correctable causes have been managed (e.g. hypothermia, coagulation factor deficiencies, fibrinogen deficiency), because of concerns of increased risk of graft thrombosis.[105] Several strategies, such as off-pump CABG, antifibrinolytic administration, haemoconcentration, mini-cardiopulmonary bypass circuits, and cell savers, have been advocated to minimize bleeding risk in CABG patients, but few have been tested in NSTE-ACS patients. In a large-scale RCT ($n$=4752, of which 39% underwent urgent surgery for ACS), off-pump CABG was associated with a decreased rate of blood product transfusion and reoperation for bleeding complications compared with on-pump surgery, but it increased the risk of early repeat revascularization and was neutral on mortality.[106]

### 5.4.8 Transfusion therapy

Red blood cell transfusions are administered in up to 10% of patients presenting with ACS.[107] In a retrospective cohort study of 2 258 711 patient visits from the CathPCI Registry (enrolling all patients undergoing PCI), the overall transfusion rate was 2.14%.[108] Women, older people, and patients with baseline anaemia, diabetes mellitus, advanced renal dysfunction, history of MI, history of heart failure, and multivessel CAD are more likely to receive transfusions.[107–109] Irrespective of bleeding complications, the need for blood transfusion is associated with an approximately four-fold increase in early mortality and a three-fold increase in death or MI in ACS patients.[107–109] An increase in platelet reactivity following transfusions may account for the excess of ischaemic events.[110] The nadir haemoglobin cut-off value mandating transfusion is not standardized and varies between hospitals.[108,111–113] In the majority of studies investigating different transfusion protocols, a liberal blood transfusion strategy has been defined as any red blood cell transfusion at a haemoglobin level <9.0 g/dL, while a restrictive blood transfusion strategy has been defined as any transfusion at a haemoglobin level <7.0 g/dL.[111–114] A meta-analysis of 10 studies totalling 203 665 patients (nine observational studies and one RCT with 45 patients) with ACS (both STEMI and NSTE-ACS) has reported that blood transfusion or a liberal transfusion strategy was associated with increased all-cause mortality

(18.2 vs. 10.2%, RR 2.91, 95% CI 2.46–3.44, *P*<0.001] compared with no blood transfusion or a restrictive transfusion strategy.[112] However, a transfusion or liberal transfusion strategy seemed to be associated with a significantly higher risk of 30-day death only at a nadir haematocrit >25%.[108,112] Observations from the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines (CRUSADE) initiative in 44 242 patients with NSTE-ACS showed that, among patients with haematocrit ≤24%, transfusions were associated with a trend towards in-hospital mortality reduction vs. no transfusion (11.8 vs. 15.0%, adjusted OR 0.68, 95% CI 0.45–1.02). In patients with haematocrit between 25 and 30%, transfusions had a neutral effect, while in those with haematocrit >30%, a significant increase in mortality was observed.[115] A meta-analysis of 31, largely unblinded, RCTs totalling 9813 patients (only a minority with NSTE-ACS) found no significant difference in primary clinical outcomes for a liberal vs. a restrictive blood transfusion strategy.[116] The most recent RCT (published in 2015) was conducted in 2007 largely stable patients after cardiac surgery.[117] The study found no significant difference between a liberal vs. a restrictive transfusion strategy for the primary outcome of 90-day morbidity, whereas the secondary outcome of total mortality was significantly increased in the restrictive strategy arm. Based on inconsistent study results and the lack of adequately powered RCTs in the setting of NSTE-ACS, a restrictive policy of transfusion in anaemic patients may be considered. The effect of erythropoiesis-stimulating agents on the outcomes of ACS patients with anaemia has not been investigated. However, the accumulated evidence of these compounds in patients with congestive heart failure strongly suggests that they have no beneficial effects on mortality rates, and may be harmful due to an increased risk of thromboembolism and hypertension.[111]

# 6 Invasive treatments

### 6.1.1 Routine invasive vs. selective invasive approach

**Supplementary Table 2 Overview on meta-analyses investigating a routine vs. selective invasive approach**

| Meta-analysis | Included RCTs | n | Follow-up | Effect measure | Comparison of selective invasive strategy vs. routine invasive strategy | | |
|---|---|---|---|---|---|---|---|
| | | | | | Death | Non-fatal MI | Special findings |
| Mehta *et al.*[118] | FRISC II, MATE, RITA-3, TACTICS-TIMI 18, TIMI IIIB, VANQWISH, VINO | 9212 | Weighted mean 17.3 (range 6–24) months | OR | Randomization to hospital discharge: 1.60 (1.14–2.25) | Randomization to hospital discharge: 1.24 (0.99–1.56) | Death or non-fatal MI: biomarker-positive NSTE-ACS: 0.82 (0.70–0.82) |
| | | | | | After hospital discharge to end of FU: 0.76 (0.62–0.94) | After hospital discharge to end of FU: 0.56 (0.46–0.67) | biomarker-negative NSTE-ACS: 0.90, (0.72–1.14) |
| | | | | | Randomization to end of FU: 0.92 (0.77–1.09) | Randomization to end of FU: 0.75 (0.65–0.88) | interaction *P*-value not reported |
| O'Donoghue *et al.*[119] | FRISC II, ICTUS, MATE, RITA-3, TACTICS-TIMI 18, TIMI IIIB, VANQWISH, VINO | 10 150 | 12 months | OR | 0.97 (0.71–1.32) | 0.84 (0.63–1.12) | Death, non-fatal MI, or rehospitalization: biomarker-positive NSTE-ACS: 0.59 (0.51–0.69) |
| | | | | | | | biomarker-negative NSTE-ACS: 0.79 (0.58–1.06) |
| | | | | | | | interaction *P*-value=0.18 |
| Fox *et al.*[120] | FRISC II, ICTUS, RITA-3 | 5467 | 5 years | HR | 0.90 (0.77–1.05) | 0.77 (0.65–0.90) | Cardiovascular death or non-fatal MI: low-risk patients: 0.80 (0.63–1.02) |
| | | | | | | | intermediate-risk patients: 0.81 (0.66–1.01) |
| | | | | | | | high-risk patients: 0.68 (0.53–0.86) |

*Continued*

**Supplementary Table 2** ***Continued***

| Meta-analysis | Included RCTs | n | Follow-up | Effect measure | Comparison of selective invasive strategy vs. routine invasive strategy | | |
|---|---|---|---|---|---|---|---|
| | | | | | Death | Non-fatal MI | Special findings |
| Fanning *et al.*[121] | ICTUS, Italian Elderly ACS, FRISC II, LIPSIA-NSTEMI, OASIS-5, RITA-3, TACTICS-TIMI 18, VINO | 8915 | 6–12 months | RR | 0.87 (0.64–1.18) | 0.79 (0.63–1.00) | Considered only studies conducted in the in the stent era.<br>Complications of angiography or revascularization: Bleeding: 1.73 (1.30–2.31)<br>Procedure-related MI: 1.87 (1.47–2.37) |
| Elgendy *et al.*[122] | After Eighty, Eisenberg *et al.*, FRISC II, ICTUS, Italian Elderly ACS, OASIS-5 sub-study, RITA-3, TRUCS | 6657 | Weighted mean 10.3 (range 1–15) years | OR | 1.00 (0.90–1.12) | Not reported | Death: in studies with FU 1–5 years: 0.90 (0.77–1.04)<br>in studies with FU >5 years: 1.02 (0.91–1.14) |

Included RCTs are listed in alphabetical order.

ACS = acute coronary syndromes; FRISC = FRagmin and Fast Revascularisation during InStability in Coronary artery disease; FU = follow-up; HR = hazard ratio; ICTUS = Invasive Versus Conservative Treatment in Unstable Coronary Syndromes; LIPSIA-NSTEMI = Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI; MATE = Medicine versus Angiography in Thrombolytic Exclusion; MI = myocardial infarction; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; OASIS-5 = Fifth Organization to Assess Strategies for Ischaemic Syndromes; RCT = randomized controlled trial; RITA-3 = Third Randomised Intervention Treatment of Angina; RR = risk ratio; TACTICS-TIMI = Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction; TIMI = Thrombolysis In Myocardial Infarction; TRUCS = Treatment of refractory unstable angina in geographically isolated areas without cardiac surgery. Invasive versus conservative strategy; OR = odds ratio; VANQWISH = Veterans Affairs Non-Q-Wave Myocardial Infarction Strategies In-Hospital; VINO = Value of first day coronary angiography/angioplasty In evolving Non ST-segment elevation myocardial infarction. An Open multicenter randomized trial.

**Supplementary Table 3 Overview of randomized controlled trials investigating optimal timing of invasive strategy**

| RCT | Year of publication | Region / n | GP IIb/IIa inhibitor use | Primary endpoint |
|---|---|---|---|---|
| Shen *et al.*[123] [a,b] | 2001 | 1 centre in China / 55 | Not reported | No primary endpoint defined, but the 30-day cardiac event rate was lower with an early vs. delayed strategy (0% vs. 9.2%, *P*<0.05) |
| ELISA[124] | 2003 | 1 centre in Netherlands / 220 | 54.5% (pre-treatment in the delayed group + rescue treatment in the early group) | Enzymatic infarct size as area under the lactate dehydrogenase release over 48 h curve (early vs. late): 629±503 vs. 432±444 U/L (*P*=0.02) |
| ISAR-COOL[125] | 2003 | 2 centres in Germany / 410 | 100% | Combined cumulative incidence of large MI or death from any cause during 30 days (early intervention vs. prolonged anti-thrombotic pretreatment): RR 0.51, 95% CI 0.26–0.99 |
| OPTIMA[126] [a] | 2006 | 3 centres in Netherlands / 142 | 95.1% | Composite of death, non-fatal MI, or unplanned revascularisation at 30 days (immediate vs. deferred PCI): RR 1.50, 95% CI 1.09–2.15 |
| ABOARD[127] | 2009 | 13 centres in France / 352 | 61.1% | Peak troponin value during hospitalization (immediate vs. delayed): median (IQR): 2.1 (0.3–7.1) vs 1.7 (0.3–7.2) ng/mL |
| TIMACS[128] | 2009 | 137 centres in Canada and US / 3031 | 22.8% | Composite of death, MI, or stroke within 180 days following randomization (early vs. delayed): HR 0.85, 95% CI 0.68–1.06 |
| Sciahbasi et al.[129] | 2010 | 1 centre in Italy / 54 | 100% | Myocardial blush grade post-PCI 7.4% grade 0 or 1 in both groups (immediate and early) |
| LIPSIA-NSTEMI[130] | 2012 | 6 centres in Germany / 400 | 98.3% | Peak CK-MB activity during index hospitalization (immediate vs. early): median (IQR): 0.94 (0.48–1.91) vs. 0.78 (0.47–1.60) µkat/L |
| ELISA-3[131] | 2013 | 6 centres in Netherlands / 534 | 22.3% | Combined incidence of death, reinfarction, and recurrent ischaemia at 30 days (immediate vs. delayed): 9.9% vs. 14.2% (*P*=0.135) |
| Tekin *et al.*[132] [a] | 2013 | 1 centre in in Turkey / 131 | Not reported | No primary endpoint defined, but various endpoints were better in the early vs. delayed groups |
| SISCA[133] [c] | 2015 | 11 centres in France / 170 | 49.1% (pre-hospital i.v. bolus of tirofiban in the early invasive group); no tirofiban in the delayed invasive group | Cumulative incidence of death, MI, or urgent revascularization at 30 days (early vs. delayed): 2% vs. 24% (*P*<0.001) |
| RIDDLE-NSTEMI[134] | 2016 | 1 centre in Serbia / 323 | 22.3% | Composite of death or new MI at 30 days (immediate vs. delayed): HR 0.32, 95% CI 0.13–0.74 |
| VERDICT[135] | 2017 | 9 centres in Denmark / 2147 | Not reported | Composite of death, non-fatal recurrent MI, hospital admission for refractory myocardial ischemia, or hospital admission for heart failure within 4.3 (IQR 4.1–4.4) years after randomization (very early vs. standard care): HR 0.92, 95% CI 0.78–1.08 |
| EARLY[136] | 2020 | 15 centres in France / 741 | Not reported | Composite of cardiovascular death and recurrent ischaemic events at 1 month (very early vs. delayed): HR 0.20, 95% CI 0.11–0.34 |



The primary endpoint is depicted as an effect estimate and its 95% CI unless stated otherwise.
ABOARD = Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention; CABG = coronary artery bypass graft(ing); CI = confidence interval; CK-MB = creatine kinase myocardial band; EARLY = Early or Delayed Revascularization for Intermediate- and High-Risk Non-ST-Segment Elevation Acute Coronary Syndromes?; ELISA = Early or Late Intervention in unStable Angina; GP = glycoprotein; HR = hazard ratio; IQR = interquartile range; ISAR-COOL = Intracoronary Stenting and Antithrombotic Regimen - Cooling off strategy; i.v. = intravenous; LIPSIA-NSTEMI = Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI; MI = myocardial infarction; OR = odds ratio; OPTIMA = Optimal timing of coronary intervention in unstable angina; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; RIDDLE-NSTEMI = Randomized Study of Immediate Versus Delayed Invasive Intervention in Patients With Non-ST-Segment Elevation Myocardial Infarction; RR = relative risk; SISCA = Comparison of Two Treatment Strategies in Patients With an Acute Coronary Syndrome Without ST Elevation; TIMACS = Timing of Intervention in Patients with Acute Coronary Syndromes; VERDICT = Very EaRly vs Deferred Invasive evaluation using Computerized Tomography.
[a]Patients were not randomized when angiography did not demonstrate significant coronary stenosis amenable for PCI, when CABG was judged to be the preferred treatment, or when the culprit lesion was an in-stent restenosis or a chronic total occlusion.
[b]Randomization for timing of coronary angiography also possible; not entirely clear from trial report.
[c]Randomization took place pre-hospitalization, while it occurred in hospital in all other trials.

**Supplementary Table 4** **Overview on meta-analyses investigating the optimal timing of invasive strategy**

| Meta-analysis | Included RCTs | Effect measure | Comparison of immediate/early vs. delayed invasive strategy | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Death | Non-fatal MI | RI | Stroke | Bleeding | Special findings |
| Katritsis *et al.*[137] | ABOARD, ELISA, ISAR-COOL, TIMACS | RR | 0.85 (0.64–1.11) | 0.94 (0.61–1.45) | 0.59 (0.38–0.92) | 0.84 (0.47–1.49) | 0.78 (0.57–1.07) | Used longer follow-up than published for ELISA, ISAR-COOL (1 month extended to 12 months) |
| Navarese *et al.*[138] | ABOARD, ELISA, ISAR-COOL, LIPSIA-NSTEMI, OPTIMA, TIMACS, Zhang *et al.* | OR | 0.83 (0.64–1.09) | 1.15 (0.65–2.01) | 0.55 (0.35–0.86) | Not reported | 0.76 (0.56–1.04) | Pooled additional data of observational studies, which resulted in similar findings:<br>Death: 0.80 (0.63–1.02)<br>Non-fatal MI: 0.86 (0.69–1.08)<br>Bleeding: 0.76 (0.56–1.04) |
| Milasinovic *et al.*[139] | ABOARD, ELISA, ELISA-3, ISAR-COOL, LIPSIA-NSTEMI, OPTIMA, Sciahbasi *et al.*, Tekin *et al.*, TIMACS, Zhang *et al.* | OR | 0.83 (0.64–1.08) | 1.02 (0.63–1.64) | 0.56 (0.40–0.79) | Not reported | 0.84 (0.65–1.10) | |
| Bonello *et al.*[140] | ABOARD, ELISA, ELISA-3, ISAR-COOL, LIPSIA-NSTEMI, OPTIMA, RIDDLE-NSTEMI, SISCA, TIMACS, Zhang *et al.* | OR | 0.85 (0.67–1.09) | 0.88 (0.53–1.45) | 0.55 (0.40–0.74) | Not reported | 0.94 (0.73–1.22) | |
| Jobs *et al.*[141] | ABOARD, ELISA, ELISA-3, ISAR-COOL, LIPSIA-NSTEMI, RIDDLE-NSTEMI, Sciahbasi *et al.*, TIMACS | HR | 0.81 (0.64–1.03) | 0.91 (0.57–1.46) | Not reported | Not reported | Not reported | Used a modified individual patient data approach (true individual patient data for all trials excepted TIMACS, which provided additional aggregated data not originally published):<br>Biomarker-positive patients: 0.76 (0.58–1.00)<br>Biomarker-negative patients: 1.01 (0.59–1.70)<br>Age ≥75 years: 0.65 (0.46–0.93)<br>Age <75 years: 1.04 (0.74–1.46)<br>Patients with diabetes: 0.67 (0.45–0.99)<br>Patients without diabetes: 0.92 (0.67–1.25)<br>GRACE risk score >140: 0.70 (0.52–0.95)<br>GRACE risk score ≤140: 1.04 (0.63–1.70) |
| Li *et al.*[142] | ABOARD, ELISA, ELISA-3, ISAR-COOL, LIPSIA-NSTEMI, Liu *et al.*, OPTIMA, RIDDLE-NSTEMI, Sciahbasi *et al.*, SISCA, Tekin *et al.*, TIMACS, Zhang *et al.* | OR | 0.78 (0.61–0.99) | 0.83 (0.49–1.41) | 0.50 (0.40–0.62) | Not reported | 0.79 (0.61–1.02) | Included trials of questionable quality with regard to random sequence generation and allocation concealment |
| Zhang *et al.*[143] | ELISA-3, LIPSIA-NSTEMI, OPTIMA, Sciahbasi *et al.*, Tekin *et al.*, TIMACS | OR | 0.76 (0.58-1.00) | 0.94 (0.55-1.61) | not reported | Not reported | 0.88 (0.59-1.31) | Set of included trials after study selection process was not comprehensible; short–medium term follow-up was not defined |

All meta-analyses pooled data using random effects models with the exception of the meta-analysis published by Li *et al.*,[142] which used fixed effects models. Included RCTs are listed in alphabetical order.
ABOARD = Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention; ELISA = Early or Late Intervention in unStable Angina; GRACE = Global Registry of Acute Coronary Events; HR = hazard ratio; ISAR-COOL = Intracoronary Stenting and Antithrombotic Regimen - Cooling off strategy; LIPSIA-NSTEMI = Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI; MI = myocardial infarction; OPTIMA = Optimal timing of coronary intervention in unstable angina; OR = odds ratio; RCT = randomized controlled trial; RI = recurrent/refractory ischaemia; RIDDLE-NSTEMI = Randomized Study of Immediate Versus Delayed Invasive Intervention in Patients With Non-ST-Segment Elevation Myocardial Infarction; RR = risk ratio SISCA = Comparison of Two Treatment Strategies in Patients With an Acute Coronary Syndrome Without ST Elevation; TIMACS = Timing of Intervention in Patients with Acute Coronary Syndromes.

### 6.1.3 Pattern of coronary artery disease in non-ST-segment elevation acute coronary syndrome

Up to 20% of patients presenting with NSTE-ACS have no obstructive lesions of the epicardial coronary arteries (*section 7*),[81,128,130] while 40–80% of patients with obstructive CAD have multivessel CAD.[79,81,128,130] Bypass graft failures and left main CAD may be the underlying condition in 5% and up to 10% of patients, respectively. The LAD is the most frequent culprit vessel, in up to 40% of patients.[81,128,130,144–146] Culprit lesions in NSTE-ACS are more often located within the proximal and mid segments, with approximately the same frequency in these two segments.[145,146]

### 6.1.4 How to identify the culprit lesion?

At least two of the following morphological features suggestive of acute plaque rupture should be present:[145,147,148]

(1) Intraluminal filling defects consistent with thrombus (i.e. acute occlusion abruptly ending with a squared-off or convex upstream termination, or an intraluminal filling defect in a patent vessel within or adjacent to a stenotic region with surrounding homogeneous contrast opacification).

(2) Plaque ulceration (i.e. presence of contrast and hazy contour beyond the vessel lumen).

(3) Plaque irregularity (i.e. irregular margins or overhanging edges), dissection, or impaired flow.

Pathological and intracoronary imaging studies have documented the simultaneous occurrence of multiple vulnerable plaques, mostly as thin-cap fibroatheroma.[149–151] Angiographic studies have confirmed these findings in up to 40% of NSTEMI patients with obstructive CAD.[145,148,152,153] Another one-quarter of patients present with an acute occluded coronary artery. Of note, two-thirds of the occlusions are already collateralized. The differentiation between an acute/subacute and chronic occlusion may be challenging and the identification of the culprit may not be possible.[79,150] ECG (*section 3.3.1*), echocardiography, or left ventricular (LV) angiogram may help to identify the culprit lesion corresponding to a regional wall motion abnormality.

### 6.1.6 Fractional flow reserve, instantaneous wave-free ratio, and other resting indices

**Supplementary Table 5 Summary of available evidence concerning the use of fractional flow reserve in acute coronary syndromes**

| Study | Methodology | Population | Aim | Results |
|---|---|---|---|---|
| **FFR- vs. angio-guided management** | | | | |
| FAMOUS-NSTEMI[154] | • RCT<br>• October 2011 to May 2013 | 350 NSTEMI | FFR- vs. angio-guided management in ACS | • Proportion of patients treated by medical therapy (FFR- vs. angio-guided): 22.7% vs. 13.2%, *P*=0.022<br>• Treatment reclassification in 38 (21.6%) patients with FFR disclosure<br>• 1-year MACCE (FFR- vs. angio-guided): 7.4% vs 9.2%, *P*=0.56 |
| **Diagnostic accuracy of FFR in ACS** | | | | |
| Layland *et al.*[155] | CMR substudy of the FAMOUS-NSTEMI trial | 106 NSTEMI | Diagnostic accuracy of FFR compared with 3.0-T stress CMR perfusion | FFR ≤0.8 (compared to CMR perfusion):<br>• Sensitivity 91.4%<br>• Specificity 92.2%<br>• Positive predictive value 76%<br>• Negative predictive value 97% |
| Ntalianis *et al.*[156] | Registry | 101 AMI (NSTEMI 26%) | Reliability of FFR of non-culprit coronary stenoses during PCI in AMI | FFR of non-culprit stenoses (acute phase vs. at follow-up): 0.77±0.13 vs. 0.77±0.13, *P*=NS |
| **FFR-guided PCI in ACS vs. non-ACS** | | | | |
| Sels *et al.*[157] | Subanalysis of the randomized FAME trial | 1005 patients (ACS 33%) | Benefit of FFR-guided PCI in ACS vs. stable CAD | MACE at 2 years (ACS vs. stable CAD): ARR 5.1% vs. 3.7%, *P*=0.92 |
| Hakeem *et al.*[158] | • Registry<br>• March 2009 to October 2014 | 576 patients (ACS 36%) | Clinical and prognostic utility of FFR in ACS patients with PCI deferred on the basis of non-ischaemic FFR | • 3.4-year MACE (ACS vs. stable CAD): 25% vs. 12%, *P*<0.0001 (propensity score)<br>• HR of ACS for MACE: 2.8, 95% CI 1.9–4.0, *P*<0.0001 (Cox proportional hazard analysis) |

*Continued*

**Supplementary Table 5** ***Continued***

| Study | Methodology | Population | Aim | Results |
|---|---|---|---|---|
| Masrani Mehta *et al.*[159] | • Registry<br>• October 2002 to July 2010 | 674 patients (ACS 50%) | Association of FFR and MACE among patients with coronary lesions deferred for revascularization based on FFR in the setting of ACS vs. non-ACS | HR of FFR (for every 0.01 decrease in FFR) for the composite endpoint (death, MI, or deferred lesion intervention):<br>• 1.08, 95% CI 1.03−1.12, *P*=0.08 in ACS<br>• 1.01, 95% CI 0.96−1.06, *P*=NS in non-ACS<br>(Cox proportional hazard analysis) |
| | | | | One-third of the subsequent MIs that occurred during follow-up were attributable to the lesion initially deferred based on FFR assessment |
| Lee *et al.*[160] | • Pooled 'Korean 4-centers registry' and '3-vessel FFR FRIENDS study'<br>• 2003−2014 | 1596 patients (ACS 19%) | Compare FFR-guided deferral of non-culprit lesion in ACS vs. stable CAD patients | • 2 year-MACE (ACS vs. stable CAD): 3.8% vs. 1.6%, *P*=0.016<br>• ACS was the most powerful independent predictor of MACE (HR 2.74, 95% CI 1.13−6.64, *P*=0.026 |
| PRIME-FFR[161] | Pooled R3F and POST-IT prospective registries | 1983 patients (ACS 27%) | Evaluation of:<br>• Reclassification of the clinical management<br>• 1-year outcomes after FFR guidance | Treatment reclassification (ACS vs. non-ACS): 38% vs. 39%, *P*=NS |
| | | | | 1-year MACE:<br>• ACS reclassified vs. non-reclassified: 8.0% vs. 11.6%, *P*=0.20<br>• ACS vs. non-ACS patients after FFR-based deferral to medical treatment: 8.0% vs. 8.5%, *P*=0.83 |
| Escaned *et al.*[162] | Pooled analyses of the per-protocol deferred population of the iFR-SWEDEHEART and DEFINE-FLAIR RCTs | 2130 patients (ACS 21%) | Investigate the clinical outcomes after revascularization deferral based on iFR or FFR in ACS and stable CAD patients | MACE:<br>• iFR vs. FFR: 4.12% vs. 4.05%, *P*=0.60<br>• ACS vs. stable CAD: 5.91% vs. 3.64%, *P*=0.04 |
| **iFR- vs. FFR-guided PCI** | | | | |
| iFR-SWEDEHEART[163] | • RCT<br>• May 2014 to October 2015 | 2037 patients (ACS 38%) | Compare iFR- vs. FFR-guided PCI | • 1-year MACE (iFR vs. FFR): 6.7% vs. 6.1%, *P*=0.007 for non-inferiority<br>• Chest discomfort (iFR vs. FFR): 3% vs. 68%, *P*<0.001 |
| DEFINE-FLAIR[164] | • RCT<br>• January 2014 to December 2015 | 2492 (ACS 18%) | Compare iFR- vs. FFR-guided PCI | • 1-year MACE (iFR vs. FFR): 6.8% vs. 7.0%, *P*<0.001 for non-inferiority<br>• Chest pain or dyspnoea (iFR vs. FFR): 3% vs. 31%, *P*<0.001 |
| DEFINE REAL[165] | Registry, prospective | 484 patients (ACS 18%) | Impact of routine FFR guidance on treatment reclassification | Reclassification of:<br>• Vessel management: 30.0% of vessels<br>• Patient management: 26.9% of patients<br>• Overall management: 45.7% of patients |

*Continued*

**Supplementary Table 5** *Continued*

| Study | Methodology | Population | Aim | Results |
|---|---|---|---|---|
| **Functionally complete revascularization** | | | | |
| Kobayashi *et al.*[166] | Pooled analyses of the ACS cohorts of the DANAMI3-PRIMULTI, FAMOUS-NSTEMI, FAME RCTs | 547 ACS | Determine whether the residual SYNTAX Score could predict outcomes in patients with ACS who undergo FFR-guided functionally complete revascularization | • Residual SYNTAX Score (patients with vs. without MACE): 7.2±5.5 vs. 6.6±5.9, *P*=0.23<br>• HR of residual SYNTAX Score for 2-year MACE: 1.01, 95% CI 0.98–1.05, *P*=0.46 |



ACS = acute coronary syndromes; AMI = acute myocardial infarction; ARR = absolute risk reduction; CAD = coronary artery disease; CI = confidence interval; CMR = cardiac magnetic resonance; DANAMI 3-PRIMULTI = Primary PCI in Patients With ST-Elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization; DEFINE-FLAIR = Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation; DEFINE REAL = REal-life information for the utilization of instantaneous wave-free ratio; FAME = Fractional flow reserve versus Angiography for Multivessel Evaluation; FAMOUS-NSTEMI = Fractional flow reserve versus angiography in guiding management to optimize outcomes in non-ST-elevation myocardial infarction; FFR = fractional flow reserve; HR = hazard ratio; iFR = instantaneous wave-free ratio; iFR-SWEDEHEART = Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome; MACCE = major adverse cardiovascular and cerebrovascular events; MACE = major adverse cardiovascular events; MI = myocardial infarction; NS = not significant; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; POST-IT = Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease; PRIME-FFR = Insights From the POST-IT and R3F Integrated Multicenter Registries - Implementation of FFR in Routine Practice; R3F = French FFR Registry; RCT = randomized controlled trial; SYNTAX = Synergy between PCI with Taxus and cardiac surgery.

# 8 Special populations

## 8.1 Heart failure and cardiogenic shock

**Supplementary Table 6 Ongoing trials in cardiogenic shock investigating the role of percutaneous mechanical circulatory support**

| Study name | RCT identification | Start–completion date[a] | Key inclusion criteria | Experimental arm | Comparator arm | n | Primary endpoint |
|---|---|---|---|---|---|---|---|
| ANCHOR | NCT04184635 | 2020–2023 | AMI + CS | VA-ECMO + IABP | Conventional circulatory support | 400 | Death in the ECMO group and death OR rescue ECMO in the control group |
| DanGer (formerly DanShock) | NCT01633502 | 2012–2022 | STEMI + CS + LVEF <45% | Impella CP | Conventional circulatory support | 360 | All-cause mortality |
| ECMO-CS | NCT02301819 | 2014–2021 | CS | VA-ECMO | Conventional circulatory support | 120 | All-cause mortality or resuscitated cardiac arrest or another mechanical circulatory support device implantation |
| ECMO-RRT | NCT02870946 | 2016–2021 | CS + ECMO | ECMO + RRT | ECMO | 262 | All-cause mortality |
| ECLS-SHOCK | NCT03637205 | 2019–2022 | AMI + CS | ECLS + PCI (or CABG surgery) | PCI (or CABG surgery) | 420 | All-cause mortality |
| EUROSHOCK | NCT03813134 | 2019–2023 | ACS + CS + PCI | VA-ECMO + PCI | PCI | 428 | All-cause mortality or heart failure |
| HYPO-ECMO | NCT02754193 | 2016–2021 | CS + VA-ECMO | ECMO + hypothermia | ECMO | 334 | All-cause mortality |
| IABP18 | NCT03635840 | 2018–2021 | AMI + CS | IABP prior to revascularization | Revascularization | 92 | All-cause mortality |

*Continued*

**Supplementary Table 6** ***Continued***

| Study name | RCT identification | Start–completion date[a] | Key inclusion criteria | Experimental arm | Comparator arm | n | Primary endpoint |
|---|---|---|---|---|---|---|---|
| Prague OHCA | NCT01511666 | 2013–2021 | OHCA ± CS | Prehospital mechanical compressions, cooling, and in-hospital ECLS | Standard care | 170 | 6-month survival with good neurological outcome (CPC 1–2) |
| REVERSE | NCT03431467 | 2018–2021 | CS | Impella + VA-ECMO | VA-ECMO | 96 | Recovery from shock |

ACS = acute coronary syndromes; AMI = acute myocardial infarction; CABG = coronary artery bypass graft(ing); CPC = cerebral performance category; CS = cardiogenic shock (definition may vary according to study protocol); ECLS = extracorporeal life support; ECLS-SHOCK = Extracorporeal Life Support in Cardiogenic Shock; ECMO = extracorporeal membrane oxygenation; ECMO-CS = ExtraCorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock; EUROSHOCK = Testing the Value of Novel Strategy and Its Cost Efficacy in Order to Improve the Poor Outcomes in Cardiogenic Shock; HYPO-ECMO = Effects of Induced Moderate HYPOthermia on Mortality in Cardiogenic Shock Patients Rescued by Veno-arterial ExtraCorporeal Membrane Oxygenation; IABP = intra-aortic balloon pump; LVEF = left ventricular ejection fraction; OHCA = out-of-hospital cardiac arrest; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; REVERSE = Impella CP With VA ECMO for Cardiogenic Shock; RRT = renal replacement therapy; STEMI = ST-segment elevation myocardial infarction; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
[a]Estimated.

## 8.5 Thrombocytopenia

Thrombocytopenia in the context of NSTE-ACS is an independent predictor of poor outcomes, including death, major bleeds, and life-threatening prothrombotic events.[167–170] Clinically significant thrombocytopenia is defined as a platelet count ≤100 000/mL or a relative drop of 50% from baseline. Causes include haemodilution, in vitro artefacts, increased platelet consumption/sequestration/destruction, and decreased platelet production.[170] Blood sampling should be in non-ethylenediaminetetraacetic acid tubes, as ethylenediaminetetraacetic acid may lead to platelet clumping and pseudothrombocytopenia.[170]

### 8.5.1 Thrombocytopenia related to glycoprotein IIb/IIIa inhibitors

In patients undergoing PCI, mild thrombocytopenia (platelet count of 50 000–100 000/mL) was reported in 4.2% of abciximab- vs. 2.0% of placebo-treated patients (OR 2.14, 95% CI 1.52–3.04, $P<0.001$), whereas severe thrombocytopenia (defined as a platelet count of 20 000–50 000/mL) was reported in 1.0% (abciximab) vs. 0.4% (placebo) of patients (OR 2.48, 95% CI 1.18–5.85, $P=0.01$).[171] In a meta-analysis of 23 RCTs, there was a 51% increase in the incidence of any thrombocytopenia with tirofiban treatment vs. placebo (OR 1.51, 95% CI 1.06–2.16, $P=0.02$).[172]

Patients treated with glycoprotein (GP) IIb/IIIa inhibitors should have a platelet count within 8–12 h of first drug administration, at the time of any bleeding complications, and again after 24 h. Patients treated with abciximab require an additional platelet count within 4 h of first drug administration. GP IIb/IIIa inhibitor infusion should be discontinued if the platelet count falls to <100 000/mL or by 50% from baseline. Platelet transfusions are recommended when there is active bleeding associated with profound thrombocytopenia defined as platelet count <20 000/mL.[171,173] Platelet transfusion may be ineffective while reversibly binding GP IIb/IIIa inhibitors (eptifibatide or tirofiban) remain in circulation (half-life ∼2 h for both drugs).[174] In patients with ongoing major bleeding, fibrinogen supplementation with fresh frozen plasma or cryoprecipitate may be considered. Supportive measures in case of profound thrombocytopenia may include i.v. immunoglobulins and corticosteroids.[175] Patients who experience thrombocytopenia following GP IIb/IIIa inhibitors should be counselled to avoid subsequent exposure.

### 8.5.2 Heparin-induced thrombocytopenia

Non-immune mediated mild thrombocytopenia (platelet count 100 000/mL) presents within 48–72 h of the onset of therapy in 10–20% of patients treated with unfractionated heparin (UFH); this generally resolves without complications despite continued UFH use. By contrast, immune-mediated heparin-induced thrombocytopenia (HIT) is a potentially fatal prothrombotic disorder occurring in 0.5–3% of patients who receive UFH, a low-molecular-weight heparin, or other heparin products.[168,176,177] HIT should be considered when the platelet count drops to <100 000/mL (although it does not usually drop <10 000–20 000/mL).[170,173,178] HIT usually occurs 5–10 days after a first UFH exposure, or within hours if a patient has previously received heparin.[179] In the absence of heparin-dependent antibodies, re-exposure does not necessarily cause a relapse of the syndrome.[179] Once HIT is suspected, heparin (including flushes, coated catheters, etc.) must be discontinued. Given that HIT predisposes to thrombosis, alternative antithrombotic therapy with non-heparin anticoagulants – such as argatroban danaparoid – is necessary. Fondaparinux and bivalirudin are potential alternatives, but not approved for HIT.[180] Platelet transfusions may exacerbate the situation.

## 8.7 Frailty

**Supplementary Table 7 Outcomes instruments to measure frailty**

| Name | References |
|---|---|
| Frailty phenotype | 181–184 |
| Frailty index, accumulation of deficits | 182,184–186 |
| Modified functional independence measure | 187 |
| Instrument 'Carriere' | 188 |
| Instrument 'Gealey' | 189 |
| Gronnigan Frailty Indicator | 190 |
| Frail Elderly Functional Assessment Questionnaire | 191,192 |
| Instrument 'Guilley' | 193 |
| Instrument 'Rothman' | 194 |
| Clinical Global Impression of Change in Physical Frailty | 195 |
| Vulnerable Elders Survey | 196,197 |
| Study of Osteoporotic Fractures instrument | 183 |
| Instrument 'Chin A Paw' | 198 |
| Instrument 'Puts' | 199 |
| Instrument 'Ravaglia' | 200 |
| Instrument 'Winograd' | 201 |
| Grip strength as a single marker | 202 |
| 1994 Frailty Measure | 182,203 |
| Self-report Screening Measurement | 204 |
| Geriatric Functional Evaluation | 205 |
| Frailty Index-comprehensive Geriatric Assessment | 206,207 |

Results are based on the results of a systematic review by de Vries *et al.*[208]

# 9 Long-term management of non-ST-segment elevation acute coronary syndrome

The general aim of long-term secondary prevention is to reduce the risk of recurrence, reduce symptoms, and reduce the risk of developing LV systolic dysfunction and heart failure, and thus improve prognosis and increase event-free life expectancy through appropriate medications and interventions, and control of risk factors including lifestyle behaviours.[209–211] However, there is still insufficient awareness among lay people, patients, and even physicians about the link between risk factors and cardiovascular disease (CVD) in later life;[212–215] even worse is the number of people converting this knowledge into practice.[212] A critical event such as an NSTE-ACS can help trigger active secondary prevention.

Optimal medical therapy should be given alongside promotion of medication adherence, behavioural counselling, and support for managing lifestyle risk factors.[211,216] Achieving optimal management may be best accomplished through a multidisciplinary team approach that can provide tailored and flexible support to patients.[211]

Patient-reported outcome measures (PROMs) can provide relevant and systematic information about patients' symptoms, functioning, and concerns.[211] Increasingly, PROMs are being implemented sequentially in healthcare, and have been shown to improve clinical care and patient experiences, communication between providers and patients (including sensitive subjects), save time in consultations, and improve provider satisfaction.[211,217]

## 9.1 Lifestyle management

Lifestyle recommendations and interventions are described in more detail in the 2016 joint European Guidelines on CVD prevention in clinical practice[218] and the 2019 ESC chronic coronary syndromes (CCS) Guidelines.[211] Lifestyle factors are important, and implementing healthy behaviours (e.g. smoking cessation, physical activity, healthy diet, and maintaining a healthy weight) significantly decreases the risk of future cardiovascular events and death, even when controlling for evidence-based secondary prevention therapy and interventions.[143,211,219–224] Benefits are evident as early as 6 months after an index event such as NSTE-ACS.[211,219]

Primary care providers have an important role to play in prevention. The primary care arm of the EUROACTION cluster-RCT demonstrated that a nurse-coordinated programme in primary care was more effective in helping patients achieve lifestyle and risk factor goals than usual care.[225]

**Supplementary Table 8 Lifestyle recommendations**

| | |
|---|---|
| Smoking cessation | Use pharmacological and behavioural strategies to help patients quit smoking. Avoid passive smoking. |
| Healthy diet | Diet high in vegetables, fruit, whole grains; limit saturated fat to <10% of total. Limit alcohol to <100 g/week or 15 g/day. |
| Physical activity | 30–60 min moderate physical activity most days, but even irregular activity is beneficial. |
| Healthy weight | Obtain and maintain a healthy weight (BMI 18.5–25 kg/m$^2$) or reduce weight through recommended energy intake and increased physical activity. |
| Other | Take medication as prescribed. |
| | Sexual activity is low risk for stable patients who are not symptomatic at low-to-moderate activity levels. |

Lifestyle recommendations are based on 2019 ESC CCS Guidelines.[211]
BMI = body mass index; CCS = chronic coronary syndromes; ESC = European Society of Cardiology.

### 9.1.1 Smoking

Smoking cessation improves the prognosis of patients with CAD, including a 36% risk reduction in mortality for those who quit.[226] Measures to promote smoking cessation include brief advice, counselling, and behavioural interventions, and pharmacological therapy including nicotine replacement.[211,218,227–229] Patients should also avoid passive smoking. Combining behavioural and pharmacological approaches (nicotine-replacement therapy, bupropion, varenicline) are effective and highly recommended.[211,227,228,230] The use of e-cigarettes is not an alternative to conventional cigarettes or a real alternative to smoking cessation; severe short-term toxic effects and

methemoglobinemia have been reported.[231,232] E-cigarettes can deliver nicotine and other constituents such as carbonyls and fine and ultrafine particulates.[211,228,233] In a recent large clinical trial of 886 smokers, those assigned to e-cigarettes to help quitting had a sustained 1-year abstinence rate of 18.0% compared to 9.9% for nicotine-replacement therapy (relative risk 1.83, 95% CI 1.30–2.58, $P<0.001$).[234] Cardiovascular effects of newer e-cigarettes over the longer term remain unknown, as well as their sustained effectiveness in smoking cessation.[228] In clinical encounters with smokers, clinicians should follow the 'Five A's': Ask about smoking, Advise to quit, Assess readiness to quit, Assist with smoking cessation, and Arrange follow-up.[218]

### 9.1.2 Diet and alcohol

Changes to healthy eating patterns in patients with CAD are associated with a reduced risk of mortality and cardiovascular events[211,228,235] (see *Supplementary Table 9* for recommended diet characteristics). A Mediterranean dietary pattern — high in fruit, vegetables, legumes, fibre, polyunsaturated fats, nuts, and fish, while avoiding or limiting refined carbohydrates, red meat, dairy, and saturated fat — is advocated.[211,228,236–239] The effect of a healthy diet is enhanced by physical activity.[240] Although light-to-moderate alcohol intake (1–2 drinks per day) does not increase the risk of MI, levels above 100 g/week were associated with higher all-cause mortality in a large individual data meta-analysis.[241] The Global Burden of Disease 1990–2016 analysis concluded that zero alcohol intake was the level at which risk of death and disability was minimized.[242]

**Supplementary Table 9 Healthy diet[211,218,235,237,243,244]**

| |
|---|
| Increase consumption of fruit and vegetables (≥200 g each per day) |
| 35–45 g of fibre per day, preferably from whole grains |
| Moderate nut consumption (30 g unsalted) |
| 1–2 servings of fish per week (one to be oily fish) |
| Limited lean meat, low-fat dairy products, and liquid vegetable oils |
| Saturated fats to account for <10% of total energy intake, replace with polyunsaturated fats |
| Trans unsaturated fats as low as possible, preferably no intake from processed food, and <1% of total energy intake |
| ≤5–6 g of salt per day |
| If alcohol is consumed, limiting intake to ≤100 g/week or <15 g/day is recommended |
| Avoid energy-dense foods such as sugar-sweetened soft drinks |

### 9.1.3 Weight management

In a population-based study, lifetime risk of incident CVD and cardiovascular morbidity and mortality were higher in those who were overweight or obese compared to those with a healthy body mass index (BMI) (20–25 kg/m$^2$).[245] Obesity was associated with a shorter overall lifespan, and being overweight was associated with developing CVD at an earlier age.[245] However, this association between body weight and cardiovascular and all-cause mortality was not found in patients with CAD, in whom a BMI of 25–30 kg/m$^2$ seemed to be optimal.

Waist circumference is a marker of central obesity and is strongly associated with developing CVD and diabetes. Waist circumference <94 cm for men (<90 cm for South Asian and Asian men) and <80 cm for women is recommended.[218]

In those with CAD, intentional weight loss has been found to be associated with a significantly lower risk of adverse clinical outcomes.[246] Although there has been much argument regarding the relative benefits of low-fat vs. low-carbohydrate diets, Gardner *et al.*[247] found similar weight loss and benefit in patients randomized to either healthy low-fat or low-carbohydrate diets, regardless of patients' genotype pattern and baseline insulin secretion. Healthy diets with energy intake limited to the amount needed to obtain and maintain a healthy weight (BMI <25 kg/m$^2$) and increasing physical activity (and decreased sedentary time) is recommended for weight management.

### 9.1.3 Physical activity

Exercise has been referred to as a 'polypill' due to its numerous beneficial effects on cardiovascular risk factors and cardiovascular system physiology.[248,249,341] Exercise improves angina through enhanced oxygen delivery to the myocardium, and increasing exercise capacity is an independent predictor of increased survival among men and women with CCS, even among those with a regimen consistent with evidence-based management.[221,248,250] Every 1 mL/kg/min increase in peak oxygen uptake has been associated with a 14 - 17% reduction in risk for cardiovascular and all-cause death in women and men.[221]

Physical activity recommendations for CCS patients are 30–60 min of moderate-intensity aerobic activity at least 5 days per week.[251–253] Even irregular leisure-time physical activity decreases mortality risk among previously sedentary patients,[254] and increasing activity is associated with lower cardiovascular mortality.[224,255–258] Previously sedentary patients will need support to work up to 30 - 60 min most days, reassurance that exercise is beneficial, and education regarding what to do if angina occurs while being active. Resistance exercises maintain muscle mass, strength, and function, and benefit insulin sensitivity and control of lipids and blood pressure.[259]

### 9.1.4 Cardiac rehabilitation

Multidisciplinary cardiac rehabilitation has consistently demonstrated its effectiveness in reducing cardiovascular mortality and hospitalizations compared to no exercise in patients with CAD, and this benefit persists in the modern era.[258,260–262] Most patients participating in cardiac rehabilitation are referred following an acute MI (AMI) or after revascularization, with 0 - 24% of patients found to be referred for CCS in 12 European countries.[263] Importantly, the benefits of cardiac rehabilitation occur across diagnostic categories.[258,260,261] Therefore, increasing referral rate to a multidisciplinary cardiac rehabilitation programme should be considered; participation in a cardiac rehabilitation is strongly recommended in all patients with NSTEMI.

### 9.1.5 Psychosocial factors

Patients with heart disease have a two-fold increased risk of mood and anxiety disorders compared to people without heart disease.[264–266] Psychosocial stress, depression, and anxiety are associated with worse outcomes, and make it difficult for patients to make positive changes in their lifestyles or adhere to a therapeutic regimen.

Also, sleep disorders and obstructive sleep apnoea syndrome are associated with increased cardiovascular risk; people sleeping <6 or >10 hours/night are at increased risk of cardiovascular events.[267] The 2016 joint European Guidelines on CVD prevention recommend assessment for psychosocial risk factors.[218] Clinical trials have shown that psychological (e.g. counselling, cognitive behavioural therapy) and pharmacological interventions have a beneficial effect on depression, anxiety, and stress, with some evidence for a reduction in cardiac mortality and events.[268–270]

#### 9.1.6 Environmental factors

Air pollutants have been estimated to be one of the 10 leading risk factors for global mortality.[271] Exposure to air pollution increases the risk of MI as well as hospitalization and death from heart failure, stroke, and arrhythmia.[272,273] Patients with CCS should avoid heavily traffic-congested areas. Air purifiers with high-efficiency particulate air filters reduce indoor pollution, and wearing N95 respirator facemasks in heavily polluted areas has been shown to be protective.[272,274] Studies have also shown that environmental noise increases the risk of CVD.[275] Policies and regulations that reduce air pollution and environmental noise should be supported, and patients should be advised regarding these risks.

#### 9.1.7 Sexual activity

Patients with CCS often worry about the risk of sexual activity and/or experience sexual dysfunction.[276] The risk of triggering sudden death or an AMI is very low, especially when sexual activity is with a stable partner in a familiar environment without stress or excessive intake of food or alcohol beforehand.[277,278] Although sexual activity transiently increases the risk of MI, it is the cause of <1% of AMIs, and <1 - 1.7% of sudden deaths occurred during sexual activity.[278] The energy expenditure during sexual activity is generally low to moderate (3 - 5 metabolic equivalents [METs]), and climbing two flights of stairs is often used as an equivalent activity in terms of energy expended.[277,278] Regular physical activity decreases the risk of adverse events during sexual activity.[279] Sexual dysfunction in patients with CCS includes decreased libido and sexual activity, and a high prevalence of erectile dysfunction. Sexual dysfunction may be caused by underlying vascular conditions, psychosocial factors, specific medications, number of medications, and changes in relationships.[280] Thiazide diuretics and beta-blockers (except nebivolol) may negatively influence erectile function, but studies published since 2011 have not found a consistent relationship between most contemporary cardiovascular medications and erectile dysfunction.[276,278,279] Phosphodiesterase 5 inhibitors to treat erectile dysfunction are generally safe in CCS patients, but should not be used in those taking nitrates.[278] Healthcare providers should ask patients about sexual activity and offer advice and counselling.

#### 9.1.8 Adherence and sustainability

Adherence to lifestyle modifications and medications is a challenge. A systematic review of epidemiological studies has indicated that a substantial proportion of patients do not adhere to cardiovascular medications, and that 9% of cardiovascular events in Europe were attributable to poor adherence.[281] In older men with ischaemic heart disease, greater adherence to medication appears to be positively associated with better clinical outcomes, independent of other conditions.[282] Polypharmacy can play a negative role in adherence to treatment[283] and complexity of a drug regimen is associated with non-adherence and higher rates of hospitalizations.[284] Drug prescriptions should prioritize medications that have proven their benefit with the highest level of evidence and those for which the amplitude of benefit is largest. Simplifying medication regimens may help, and there is some evidence for cognitive educational strategies, electronically monitored feedback, and support by nurse case managers. Medication reviews by primary care providers may be helpful in patients with multiple comorbidities to minimize the risk of adverse interactions and to simplify medication regimens.[216,223,285–287] Promoting behaviour change and medication adherence should be part of each clinical encounter in primary care and specialist follow-up, emphasizing its importance, referring for support when needed, and congratulating patients for achievements. Long-term support (intensive in the first 6 months, then every 6 months for 3 years) as in the Global Secondary Prevention Strategies to Limit Event Recurrence after Myocardial Infarction (GOSPEL) trial resulted in significant improvements in risk factors and decreases in several clinical mortality and morbidity endpoints.[220] The Multicentre Lifestyle Demonstration Project showed that CCS patients could make intensive lifestyle changes and improve their risk factors and fitness, with changes sustained at 12 months.[288] Finally, the use of a polypill, e.g. combinations such as an angiotensin-converting enzyme (ACE) inhibitor, aspirin, plus a statin, can help to improve adherence.[289,290]

#### 9.1.9 Influenza vaccination

An annual influenza vaccination can improve AMI prevention in CCS patients,[291,292] change heart failure prognosis,[293] and decrease cardiovascular mortality in adults aged 65 years and older.[294–296] Therefore, annual influenza vaccination is recommended for patients with CAD, especially for older patients.

## 9.2 Pharmacological management

The aims of the pharmacological management of CCS patients are to reduce angina symptoms, exercise-induced ischaemia, cardiovascular events, LV dysfunction, heart failure, and cardiovascular and all-cause mortality. Immediate relief of anginal symptoms – or prevention of symptoms under circumstances likely to elicit angina – is usually obtained with rapidly acting formulations of nitroglycerin. Anti-ischaemic drugs – but also lifestyle changes, regular exercise training, patient education, and revascularization – all have a role to play in minimizing or eradicating symptoms over the long term (long-term prevention).

Prevention of cardiovascular events targets MI and death associated with CAD and focuses primarily on reducing the incidence of acute thrombotic events and the development of ventricular dysfunction.

Strategies include pharmacological and lifestyle interventions as detailed in the 2016 European Guidelines on CVD prevention in clinical practice.[218]

#### 9.2.1 Anti-ischaemic drugs

*9.2.1.1 Beta-blockers*

In certain patients with recent MI and those with chronic heart failure with reduced ejection fraction (most certainly in those with sinus

rhythm), beta-blockers have been associated with a significant reduction in mortality and/or cardiovascular events.[297–303] Low doses (<25% of target) seem similarly effective as higher doses after MI.[300] However, the protective benefit in patients with CAD without prior MI or heart failure is less well established and lacks placebo-controlled trials.[304] A retrospective analysis of 21 860 matched patients from the REduction of Atherothrombosis for Continued Health (REACH) registry showed no reduction in cardiovascular mortality with β-blockers in patients with CAD with risk factors only, known prior MI, or known CAD without MI.[305] In a retrospective, national registry of 755 215 patients ≥65 years of age with a history of CAD without prior MI or heart failure with reduced ejection fraction undergoing elective PCI, beta-blocker use at discharge was not associated with any reduction in cardiovascular morbidity or mortality at 30-day and 3-year follow-up.[306] However, in patients with or without previous MI undergoing CABG, beta-blockers were associated with a lower risk of long-term mortality and adverse cardiovascular events.[307] Other observational studies or meta-analyses have questioned the benefit of long-term (>1 year) beta-blocker therapy in patients with prior MI.[304,308–311] This is still a matter of debate[312] and uncertainties remain on the comparative role of beta-blockers and ACE inhibitors.

The dose of beta-blockers should be adjusted to limit the heart rate to 55 - 60 beats per min at rest.[313,314] Discontinuation should be tapered rather than abrupt. Beta-blockers can be combined with dihydropyridine calcium channel blockers in patients with symptomatic angina pectoris to reduce the dihydropyridine-induced tachycardia, but with uncertain incremental clinical value.[315–318] Caution is warranted when a beta-blocker is combined with verapamil or diltiazem due to the potential for developing (worsening) heart failure, excessive bradycardia, and/or atrioventricular block. Combination of a beta-blocker with a nitrate attenuates the reflex tachycardia of the latter. The principal side effects of beta-blockers are dose-dependent bradycardia, heart block, postural hypotension, and fatigue. Although bronchospasm may occur, beta-blockers are only relatively contraindicated in patients with asthma and not in chronic obstructive pulmonary disease, although a more selective β1-adrenoreceptor antagonist (i.e. bisoprolol, metoprolol succinate, or nebivolol) may be preferred.[319–322] The contraindication of beta-blockers in asthma, as mentioned on pharmacy leaflets, is based on small case series published in the 1980s and late 1990s with very high (oral) initial dosages in young patients with severe asthma. In clinical practice, starting with a low dose of cardioselective beta-blockers combined with close monitoring of signs of airway obstruction (wheezing, shortness of breath with lengthening of the expirium) may allow the use of beta-blockers.[320] Therefore, according to the Global Initiative for Asthma (GINA) global strategy report,[323] asthma is not an *absolute* contraindication.

The need for, and duration of, beta-blocker therapy following MI to maintain a protective effect on cardiac events in the absence of LV systolic dysfunction are unknown and are currently being investigated in several RCTs [Beta Blocker Interruption After Uncomplicated Myocardial Infarction (AβYSS), Evaluation of Decreased Usage of Betablockers After Myocardial Infarction in the SWEDEHEART Registry (REDUCE-SWEDEHEART), and TREatment With Beta-blockers After myOcardial Infarction withOut Reduced Ejection fracTion (REBOOT-CNIC)].[324]

### 9.2.3 Proton pump inhibitors

Proton pump inhibitors reduce the risk of gastrointestinal bleeding in patients treated with antiplatelet agents and are a useful adjunctive treatment for improving safety;[325] indications for this treatment are summarized in *Table 12* (*section 5.3*). Long-term proton pump inhibitor use is associated with hypomagnesaemia, but the role of monitoring serum magnesium levels is uncertain. Proton pump inhibitors that inhibit *CYP2C19*, particularly omeprazole and esomeprazole, may reduce the pharmacodynamic response to clopidogrel, but without an established increased risk of ischaemic events or stent thrombosis. Co-administration of omeprazole or esomeprazole with clopidogrel is generally not recommended.

### 9.2.6 Renin-angiotensin-aldosterone system blockers

ACE inhibitors can reduce mortality, MI, stroke, and heart failure among patients with LV dysfunction,[326–328] previous vascular disease,[329] and high-risk diabetes.[330] It is recommended to consider ACE inhibitors (or angiotensin receptor blockers in case of intolerance) for the treatment of patients with CCS with co-existing hypertension, LV ejection fraction (LVEF) ≤40%, diabetes, or chronic kidney disease, unless contraindicated (e.g. severe renal impairment, hyperkalaemia, etc.). However, not all trials have demonstrated that ACE inhibitors reduce all-cause mortality, cardiovascular mortality, non-fatal MI, stroke, and heart failure in patients with atherosclerosis and without impaired LV function.[329,331,332] A meta-analysis, including 24 trials and 61 961 patients, documented that, in CCS patients without heart failure, renin-angiotensin system inhibitors reduced cardiovascular events and death when compared with placebo but not when compared with active controls.[333] Hence, ACE inhibitor therapy in CCS patients without heart failure or high cardiovascular risk is not generally recommended, unless required to meet blood pressure targets. Neprilysin is an endogenous enzyme that degrades vasoactive peptides such as bradykinin and natriuretic peptides. Pharmacological inhibition of neprilysin raises the levels of these peptides, enhancing diuresis, natriuresis, myocardial relaxation, and anti-remodelling and reducing renin and aldosterone secretion. The first-in-class angiotensin receptor and neprilysin inhibitor is a combination of valsartan and sacubitril (neprilysin inhibitor) in a single pill. In patients with heart failure (LVEF ≤35%) who remain symptomatic despite optimal treatment with an ACE inhibitor, a beta-blocker, and a mineralocorticoid receptor antagonist, sacubitril/valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of heart failure hospitalization and death in ambulatory patients.[334]

### 9.2.7 Mineralocorticoid receptor antagonist therapy

Aldosterone antagonist therapy is recommended in patients with LV dysfunction (LVEF ≤40%) and heart failure or diabetes after NSTE-ACS. Eplerenone therapy has been shown to reduce morbidity and mortality in these patients after ACS.[335–338] Caution should be exercised when mineralocorticoid receptor antagonists are used in patients with impaired renal function (estimated glomerular filtration rate <45 mL/min/1.73 $m^2$) and in those with serum potassium levels ≥5.0 mmol/L.[320]

### 9.2.8 Antihypertensive therapy

Antihypertensive therapy is recommended according to the 2018 ESC/ESH Guidelines for the management of arterial hypertension.[339] The first treatment goal is blood pressure <140/90 mmHg in all patients and,

provided that the treatment is well tolerated, treated blood pressure values should be targeted to 130/80 mmHg or lower in most patients.[339] In patients aged <65 years receiving blood pressure-lowering drugs, it is recommended that SBP should be lowered to 120–129 mmHg in most patients.[339] In older patients (≥65 years) receiving blood pressure-lowering drugs, the SBP should be targeted to 130–139 mmHg.[339]

### 9.2.9 Hormone replacement therapy

The results from large randomized trials have shown that hormone replacement therapy provides no prognostic benefit and increases the risk of CVD in women above the age of 60 years.[340]

## 10 References


1. Campeau L. Letter: grading of angina pectoris. *Circulation* 1976;**54**:522–523.
2. 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, ESC Scientific Document 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.
3. Canto JG, Fincher C, Kiefe CI, Allison JJ, Li Q, Funkhouser E, Centor RM, Selker HP, Weissman NW. Atypical presentations among Medicare beneficiaries with unstable angina pectoris. *Am J Cardiol* 2002;**90**:248–253.
4. Mackay MH, Ratner PA, Johnson JL, Humphries KH, Buller CE. Gender differences in symptoms of myocardial ischaemia. *Eur Heart J* 2011;**32**:3107–3114.
5. Rubini Gimenez M, Reiter M, Twerenbold R, Reichlin T, Wildi K, Haaf P, Wicki K, Zellweger C, Hoeller R, Moehring B, Sou SM, Mueller M, Denhaerynck K, Meller B, Stallone F, Henseler S, Bassetti S, Geigy N, Osswald S, Mueller C. Sex-specific chest pain characteristics in the early diagnosis of acute myocardial infarction. *JAMA Intern Med* 2014;**174**:241–249.
6. Boeddinghaus J, Nestelberger T, Twerenbold R, Neumann JT, Lindahl B, Giannitsis E, Sorensen NA, Badertscher P, Jann JE, Wussler D, Puelacher C, Rubini Gimenez M, Wildi K, Strebel I, Du Fay de Lavallaz J, Selman F, Sabti Z, Kozhuharov N, Potlukova E, Rentsch K, Miro O, Martin-Sanchez FJ, Morawiec B, Parenica J, Lohrmann J, Kloos W, Buser A, Geigy N, Keller DI, Osswald S, Reichlin T, Westermann D, Blankenberg S, Mueller C, APACE, BACC, and TRAPID-AMI Investigators. Impact of age on the performance of the ESC 0/1h-algorithms for early diagnosis of myocardial infarction. *Eur Heart J* 2018;**39**:3780–3794.
7. Twerenbold R, Badertscher P, Boeddinghaus J, Nestelberger T, Wildi K, Puelacher C, Sabti Z, Rubini Gimenez M, Tschirky S, du Fay de Lavallaz J, Kozhuharov N, Sazgary L, Mueller D, Breidthardt T, Strebel I, Flores Widmer D, Shrestha S, Miro O, Martin-Sanchez FJ, Morawiec B, Parenica J, Geigy N, Keller DI, Rentsch K, von Eckardstein A, Osswald S, Reichlin T, Mueller C. 0/1-hour triage algorithm for myocardial infarction in patients with renal dysfunction. *Circulation* 2018;**137**:436–451.
8. Persson A, Hartford M, Herlitz J, Karlsson T, Omland T, Caidahl K. Long-term prognostic value of mitral regurgitation in acute coronary syndromes. *Heart* 2010;**96**:1803–1808.
9. Holmvang L, Clemmensen P, Lindahl B, Lagerqvist B, Venge P, Wagner G, Wallentin L, Grande P. Quantitative analysis of the admission electrocardiogram identifies patients with unstable coronary artery disease who benefit the most from early invasive treatment. *J Am Coll Cardiol* 2003;**41**:905–915.
10. Kaul P, Fu Y, Chang WC, Harrington RA, Wagner GS, Goodman SG, Granger CB, Moliterno DJ, Van de Werf F, Califf RM, Topol EJ, Armstrong PW, PARAGON-A and GUSTO-IIb Investigators. Prognostic value of ST segment depression in acute coronary syndromes: insights from PARAGON-A applied to GUSTO-IIb. PARAGON-A and GUSTO IIb Investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute Global Organization Network. *J Am Coll Cardiol* 2001;**38**:64–71.
11. Mueller C, Neumann FJ, Perach W, Perruchoud AP, Buettner HJ. Prognostic value of the admission electrocardiogram in patients with unstable angina/non-ST-segment elevation myocardial infarction treated with very early revascularization. *Am J Med* 2004;**117**:145–150.
12. Savonitto S, Cohen MG, Politi A, Hudson MP, Kong DF, Huang Y, Pieper KS, Mauri F, Wagner GS, Califf RM, Topol EJ, Granger CB. Extent of ST-segment depression and cardiac events in non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2005;**26**:2106–2113.
13. Damman P, Holmvang L, Tijssen JG, Lagerqvist B, Clayton TC, Pocock SJ, Windhausen F, Hirsch A, Fox KA, Wallentin L, de Winter RJ. Usefulness of the admission electrocardiogram to predict long-term outcomes after non-ST-elevation acute coronary syndrome (from the FRISC II, ICTUS, and RITA-3 [FIR] Trials). *Am J Cardiol* 2012;**109**:6–12.
14. Holmvang L, Luscher MS, Clemmensen P, Thygesen K, Grande P. Very early risk stratification using combined ECG and biochemical assessment in patients with unstable coronary artery disease (A thrombin inhibition in myocardial ischemia [TRIM] substudy). The TRIM Study Group. *Circulation* 1998;**98**:2004–2009.
15. Jacobsen MD, Wagner GS, Holmvang L, Kontny F, Wallentin L, Husted S, Swahn E, Stahle E, Steffensen R, Clemmensen P. Quantitative T-wave analysis predicts 1 year prognosis and benefit from early invasive treatment in the FRISC II study population. *Eur Heart J* 2005;**26**:112–118.
16. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, Akkerhuis KM, Harrington RA, Deckers JW, Armstrong PW, Lincoff AM, Califf RM, Topol EJ, Simoons ML. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation* 2000;**101**:2557–2567.
17. Tan NS, Goodman SG, Yan RT, Elbarouni B, Budaj A, Fox KA, Gore JM, Brieger D, Lopez-Sendon J, Langer A, van de Werf F, Steg PG, Yan AT. Comparative prognostic value of T-wave inversion and ST-segment depression on the admission electrocardiogram in non-ST-segment elevation acute coronary syndromes. *Am Heart J* 2013;**166**:290–297.
18. Yamaji H, Iwasaki K, Kusachi S, Murakami T, Hirami R, Hamamoto H, Hina K, Kita T, Sakakibara N, Tsuji T. Prediction of acute left main coronary artery obstruction by 12-lead electrocardiography. ST segment elevation in lead aVR with less ST segment elevation in lead V(1). *J Am Coll Cardiol* 2001;**38**:1348–1354.
19. Yan AT, Yan RT, Kennelly BM, Anderson FA, Jr., Budaj A, Lopez-Sendon J, Brieger D, Allegrone J, Steg G, Goodman SG, GRACE Investigators. Relationship of ST elevation in lead aVR with angiographic findings and outcome in non-ST elevation acute coronary syndromes. *Am Heart J* 2007;**154**:71–78.
20. Blondheim DS, Kleiner-Shochat M, Asif A, Kazatsker M, Frimerman A, Abu-Fanne R, Neiman E, Barel M, Levy Y, Amsalem N, Shotan A, Meisel SR. Characteristics, management, and outcome of transient ST-elevation versus persistent ST-elevation and non-ST-elevation myocardial infarction. *Am J Cardiol* 2018;**121**:1449–1455.
21. Patel JH, Gupta R, Roe MT, Peng SA, Wiviott SD, Saucedo JF. Influence of presenting electrocardiographic findings on the treatment and outcomes of patients with non-ST-segment elevation myocardial infarction. *Am J Cardiol* 2014;**113**:256–261.
22. Lemkes JS, Janssens GN, van der Hoeven NW, van de Ven PM, Marques KMJ, Nap A, van Leeuwen MAH, Appelman YEA, Knaapen P, Verouden NJW, Allaart CP, Brinckman SL, Saraber CE, Plomp KJ, Timmer JR, Kedhi E, Hermanides RS, Meuwissen M, Schaap J, van der Weerdt AP, van Rossum AC, Nijveldt R, van Royen N. Timing of revascularization in patients with transient ST-segment elevation myocardial infarction: a randomized clinical trial. *Eur Heart J* 2019;**40**:283–291.
23. Khan AR, Golwala H, Tripathi A, Bin Abdulhak AA, Bavishi C, Riaz H, Mallipedi V, Pandey A, Bhatt DL. Impact of total occlusion of culprit artery in acute non-ST elevation myocardial infarction: a systematic review and meta-analysis. *Eur Heart J* 2017;**38**:3082–3089.
24. de Zwaan C, Bar FW, Wellens HJ. Characteristic electrocardiographic pattern indicating a critical stenosis high in left anterior descending coronary artery in patients admitted because of impending myocardial infarction. *Am Heart J* 1982;**103**:730–736.
25. de Zwaan C, Bar FW, Janssen JH, Cheriex EC, Dassen WR, Brugada P, Penn OC, Wellens HJ. Angiographic and clinical characteristics of patients with unstable angina showing an ECG pattern indicating critical narrowing of the proximal LAD coronary artery. *Am Heart J* 1989;**117**:657–665.
26. de Winter RJ, Verouden NJ, Wellens HJ, Wilde AA, Interventional Cardiology Group of the Academic Medical Center. A new ECG sign of proximal LAD occlusion. *N Engl J Med* 2008;**359**:2071–2073.
27. Gerson MC, McHenry PL. Resting U wave inversion as a marker of stenosis of the left anterior descending coronary artery. *Am J Med* 1980;**69**:545–550.
28. Tan NS, Goodman SG, Yan RT, Tan MK, Fox KA, Gore JM, Brieger D, Steg PG, Langer A, Yan AT, GRACE ECG substudy and Canadian ACS I Registry investigators. Prognostic significance of low QRS voltage on the admission electrocardiogram in acute coronary syndromes. *Int J Cardiol* 2015;**190**:34–39.
29. Batra G, Svennblad B, Held C, Jernberg T, Johanson P, Wallentin L, Oldgren J. All types of atrial fibrillation in the setting of myocardial infarction are associated with impaired outcome. *Heart* 2016;**102**:926–933.
30. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA, Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;**163**:2345–2353.

31. Simms AD, Reynolds S, Pieper K, Baxter PD, Cattle BA, Batin PD, Wilson JI, Deanfield JE, West RM, Fox KA, Hall AS, Gale CP. Evaluation of the NICE mini-GRACE risk scores for acute myocardial infarction using the Myocardial Ischaemia National Audit Project (MINAP) 2003-2009: National Institute for Cardiovascular Outcomes Research (NICOR). *Heart* 2013;**99**:35–40.
32. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KA, Investigators GRACE. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004;**291**:2727–2733.
33. Meune C, Drexler B, Haaf P, Reichlin T, Reiter M, Meissner J, Twerenbold R, Stelzig C, Freese M, Winkler K, Mueller C. The GRACE score's performance in predicting in-hospital and 1-year outcome in the era of high-sensitivity cardiac troponin assays and B-type natriuretic peptide. *Heart* 2011;**97**:1479–1483.
34. Chew DP, Junbo G, Parsonage W, Kerkar P, Sulimov VA, Horsfall M, Mattchoss S, Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndrome Patients (PREDICT) Study Investigators. Perceived risk of ischemic and bleeding events in acute coronary syndromes. *Circ Cardiovasc Qual Outcomes* 2013;**6**:299–308.
35. Elbarouni B, Goodman SG, Yan RT, Welsh RC, Kornder JM, Deyoung JP, Wong GC, Rose B, Grondin FR, Gallo R, Tan M, Casanova A, Eagle KA, Yan AT, Canadian Global Registry of Acute Coronary Events (GRACE/GRACE(2)) Investigators. Validation of the Global Registry of Acute Coronary Event (GRACE) risk score for in-hospital mortality in patients with acute coronary syndrome in Canada. *Am Heart J* 2009;**158**:392–399.
36. Lin A, Devlin G, Lee M, Kerr AJ. Performance of the GRACE scores in a New Zealand acute coronary syndrome cohort. *Heart* 2014;**100**:1960–1966.
37. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA, Jr., Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006;**333**:1091.
38. Fox KA, Fitzgerald G, Puymirat E, Huang W, Carruthers K, Simon T, Coste P, Monsegu J, Gabriel Steg P, Danchin N, Anderson F. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open* 2014;**4**:e004425.
39. Fox KA, Carruthers KF, Dunbar DR, Graham C, Manning JR, De Raedt H, Buysschaert I, Lambrechts D, Van de Werf F. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). *Eur Heart J* 2010;**31**:2755–2764.
40. Kubica J, Adamski P, Ostrowska M, Sikora J, Kubica JM, Sroka WD, Stankowska K, Buszko K, Navarese EP, Jilma B, Siller-Matula JM, Marszall MP, Rosc D, Kozinski M. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. *Eur Heart J* 2016;**37**:245–252.
41. Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, Cameron P, Barger B, Ellims AH, Taylor AJ, Meredith IT, Kaye DM, AVOID Investigators. Air versus oxygen in ST-segment-elevation myocardial infarction. *Circulation* 2015;**131**:2143–2150.
42. Kontos MC, Diercks DB, Ho PM, Wang TY, Chen AY, Roe MT. Treatment and outcomes in patients with myocardial infarction treated with acute beta-blocker therapy: results from the American College of Cardiology's NCDR(®). *Am Heart J* 2011;**161**:864–870.
43. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermans AA, Vis MM, Tijsen 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.
44. 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.
45. 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.
46. Gibson CM, Pinto DS, Chi G, Arbetter D, Yee M, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Burton P, van Eickels M, Korjian S, Daaboul Y, Jain P, Lip GY, Cohen M, Peterson ED, Fox KA. Recurrent hospitalization among patients with atrial fibrillation undergoing intracoronary stenting treated with 2 treatment strategies of rivaroxaban or a dose-adjusted oral vitamin k antagonist treatment strategy. *Circulation* 2017;**135**:323–333.
47. 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, RE-DUAL PCI Steering Committee and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017;**377**:1513–1524.
48. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, Goodman SG, Windecker S, Darius H, Li J, Averkov O, Bahit MC, Berwanger O, Budaj A, Hijazi Z, Parkhomenko A, Sinnaeve P, Storey RF, Thiele H, Vinereanu D, Granger CB, Alexander JH, Investigators AUGUSTUS. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med* 2019;**380**:1509–1524.
49. Vranckx P, Lewalter T, Valgimigli M, Tijssen JG, Reimitz PE, Eckardt L, Lanz HJ, Zierhut W, Smolnik R, Goette A. Evaluation of the safety and efficacy of an edoxaban-based antithrombotic regimen in patients with atrial fibrillation following successful percutaneous coronary intervention (PCI) with stent placement: rationale and design of the ENTRUST-AF PCI trial. *Am Heart J* 2018;**196**:105–112.
50. Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T, Gargiulo G, Batushkin V, Campo G, Lysak Z, Vakaliuk I, Milewski K, Laeis P, Reimitz PE, Smolnik R, Zierhut W, Goette A. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet* 2019;**394**:1335–1343.
51. Golwala HB, Cannon CP, Steg PG, Doros G, Qamar A, Ellis SG, Oldgren J, Ten Berg JM, Kimura T, Hohnloser SH, Lip GYH, Bhatt DL. Safety and efficacy of dual vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J* 2018;**39**:1726–1735a.
52. Gargiulo G, Goette A, Tijssen J, Eckardt L, Lewalter T, Vranckx P, Valgimigli M. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J* 2019;**40**:3757–3767.
53. Lopes RD, Leonardi S, Wojdyla DM, Vora AN, Thomas L, Storey RF, Vinereanu D, Granger CB, Goodman SG, Aronson R, Windecker S, Thiele H, Valgimigli M, Mehran R, Alexander JH. Stent thrombosis in patients with atrial fibrillation undergoing coronary stenting in the AUGUSTUS trial. *Circulation* 2020;**141**:781–783.
54. Dutton RP. Haemostatic resuscitation. *Br J Anaesth* 2012;**109 Suppl 1**:i39–i46.
55. Di Minno G, Silver MJ, Murphy S. Monitoring the entry of new platelets into the circulation after ingestion of aspirin. *Blood* 1983;**61**:1081–1085.
56. Vilahur G, Choi BG, Zafar MU, Viles-Gonzalez JF, Vorchheimer DA, Fuster V, Badimon JJ. Normalization of platelet reactivity in clopidogrel-treated subjects. *J Thromb Haemost* 2007;**5**:82–90.
57. Hansson EC, Shams Hakimi C, Astrom-Olsson K, Hesse C, Wallen H, Dellborg M, Albertsson P, Jeppsson A. Effects of ex vivo platelet supplementation on platelet aggregability in blood samples from patients treated with acetylsalicylic acid, clopidogrel, or ticagrelor. *Br J Anaesth* 2014;**112**:570–575.
58. Zafar MU, Santos-Gallego C, Vorchheimer DA, Viles-Gonzalez JF, Elmariah S, Giannarelli C, Sartori S, Small DS, Jakubowski JA, Fuster V, Badimon JJ. Platelet function normalization after a prasugrel loading-dose: time-dependent effect of platelet supplementation. *J Thromb Haemost* 2013;**11**:100–106.
59. Buchanan A, Newton P, Pehrsson S, Inghardt T, Antonsson T, Svensson P, Sjogren T, Oster L, Janefeldt A, Sandinge AS, Keyes F, Austin M, Spooner J, Gennemark P, Penney M, Howells G, Vaughan T, Nylander S. Structural and functional characterization of a specific antidote for ticagrelor. *Blood* 2015;**125**:3484–3490.
60. Pehrsson S, Johansson KJ, Janefeldt A, Sandinge AS, Maqbool S, Goodman J, Sanchez J, Almquist J, Gennemark P, Nylander S. Hemostatic effects of the ticagrelor antidote MEDI2452 in pigs treated with ticagrelor on a background of aspirin. *J Thromb Haemost* 2017;**15**:1213–1222.
61. Patel RJ, Witt DM, Saseen JJ, Tillman DJ, Wilkinson DS. Randomized, placebo-controlled trial of oral phytonadione for excessive anticoagulation. *Pharmacotherapy* 2000;**20**:1159–1166.
62. Ageno W, Crowther M, Steidl L, Ultori C, Mera V, Dentali F, Squizzato A, Marchesi C, Venco A. Low dose oral vitamin K to reverse acenocoumarol-induced coagulopathy: a randomized controlled trial. *Thromb Haemost* 2002;**88**:48–51.
63. Fondevila CG, Grosso SH, Santarelli MT, Pinto MD. Reversal of excessive oral anticoagulation with a low oral dose of vitamin K1 compared with acenocoumarine discontinuation. A prospective, randomized, open study. *Blood Coagul Fibrinolysis* 2001;**12**:9–16.
64. Ageno W, Garcia D, Silingardi M, Galli M, Crowther M. A randomized trial comparing 1 mg of oral vitamin K with no treatment in the management of warfarin-associated coagulopathy in patients with mechanical heart valves. *J Am Coll Cardiol* 2005;**46**:732–733.
65. Crowther MA, Ageno W, Garcia D, Wang L, Witt DM, Clark NP, Blostein MD, Kahn SR, Vesely SK, Schulman S, Kovacs MJ, Rodger MA, Wells P, Anderson D,

Ginsberg J, Selby R, Siragusa S, Silingardi M, Dowd MB, Kearon C. Oral vitamin K versus placebo to correct excessive anticoagulation in patients receiving warfarin: a randomized trial. *Ann Intern Med* 2009;**150**:293–300.
66. Crowther MA, Julian J, McCarty D, Douketis J, Kovacs M, Biagoni L, Schnurr T, McGinnis J, Gent M, Hirsh J, Ginsberg J. Treatment of warfarin-associated coagulopathy with oral vitamin K: a randomised controlled trial. *Lancet* 2000;**356**:1551–1553.
67. Ageno W, Garcia D, Aguilar MI, Douketis J, Finazzi G, Imberti D, Iorio A, Key NS, Lim W, Marietta M, Prisco D, Sarode R, Testa S, Tosetto A, Crowther M. Prevention and treatment of bleeding complications in patients receiving vitamin K antagonists, part 2: treatment. *Am J Hematol* 2009;**84**:584–588.
68. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;**141**:e44S–e88S.
69. Liesenfeld KH, Staab A, Hartter S, Formella S, Clemens A, Lehr T. Pharmacometric characterization of dabigatran hemodialysis. *Clin Pharmacokinet* 2013;**52**:453–462.
70. Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, Florido R, Hucker W, Mehran R, Messe SR, Pollack CV, Jr., Rodriguez F, Sarode R, Siegal D, Wiggins BS. 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol* 2017;**70**:3042–3067.
71. Pollack CV, Jr., Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kam CW, Kamphuisen PW, Kreuzer J, Levy JH, Royle G, Sellke FW, Stangier J, Steiner T, Verhamme P, Wang B, Young L, Weitz JI. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. *N Engl J Med* 2017;**377**:431-441.
72. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011;**124**:1573–1579.
73. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, Yue P, Bronson MD, Lu G, Conley PB, Verhamme P, Schmidt J, Middeldorp S, Cohen AT, Beyer-Westendorf J, Albaladejo P, Lopez-Sendon J, Demchuk AM, Pallin DJ, Concha M, Goodman S, Leeds J, Souza S, Siegal DM, Zotova E, Meeks B, Ahmad S, Nakamya J, Milling TJ, Jr., ANNEXA-4 Investigators. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med* 2019;**380**:1326–1335.
74. Connolly SJ, Milling TJ, Jr., Eikelboom JW, Gibson CM, Curnutte JT, Gold A, Bronson MD, Lu G, Conley PB, Verhamme P, Schmidt J, Middeldorp S, Cohen AT, Beyer-Westendorf J, Albaladejo P, Lopez-Sendon J, Goodman S, Leeds J, Wiens BL, Siegal DM, Zotova E, Meeks B, Nakamya J, Lim WT, Crowther M, ANNEXA-4 Investigators. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med* 2016;**375**:1131–1141.
75. Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH, French J, Held C, Horrow J, Husted S, Lopez-Sendon J, Lassila R, Mahaffey KW, Storey RF, Harrington RA, Wallentin L. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. *Eur Heart J* 2011;**32**:2933–2944.
76. Ndrepepa G, Schulz S, Neumann FJ, Byrne RA, Hoppmann P, Cassese S, Ott I, Fusaro M, Ibrahim T, Tada T, Richardt G, Laugwitz KL, Schunkert H, Kastrati A. Bleeding after percutaneous coronary intervention in women and men matched for age, body mass index, and type of antithrombotic therapy. *Am Heart J* 2013;**166**:534–540.
77. Verheugt FW, Steinhubl SR, Hamon M, Darius H, Steg PG, Valgimigli M, Marso SP, Rao SV, Gershlick AH, Lincoff AM, Mehran R, Stone GW. Incidence, prognostic impact, and influence of antithrombotic therapy on access and nonaccess site bleeding in percutaneous coronary intervention. *JACC Cardiovasc Interv* 2011;**4**:191–197.
78. Vranckx P, Campo G, Anselmi M, Bolognese L, Colangelo S, Biondi-Zoccai G, Moreno R, Piva T, Favero L, Prati F, Nazzaro M, Diaz Fernandez JF, Ferrari R, Valgimigli M, Multicenter Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab with Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study. Does the site of bleeding matter? A stratified analysis on location of TIMI-graded bleedings and their impact on 12-month outcome in patients with ST-segment elevation myocardial infarction. *EuroIntervention* 2012;**8**:71–78.
79. 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.
80. Lopes RD, Subherwal S, Holmes DN, Thomas L, Wang TY, Rao SV, Magnus Ohman E, Roe MT, Peterson ED, Alexander KP. The association of in-hospital major bleeding with short-, intermediate-, and long-term mortality among older patients with non-ST-segment elevation myocardial infarction. *Eur Heart J* 2012;**33**:2044–2053.
81. 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.
82. Munson JC, Bynum JP, Bell JE, Cantu R, McDonough C, Wang Q, Tosteson TD, Tosteson AN. Patterns of prescription drug use before and after fragility fracture. *JAMA Intern Med* 2016;**176**:1531–1538.
83. Stone GW, White HD, Ohman EM, Bertrand ME, Lincoff AM, McLaurin BT, Cox DA, Pocock SJ, Ware JH, Feit F, Colombo A, Manoukian SV, Lansky AJ, Mehran R, Moses JW, Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial investigators. Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. *Lancet* 2007;**369**:907–919.
84. 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.
85. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;**123**:2736–2747.
86. Ndrepepa G, Schuster T, Hadamitzky M, Byrne RA, Mehilli J, Neumann FJ, Richardt G, Schulz S, Laugwitz KL, Massberg S, Schomig A, Kastrati A. Validation of the Bleeding Academic Research Consortium definition of bleeding in patients with coronary artery disease undergoing percutaneous coronary intervention. *Circulation* 2012;**125**:1424–1431.
87. Baber U, Kovacic J, Kini AS, Sharma SK, Dangas G, Mehran R. How serious a problem is bleeding in patients with acute coronary syndromes? *Curr Cardiol Rep* 2011;**13**:312–319.
88. Ndrepepa G, Guerra E, Schulz S, Fusaro M, Cassese S, Kastrati A. Weight of the bleeding impact on early and late mortality after percutaneous coronary intervention. *J Thromb Thrombolysis* 2015;**39**:35–42.
89. 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.
90. 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.
91. Leibundgut G, Pache J, Schulz S, Berger PB, Ferenc M, Gick M, Mehilli J, Kastrati A, Neumann FJ. Collagen plug vascular closure devices and reduced risk of bleeding with bivalirudin versus heparin plus abciximab in patients undergoing percutaneous coronary intervention for non st-segment elevation myocardial infarction. *J Interv Cardiol* 2013;**26**:623–629.
92. Ndrepepa G, Neumann FJ, Richardt G, Schulz S, Tolg R, Stoyanov KM, Gick M, Ibrahim T, Fiedler KA, Berger PB, Laugwitz KL, Kastrati A. Prognostic value of access and non-access sites bleeding after percutaneous coronary intervention. *Circ Cardiovasc Interv* 2013;**6**:354–361.
93. Marso SP, Amin AP, House JA, Kennedy KF, Spertus JA, Rao SV, Cohen DJ, Messenger JC, Rumsfeld JS, National Cardiovascular Data Registry. Association between use of bleeding avoidance strategies and risk of periprocedural bleeding among patients undergoing percutaneous coronary intervention. *JAMA* 2010;**303**:2156–2164.
94. 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.
95. Schulz-Schupke S, Helde S, Gewalt S, Ibrahim T, Linhardt M, Haas K, Hoppe K, Bottiger C, Groha P, Bradaric C, Schmidt R, Bott-Flugel L, Ott I, Goedel J, Byrne RA, Schneider S, Burgdorf C, Morath T, Kufner S, Joner M, Cassese S, Hoppmann P, Hengstenberg C, Pache J, Fusaro M, Massberg S, Mehilli J, Schunkert H, Laugwitz KL, Kastrati A, Instrumental Sealing of Arterial Puncture Site—CLOSURE Device vs Manual Compression (ISAR-CLOSURE) Trial

Investigators. Comparison of vascular closure devices vs manual compression after femoral artery puncture: the ISAR-CLOSURE randomized clinical trial. *JAMA* 2014;**312**:1981–1987.
96. Shi J, Ji H, Ren F, Wang G, Xu M, Xue Y, Chen M, Qi J, Li L. Protective effects of tranexamic acid on clopidogrel before coronary artery bypass grafting: a multicenter randomized trial. *JAMA Surg* 2013;**148**:538–547.
97. Held C, Asenblad N, Bassand JP, Becker RC, Cannon CP, Claeys MJ, Harrington RA, Horrow J, Husted S, James SK, Mahaffey KW, Nicolau JC, Scirica BM, Storey RF, Vintila M, Ycas J, Wallentin L. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. *J Am Coll Cardiol* 2011;**57**:672–684.
98. Paone G, Likosky DS, Brewer R, Theurer PF, Bell GF, Cogan CM, Prager RL, Membership of the Michigan Society of Thoracic and Cardiovascular Surgeons. Transfusion of 1 and 2 units of red blood cells is associated with increased morbidity and mortality. *Ann Thorac Surg* 2014;**97**:87–93; discussion 93–84.
99. Mehta RH, Sheng S, O'Brien SM, Grover FL, Gammie JS, Ferguson TB, Peterson ED, Society of Thoracic Surgeons National Cardiac Surgery Database Investigators. Reoperation for bleeding in patients undergoing coronary artery bypass surgery: incidence, risk factors, time trends, and outcomes. *Circ Cardiovasc Qual Outcomes* 2009;**2**:583–590.
100. Vivacqua A, Koch CG, Yousuf AM, Nowicki ER, Houghtaling PL, Blackstone EH, Sabik JF, 3rd. Morbidity of bleeding after cardiac surgery: is it blood transfusion, reoperation for bleeding, or both? *Ann Thorac Surg* 2011;**91**:1780–1790.
101. Ferraris VA, Saha SP, Oestreich JH, Song HK, Rosengart T, Reece TB, Mazer CD, Bridges CR, Despotis GJ, Jointer K, Clough ER, Society of Thoracic Surgeons. 2012 update to the Society of Thoracic Surgeons guideline on use of antiplatelet drugs in patients having cardiac and noncardiac operations. *Ann Thorac Surg* 2012;**94**:1761–1781.
102. 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.
103. 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, Schauerte 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.
104. 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.
105. Hardy JF, Belisle S, Van der Linden P. Efficacy and safety of activated recombinant factor VII in cardiac surgical patients. *Curr Opin Anaesthesiol* 2009;**22**:95–99.
106. 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, Vaijyanath P, Reddy S, Tao L, Olavegogeascoechea 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.
107. Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, Moliterno DJ, Lindblad L, Pieper K, Topol EJ, Stamler JS, Califf RM. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA* 2004;**292**:1555–1562.
108. Sherwood MW, Wang Y, Curtis JP, Peterson ED, Rao SV. Patterns and outcomes of red blood cell transfusion in patients undergoing percutaneous coronary intervention. *JAMA* 2014;**311**:836–843.
109. Nikolsky E, Mehran R, Sadeghi HM, Grines CL, Cox DA, Garcia E, Tcheng JE, Griffin JJ, Guagliumi G, Stuckey T, Turco M, Fahy M, Lansky AJ, Stone GW. Prognostic impact of blood transfusion after primary angioplasty for acute myocardial infarction: analysis from the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial. *JACC Cardiovasc Interv* 2009;**2**:624–632.
110. Silvain J, Abtan J, Kerneis M, Martin R, Finzi J, Vignalou JB, Barthelemy O, O'Connor SA, Luyt CE, Brechot N, Mercadier A, Brugier D, Galier S, Collet JP, Chastre J, Montalescot G. Impact of red blood cell transfusion on platelet aggregation and inflammatory response in anemic coronary and noncoronary patients: the TRANSFUSION-2 study (impact of transfusion of red blood cell on platelet activation and aggregation studied with flow cytometry use and light transmission aggregometry). *J Am Coll Cardiol* 2014;**63**:1289–1296.
111. Kansagara D, Dyer E, Englander H, Fu R, Freeman M, Kagen D. Treatment of anemia in patients with heart disease: a systematic review. *Ann Intern Med* 2013;**159**:746–757.
112. Chatterjee S, Wetterslev J, Sharma A, Lichstein E, Mukherjee D. Association of blood transfusion with increased mortality in myocardial infarction: a meta-analysis and diversity-adjusted study sequential analysis. *JAMA Intern Med* 2013;**173**:132–139.
113. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev* 2012:CD002042.
114. Cooper HA, Rao SV, Greenberg MD, Rumsey MP, McKenzie M, Alcorn KW, Panza JA. Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT Randomized Pilot Study). *Am J Cardiol* 2011;**108**:1108–1111.
115. Alexander KP, Chen AY, Wang TY, Rao SV, Newby LK, LaPointe NM, Ohman EM, Roe MT, Boden WE, Harrington RA, Peterson ED, CRUSADE Investigators. Transfusion practice and outcomes in non-ST-segment elevation acute coronary syndromes. *Am Heart J* 2008;**155**:1047–1053.
116. Holst LB, Petersen MW, Haase N, Perner A, Wetterslev J. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. *BMJ* 2015;**350**:h1354.
117. Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, Reeves BC, TITRe2 Investigators. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med* 2015;**372**:997–1008.
118. Mehta SR, Cannon CP, Fox KA, Wallentin L, Boden WE, Spacek R, Widimsky P, McCullough PA, Hunt D, Braunwald E, Yusuf S. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA* 2005;**293**:2908–2917.
119. O'Donoghue M, Boden WE, Braunwald E, Cannon CP, Clayton TC, de Winter RJ, Fox KA, Lagerqvist B, McCullough PA, Murphy SA, Spacek R, Swahn E, Wallentin L, Windhausen F, Sabatine MS. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 2008;**300**:71–80.
120. Fox KA, Clayton TC, Damman P, Pocock SJ, de Winter RJ, Tijssen JG, Lagerqvist B, Wallentin L, Collaboration FIR. 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.
121. Fanning JP, Nyong J, Scott IA, Aroney CN, Walters DL. Routine invasive strategies versus selective invasive strategies for unstable angina and non-ST elevation myocardial infarction in the stent era. *Cochrane Database Syst Rev* 2016:CD004815.
122. Elgendy IY, Mahmoud AN, Wen X, Bavry AA. Meta-analysis of randomized trials of long-term all-cause mortality in patients with non-ST-elevation acute coronary syndrome managed with routine invasive versus selective invasive strategies. *Am J Cardiol* 2017;**119**:560–564.
123. Shen W, Zhang R, Shen Y, Zhang J, Zhang D, Zhang X, Zheng A. Optimal timing of coronary stenting in unstable angina patients. *Chin Med J (Engl)* 2001;**114**:59–61.
124. van 't Hof AW, de Vries ST, Dambrink JH, Miedema K, Suryapranata H, Hoorntje JC, Gosselink AT, Zijlstra F, de Boer MJ. A comparison of two invasive strategies in patients with non-ST elevation acute coronary syndromes: results of the Early or Late Intervention in unStable Angina (ELISA) pilot study. 2b/3a upstream therapy and acute coronary syndromes. *Eur Heart J* 2003;**24**:1401–1405.
125. Neumann FJ, Kastrati A, Pogatsa-Murray G, Mehilli J, Bollwein H, Bestehorn HP, Schmitt C, Seyfarth M, Dirschinger J, Schomig A. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. *JAMA* 2003;**290**:1593–1599.
126. Riezebos RK, Ronner E, Ter Bals E, Slagboom T, Smits PC, ten Berg JM, Kiemeneij F, Amoroso G, Patterson MS, Suttorp MJ, Tijssen JG, Laarman GJ, OPTIMA trial. Immediate versus deferred coronary angioplasty in non-ST-segment elevation acute coronary syndromes. *Heart* 2009;**95**:807–812.
127. Montalescot G, Cayla G, Collet JP, Elhadad S, Beygui F, Le Breton H, Choussat R, Leclercq F, Silvain J, Duclos F, Aout M, Dubois-Rande JL, Barthelemy O, Ducrocq G, Bellemain-Appaix A, Payot L, Steg PG, Henry P, Spaulding C, Vicaut E, ABOARD Investigators. Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. *JAMA* 2009;**302**:947–954.
128. 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, Investigators TIMACS. Early versus

delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 2009;**360**:2165–2175.
129. Sciahbasi A, Madonna M, De Vita M, Agati L, Scioli R, Summaria F, Romagnoli E, Patrizi R, Lanzillo C, Pendenza G, Canali E, Penco M, Lioy E. Comparison of immediate vs early invasive strategy in patients with first acute non-ST-elevation myocardial infarction. *Clin Cardiol* 2010;**33**:650–655.
130. 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.
131. Badings EA, The SH, Dambrink JH, van Wijngaarden J, Tjeerdsma G, Rasoul S, Timmer JR, van der Wielen ML, Lok DJ, van 't Hof AW. Early or late intervention in high-risk non-ST-elevation acute coronary syndromes: results of the ELISA-3 trial. *EuroIntervention* 2013;**9**:54–61.
132. Tekin K, Cagliyan CE, Tanboga IH, Balli M, Uysal OK, Ozkan B, Arik OZ, Cayli M. Influence of the timing of percutaneous coronary intervention on clinical outcomes in non-ST-elevation myocardial infarction. *Korean Circ J* 2013;**43**:725–730.
133. Reuter PG, Rouchy C, Cattan S, Benamer H, Jullien T, Beruben A, Montely JM, Assez N, Raphael V, Hennequin B, Boccara A, Javaud N, Soulat L, Adnet F, Lapostolle F. Early invasive strategy in high-risk acute coronary syndrome without ST-segment elevation. The Sisca randomized trial. *Int J Cardiol* 2015;**182**:414–418.
134. Milosevic A, Vasiljevic-Pokrajcic Z, Milasinovic D, Marinkovic J, Vukcevic V, Stefanovic B, Asanin M, Dikic M, Stankovic S, Stankovic G. Immediate versus delayed invasive intervention for non-STEMI patients: the RIDDLE-NSTEMI study. *JACC Cardiovasc Interv* 2016;**9**:541–549.
135. Kofoed KF, Kelbaek H, Hansen PR, Torp-Pedersen C, Hofsten D, Klovgaard L, Holmvang L, Helqvist S, Jorgensen E, Galatius S, Pedersen F, Bang L, Saunamaki K, Clemmensen P, Linde JJ, Heitmann M, Wendelboe Nielsen O, Raymond IE, Kristiansen OP, Svendsen IH, Bech J, Dominguez Vall-Lamora MH, Kragelund C, Hansen TF, Dahlgaard Hove J, Jorgensen T, Fornitz GG, Steffensen R, Jurlander B, Abdulla J, Lyngbaek S, Elming H, Therkelsen SK, Abildgaard U, Jensen JS, Gislason G, Kober LV, Engstrom T. Early versus standard care invasive examination and treatment of patients with non-ST-segment elevation acute coronary syndrome. *Circulation* 2018;**138**:2741–2750.
136. Lemesle G, Laine M, Pankert M, Boueri Z, Motreff P, Paganelli F, Baumstarck K, Roch A, Kerbaul F, Puymirat E, Bonello L. Optimal timing of intervention in NSTE-ACS without pre-treatment: the EARLY randomized trial. *JACC Cardiovasc Interv* 2020;**13**:907–917.
137. 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.
138. 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.
139. Milasinovic D, Milosevic A, Marinkovic J, Vukcevic V, Ristic A, Asanin M, Stankovic G. Timing of invasive strategy in NSTE-ACS patients and effect on clinical outcomes: a systematic review and meta-analysis of randomized controlled trials. *Atherosclerosis* 2015;**241**:48–54.
140. Bonello L, Laine M, Puymirat E, Lemesle G, Thuny F, Paganelli F, Michelet P, Roch A, Kerbaul F, Boyer L. Timing of coronary invasive strategy in non-ST-segment elevation acute coronary syndromes and clinical outcomes: an updated meta-analysis. *JACC Cardiovasc Interv* 2016;**9**:2267–2276.
141. 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.
142. Li Y, Zhang Z, Xiong X, Cho WC, Hu D, Gao Y, Shang H, Xing Y. Immediate/early vs. delayed invasive strategy for patients with non-st-segment elevation acute coronary syndromes: a systematic review and meta-analysis. *Front Physiol* 2017;**8**:952.
143. Zhang MB, Guo C, Li M, Lv YH, Fan YD, Wang ZL. Comparison of early and delayed invasive strategies in short-medium term among patients with non-ST segment elevation acute coronary syndrome: a systematic review and meta-analysis. *PLoS One* 2019;**14**:e0220847.
144. 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.
145. Kerensky RA, Wade M, Deedwania P, Boden WE, Pepine CJ, Veterans Affairs Non-Q-Wave Infarction Stategies 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.
146. Ndrepepa G, Mehilli J, Schulz S, Iijima R, Keta D, Byrne RA, Pache J, Seyfarth M, Schomig A, Kastrati A. Patterns of presentation and outcomes of patients with acute coronary syndromes. *Cardiology* 2009;**113**:198–206.
147. Ambrose JA, Winters SL, Stern A, Eng A, Teichholz LE, Gorlin R, Fuster V. Angiographic morphology and the pathogenesis of unstable angina pectoris. *J Am Coll Cardiol* 1985;**5**:609–616.
148. 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.
149. Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2012;**32**:2045–2051.
150. Pessanha BS, Potter K, Kolodgie FD, Farb A, Kutys R, Mont EK, Burke AP, O'Leary T J, Virmani R. Characterization of intimal changes in coronary artery specimens with MR microscopy. *Radiology* 2006;**241**:107–115.
151. Vergallo R, Ren X, Yonetsu T, Kato K, Uemura S, Yu B, Jia H, Abtahian F, Aguirre AD, Tian J, Hu S, Soeda T, Lee H, McNulty I, Park SJ, Jang Y, Prasad A, Lee S, Zhang S, Porto I, Biasucci LM, Crea F, Jang IK. Pancoronary plaque vulnerability in patients with acute coronary syndrome and ruptured culprit plaque: a 3-vessel optical coherence tomography study. *Am Heart J* 2014;**167**:59–67.
152. 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.
153. Shishehbor MH, Lauer MS, Singh IM, Chew DP, Karha J, Brener SJ, Moliterno DJ, Ellis SG, Topol EJ, Bhatt DL. In unstable angina or non-ST-segment acute coronary syndrome, should patients with multivessel coronary artery disease undergo multivessel or culprit-only stenting? *J Am Coll Cardiol* 2007;**49**:849–854.
154. Layland J, Oldroyd KG, Curzen N, Sood A, Balachandran K, Das R, Junejo S, Ahmed N, Lee MM, Shaukat 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.
155. Layland J, Rauhalammi S, Watkins S, Ahmed N, McClure J, Lee MM, Carrick D, O'Donnell A, Sood A, Petrie MC, May VT, Eteiba H, Lindsay M, McEntegart M, Oldroyd KG, Radjenovic A, Berry C. Assessment of fractional flow reserve in patients with recent non-ST-segment-elevation myocardial infarction: comparative study with 3-*t stress perfusion cardiac magnetic resonance imaging*. *Circ Cardiovasc Interv* 2015;**8**:e002207.
156. Ntalianis A, Sels JW, Davidavicius G, Tanaka N, Muller O, Trana C, Barbato E, Hamilos M, Mangiacapra F, Heyndrickx GR, Wijns W, Pijls NH, De Bruyne B. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv* 2010;**3**:1274–1281.
157. Sels JW, Tonino PA, Siebert U, Fearon WF, Van't Veer M, De Bruyne B, Pijls NH. Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) study. *JACC Cardiovasc Interv* 2011;**4**:1183–1189.
158. 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.
159. Masrani Mehta S, Depta JP, Novak E, Patel JS, Patel Y, Raymer D, Facey G, Zajarias A, Lasala JM, Singh J, Bach RG, Kurz HI. Association of lower fractional flow reserve values with higher risk of adverse cardiac events for lesions deferred revascularization among patients with acute coronary syndrome. *J Am Heart Assoc* 2015;**4**:e002172.
160. Lee JM, Choi KH, Koo BK, Shin ES, Nam CW, Doh JH, Hwang D, Park J, Zhang J, Lim HS, Yoon MH, Tahk SJ. Prognosis of deferred non-culprit lesions according to fractional flow reserve in patients with acute coronary syndrome. *EuroIntervention* 2017;**13**:e1112–e1119.
161. 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, PRIME-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.
162. Escaned J, Ryan N, Mejia-Renteria H, Cook CM, Dehbi HM, Alegria-Barrero E, Alghamdi A, Al-Lamee R, Altman J, Ambrosia A, Baptista SB, Bertilsson M, Bhindi R, Birgander M, Bojara W, Brugaletta S, Buller C, Calais F, Silva PC, Carlsson J, Christiansen EH, Danielewicz M, Di Mario C, Doh JH, Erglis A, Erlinge D, Gerber RT, Going O, Gudmundsdottir I, Harle T, Hauer D, Hellig F, Indolfi C, Jakobsen L, Janssens L, Jensen J, Jeremias A, Karegren A, Karlsson AC, Kharbanda RK, Khashaba A, Kikuta Y, Krackhardt F, Koo BK, Koul S, Laine M, Lehman SJ, Lindroos P, Malik IS, Maeng M, Matsuo H, Meuwissen M, Nam CW, Niccoli G, Nijjer SS, Olsson H, Olsson SE, Omerovic E, Panayi G, Petraco R, Piek JJ, Ribichini F, Samady H, Samuels B, Sandhall L, Sapontis J, Sen S, Seto AH, Sezer M, Sharp ASP, Shin ES, Singh J, Takashima H, Talwar S, Tanaka N, Tang K, Van Belle E, van Royen N, Varenhorst C, Vinhas H, Vrints CJ, Walters D, Yokoi H, Frobert O, Patel MR, Serruys P, Davies JE, Gotberg M. Safety of the deferral of coronary revascularization on the basis of instantaneous wave-free ratio and fractional flow reserve measurements in stable coronary artery disease and acute coronary syndromes. *JACC Cardiovasc Interv* 2018;**11**:1437–1449.
163. 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, Investigators iFR-SWEDEHEART. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med* 2017;**376**:1813–1823.
164. 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, Kharbanda 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.
165. Van Belle E, Gil R, Klauss V, Balghith M, Meuwissen M, Clerc J, Witzenbichler B, Cercek M, Vlachojannis M, Lang I, Commeau P, Vincent F, Testa L, Wasek W, Debry N, Kische S, Gabrielli G, Sardella G. Impact of routine invasive physiology at time of angiography in patients with multivessel coronary artery disease on reclassification of revascularization strategy: results from the DEFINE REAL study. *JACC Cardiovasc Interv* 2018;**11**:354–365.
166. Kobayashi Y, Lonborg J, Jong A, Nishi T, De Bruyne B, Hofsten DE, Kelbaek H, Layland J, Nam CW, Pijls NHJ, Tonino PAL, Warnoe J, Oldroyd KG, Berry C, Engstrom T, Fearon WF, DANAMI-3-PRIMULTI, FAME, and FAMOUS-NSTEMI Study Investigators. Prognostic value of the residual SYNTAX score after functionally complete revascularization in ACS. *J Am Coll Cardiol* 2018;**72**:1321–1329.
167. Ariotti S, Adamo M, Costa F, Patialiakas A, Briguori C, Thury A, Colangelo S, Campo G, Tebaldi M, Ungi I, Tondi S, Roffi M, Menozzi A, de Cesare N, Garbo R, Meliga E, Testa L, Gabriel HM, Ferlini M, Vranckx P, Valgimigli M, ZEUS Investigators. Is bare-metal stent implantation still justifiable in high bleeding risk patients undergoing percutaneous coronary intervention?: a pre-specified analysis from the ZEUS trial. *JACC Cardiovasc Interv* 2016;**9**:426–436.
168. Gore JM, Spencer FA, Gurfinkel EP, Lopez-Sendon J, Steg PG, Granger CB, FitzGerald G, Agnelli G, Investigators GRACE. Thrombocytopenia in patients with an acute coronary syndrome (from the Global Registry of Acute Coronary Events [GRACE]). *Am J Cardiol* 2009;**103**:175–180.
169. Merlini PA, Rossi M, Menozzi A, Buratti S, Brennan DM, Moliterno DJ, Topol EJ, Ardissino D. Thrombocytopenia caused by abciximab or tirofiban and its association with clinical outcome in patients undergoing coronary stenting. *Circulation* 2004;**109**:2203–2206.
170. Vora AN, Chenier M, Schulte PJ, Goodman S, Peterson ED, Pieper K, Jolicoeur ME, Mahaffey KW, White H, Wang TY. Long-term outcomes associated with hospital acquired thrombocytopenia among patients with non-ST-segment elevation acute coronary syndrome. *Am Heart J* 2014;**168**:189–196 e181.
171. Dasgupta H, Blankenship JC, Wood GC, Frey CM, Demko SL, Menapace FJ. Thrombocytopenia complicating treatment with intravenous glycoprotein IIb/IIIa receptor inhibitors: a pooled analysis. *Am Heart J* 2000;**140**:206–211.
172. Valgimigli M, Biondi-Zoccai G, Tebaldi M, van't Hof AW, Campo G, Hamm C, ten Berg J, Bolognese L, Saia F, Danzi GB, Briguori C, Okmen E, King SB, Moliterno DJ, Topol EJ. Tirofiban as adjunctive therapy for acute coronary syndromes and percutaneous coronary intervention: a meta-analysis of randomized trials. *Eur Heart J* 2010;**31**:35–49.
173. Arnold DM, Nazi I, Warkentin TE, Smith JW, Toltl LJ, George JN, Kelton JG. Approach to the diagnosis and management of drug-induced immune thrombocytopenia. *Transfus Med Rev* 2013;**27**:137–145.
174. Greinacher A, Selleng K. Thrombocytopenia in the intensive care unit patient. *Hematology Am Soc Hematol Educ Program* 2010;**2010**:135–143.
175. Tempelhof MW, Benzuly KH, Fintel D, Krichavsky MZ. Eptifibatide-induced thrombocytopenia: with thrombosis and disseminated intravascular coagulation immediately after left main coronary artery percutaneous coronary angioplasty. *Tex Heart Inst J* 2012;**39**:86–91.
176. Warkentin TE, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent M, Kelton JG. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995;**332**:1330–1335.
177. Nazy I, Clare R, Staibano P, Warkentin TE, Larche M, Moore JC, Smith JW, Whitlock RP, Kelton JG, Arnold DM. Cellular immune responses to platelet factor 4 and heparin complexes in patients with heparin-induced thrombocytopenia. *J Thromb Haemost* 2018;**16**:1402–1412.
178. Kelton JG, Arnold DM, Bates SM. Nonheparin anticoagulants for heparin-induced thrombocytopenia. *N Engl J Med* 2013;**368**:737–744.
179. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med* 2001;**344**:1286–1292.
180. Schindewolf M, Steindl J, Beyer-Westendorf J, Schellong S, Dohmen PM, Brachmann J, Madlener K, Potzsch B, Klamroth R, Hankowitz J, Banik N, Eberle S, Muller MM, Kropff S, Lindhoff-Last E. Use of fondaparinux off-label or approved anticoagulants for management of heparin-induced thrombocytopenia. *J Am Coll Cardiol* 2017;**70**:2636–2648.
181. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA, Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;**56**:M146–M156.
182. Cigolle CT, Ofstedal MB, Tian Z, Blaum CS. Comparing models of frailty: the Health and Retirement Study. *J Am Geriatr Soc* 2009;**57**:830–839.
183. Kiely DK, Cupples LA, Lipsitz LA. Validation and comparison of two frailty indexes: The MOBILIZE Boston Study. *J Am Geriatr Soc* 2009;**57**:1532–1539.
184. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. *J Gerontol A Biol Sci Med Sci* 2007;**62**:738–743.
185. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal* 2001;**1**:323–336.
186. Rockwood K, Mitnitski A, Song X, Steen B, Skoog I. Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. *J Am Geriatr Soc* 2006;**54**:975–979.
187. Carlson JE, Zocchi KA, Bettencourt DM, Gambrel ML, Freeman JL, Zhang D, Goodwin JS. Measuring frailty in the hospitalized elderly: concept of functional homeostasis. *Am J Phys Med Rehabil* 1998;**77**:252–257.
188. Carriere I, Colvez A, Favier F, Jeandel C, Blain H, EPIDOS study group. Hierarchical components of physical frailty predicted incidence of dependency in a cohort of elderly women. *J Clin Epidemiol* 2005;**58**:1180–1187.
189. Gealey SG. Quantification of the term frail as applied to the elderly client. *J Am Acad Nurse Pract* 1997;**9**:505–510.
190. Schuurmans H, Steverink N, Lindenberg S, Frieswijk N, Slaets JP. Old or frail: what tells us more? *J Gerontol A Biol Sci Med Sci* 2004;**59**:M962–M965.
191. Gloth FM, 3rd, Scheve AA, Shah S, Ashton R, McKinney R. The Frail Elderly Functional Assessment questionnaire: its responsiveness and validity in alternative settings. *Arch Phys Med Rehabil* 1999;**80**:1572–1576.
192. Gloth FM, 3rd, Walston J, Meyer J, Pearson J. Reliability and validity of the Frail Elderly Functional Assessment questionnaire. *Am J Phys Med Rehabil* 1995;**74**:45–53.
193. Guilley E, Ghisletta P, Armi F, Berchtold A, d'Epinay CL, Michel J-P, de Ribaupierre A. Dynamics of frailty and ADL dependence in a five-year longitudinal study of octogenarians. *Res Aging* 2008;**30**:299–317.
194. Rothman MD, Leo-Summers L, Gill TM. Prognostic significance of potential frailty criteria. *J Am Geriatr Soc* 2008;**56**:2211–2216.
195. Studenski S, Hayes RP, Leibowitz RQ, Bode R, Lavery L, Walston J, Duncan P, Perera S. Clinical Global Impression of Change in Physical Frailty: development of a measure based on clinical judgment. *J Am Geriatr Soc* 2004;**52**:1560–1566.
196. McGee HM, O'Hanlon A, Barker M, Hickey A, Montgomery A, Conroy R, O'Neill D. Vulnerable older people in the community: relationship between the Vulnerable Elders Survey and health service use. *J Am Geriatr Soc* 2008;**56**:8–15.
197. Saliba D, Elliott M, Rubenstein LZ, Solomon DH, Young RT, Kamberg CJ, Roth C, MacLean CH, Shekelle PG, Sloss EM, Wenger NS. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. *J Am Geriatr Soc* 2001;**49**:1691–1699.
198. Chin A Paw MJ, Dekker JM, Feskens EJ, Schouten EG, Kromhout D. How to select a frail elderly population? A comparison of three working definitions. *J Clin Epidemiol* 1999;**52**:1015–1021.
199. Puts MT, Lips P, Deeg DJ. Sex differences in the risk of frailty for mortality independent of disability and chronic diseases. *J Am Geriatr Soc* 2005;**53**:40–47.

200. Ravaglia G, Forti P, Lucicesare A, Pisacane N, Rietti E, Patterson C. Development of an easy prognostic score for frailty outcomes in the aged. *Age Ageing* 2008;**37**:161–166.
201. Winograd CH, Gerety MB, Chung M, Goldstein MK, Dominguez F, Jr., Vallone R. Screening for frailty: criteria and predictors of outcomes. *J Am Geriatr Soc* 1991;**39**:778–784.
202. Stevens PJ, Syddall HE, Patel HP, Martin HJ, Cooper C, Aihie Sayer A. Is grip strength a good marker of physical performance among community-dwelling older people? *J Nutr Health Aging* 2012;**16**:769–774.
203. Matthews M, Lucas A, Boland R, Hirth V, Odenheimer G, Wieland D, Williams H, Eleazer GP. Use of a questionnaire to screen for frailty in the elderly: an exploratory study. *Aging Clin Exp Res* 2004;**16**:34–40.
204. Brody KK, Johnson RE, Douglas Ried L. Evaluation of a self-report screening instrument to predict frailty outcomes in aging populations. *Gerontologist* 1997;**37**:182–191.
205. Scarcella P, Liotta G, Marazzi MC, Carbini R, Palombi L. Analysis of survival in a sample of elderly patients from Ragusa, Italy on the basis of a primary care level multidimensional evaluation. *Arch Gerontol Geriatr* 2005;**40**:147–156.
206. Jones D, Song X, Mitnitski A, Rockwood K. Evaluation of a frailty index based on a comprehensive geriatric assessment in a population based study of elderly Canadians. *Aging Clin Exp Res* 2005;**17**:465–471.
207. Jones DM, Song X, Rockwood K. Operationalizing a frailty index from a standardized comprehensive geriatric assessment. *J Am Geriatr Soc* 2004;**52**:1929–1933.
208. de Vries NM, Staal JB, van Ravensberg CD, Hobbelen JS, Olde Rikkert MG, Nijhuis-van der Sanden MW. Outcome instruments to measure frailty: a systematic review. *Ageing Res Rev* 2011;**10**:104–114.
209. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J* 2016;**37**:3232–3245.
210. 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, Investigators PLATO. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–1057.
211. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ, ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.
212. Grobbee DE, Pellicia A. Secondary prevention of cardiovascular disease: unmet medical need, implementation and innovation. *Eur J Prev Cardiol* 2017;**24**:5–7.
213. Kotseva K, Wood D, De Bacquer D, De Backer G, Ryden L, Jennings C, Gyberg V, Amouyel P, Bruthans J, Castro Conde A, Cifkova R, Deckers JW, De Sutter J, Dilic M, Dolzhenko M, Erglis A, Fras Z, Gaita D, Gotcheva N, Goudevenos J, Heuschmann P, Laucevicius A, Lehto S, Lovic D, Milicic D, Moore D, Nicolaides E, Oganov R, Pajak A, Pogosova N, Reiner Z, Stagmo M, Stork S, Tokgozoglu L, Vulic D, EUROASPIRE Investigators. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol* 2016;**23**:636–648.
214. Cortes-Beringola A, Fitzsimons D, Pelliccia A, Moreno G, Martin-Asenjo R, Bueno H. Planning secondary prevention: room for improvement. *Eur J Prev Cardiol* 2017;**24**:22–28.
215. Kotseva K, De Backer G, De Bacquer D, Ryden L, Hoes A, Grobbee D, Maggioni A, Marques-Vidal P, Jennings C, Abreu A, Aguiar C, Badariene J, Bruthans J, Castro Conde A, Cifkova R, Crowley J, Davletov K, Deckers J, De Smedt D, De Sutter J, Dilic M, Dolzhenko M, Dzerve V, Erglis A, Fras Z, Gaita D, Gotcheva N, Heuschmann P, Hasan-Ali H, Jankowski P, Lalic N, Lehto S, Lovic D, Mancas S, Mellbin L, Milicic D, Mirrakhimov E, Oganov R, Pogosova N, Reiner Z, Stoerk S, Tokgozoglu L, Tsioufis C, Vulic D, Wood D, EUROASPIRE Investigators. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. *Eur J Prev Cardiol* 2019;**26**:824–835.
216. Maron DJ, Boden WE, O'Rourke RA, Hartigan PM, Calfas KJ, Mancini GB, Spertus JA, Dada M, Kostuk WJ, Knudtson M, Harris CL, Sedlis SP, Zoble RG, Title LM, Gosselin G, Nawaz S, Gau GT, Blaustein AS, Bates ER, Shaw LJ, Berman DS, Chaitman BR, Weintraub WS, Teo KK, COURAGE Trial Research Group. Intensive multifactorial intervention for stable coronary artery disease: optimal medical therapy in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial. *J Am Coll Cardiol* 2010;**55**:1348–1358.
217. Rotenstein LS, Huckman RS, Wagle NW. Making patients and doctors happier - the potential of patient-reported outcomes. *N Engl J Med* 2017;**377**:1309–1312.
218. 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, ESC Scientific Document 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.
219. Chow CK, Jolly S, Rao-Melacini P, Fox KA, Anand SS, Yusuf S. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. *Circulation* 2010;**121**:750–758.
220. Giannuzzi P, Temporelli PL, Marchioli R, Maggioni AP, Balestroni G, Ceci V, Chieffo C, Gattone M, Griffo R, Schweiger C, Tavazzi L, Urbinati S, Valagussa F, Vanuzzo D, GOSPEL Investigators. Global secondary prevention strategies to limit event recurrence after myocardial infarction: results of the GOSPEL study, a multicenter, randomized controlled trial from the Italian Cardiac Rehabilitation Network. *Arch Intern Med* 2008;**168**:2194–2204.
221. Keteyian SJ, Brawner CA, Savage PD, Ehrman JK, Schairer J, Divine G, Aldred H, Ophaug K, Ades PA. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. *Am Heart J* 2008;**156**:292–300.
222. Perevoshchikov AG, Katenkamp D, Raikhlin NT. [Focal fibrous mesothelioma of the pleura (a morphological study of 7 cases]. *Arkh Patol* 1989;**51**:9–15.
223. Piepoli MF, Villani GQ. Lifestyle modification in secondary prevention. *Eur J Prev Cardiol* 2017;**24**:101–107.
224. Wen CP, Wai JP, Tsai MK, Yang YC, Cheng TY, Lee MC, Chan HT, Tsao CK, Tsai SP, Wu X. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet* 2011;**378**:1244–1253.
225. Wood DA, Kotseva K, Connolly S, Jennings C, Mead A, Jones J, Holden A, De Bacquer D, Collier T, De Backer G, Faergeman O, EUROACTION Study Group. Nurse-coordinated multidisciplinary, family-based cardiovascular disease prevention programme (EUROACTION) for patients with coronary heart disease and asymptomatic individuals at high risk of cardiovascular disease: a paired, cluster-randomised controlled trial. *Lancet* 2008;**371**:1999–2012.
226. Hackshaw A, Morris JK, Boniface S, Tang JL, Milenkovic D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. *BMJ* 2018;**360**:j5855.
227. Prochaska JJ, Benowitz NL. The past, present, and future of nicotine addiction therapy. *Annu Rev Med* 2016;**67**:467–486.
228. Skotsimara G, Antonopoulos AS, Oikonomou E, Siasos G, Ioakeimidis N, Tsalamandris S, Charalambous G, Galiatsatos N, Vlachopoulos C, Tousoulis D. Cardiovascular effects of electronic cigarettes: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2019;**26**:1219–1228.
229. 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. [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]. *G Ital Cardiol (Rome)* 2017;**18**:547–612.
230. Mills EJ, Thorlund K, Eapen S, Wu P, Prochaska JJ. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. *Circulation* 2014;**129**:28–41.
231. Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Uddin SMI, Benjamin EJ, Hall ME, DeFilippis AP, Stokes A, Bhatnagar A, Nasir K, Blaha MJ. Association between e-cigarette use and cardiovascular disease among never and current combustible-cigarette smokers. *Am J Med* 2019;**132**:949–954 e942.
232. Sahu KK, Lal A, Kumar Mishra A, Sahu SA. E-cigarettes and methemoglobinemia: a wolf in sheep's clothing. *Am J Med* 2019;**132**:e759.
233. Qasim H, Karim ZA, Rivera JO, Khasawneh FT, Alshbool FZ. Impact of electronic cigarettes on the cardiovascular system. *J Am Heart Assoc* 2017;**6**:e006353.
234. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L, Ross L, Goniewicz M, Wu Q, McRobbie HJ. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med* 2019;**380**:629–637.
235. Freeman AM, Morris PB, Barnard N, Esselstyn CB, Ros E, Agatston A, Devries S, O'Keefe J, Miller M, Ornish D, Williams K, Kris-Etherton P. Trending cardiovascular nutrition controversies. *J Am Coll Cardiol* 2017;**69**:1172–1187.
236. 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.
237. Miller V, Mente A, Dehghan M, Rangarajan S, Zhang X, Swaminathan S, Dagenais G, Gupta R, Mohan V, Lear S, Bangdiwala SI, Schutte AE, Wentzel-Viljoen E, Avezum A, Altuntas Y, Yusoff K, Ismail N, Peer N, Chifamba J, Diaz R, Rahman O, Mohammadifard N, Lana F, Zatonska K, Wielgosz A, Yusufali A, Iqbal R, Lopez-Jaramillo P, Khatib R, Rosengren A, Kutty VR, Li W, Liu J, Liu X, Yin L, Teo K, Anand S, Yusuf S, Prospective Urban Rural Epidemiology study investigators. Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): a prospective cohort study. *Lancet* 2017;**390**:2037–2049.
238. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr* 2010;**92**:1189–1196.
239. Wang X, Ouyang Y, Liu J, Zhu M, Zhao G, Bao W, Hu FB. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies. *BMJ* 2014;**349**:g4490.
240. Alvarez-Alvarez I, de Rojas JP, Fernandez-Montero A, Zazpe I, Ruiz-Canela M, Hidalgo-Santamaria M, Bes-Rastrollo M, Martinez-Gonzalez MA. Strong inverse associations of Mediterranean diet, physical activity and their combination with cardiovascular disease: The Seguimiento Universidad de Navarra (SUN) cohort. *Eur J Prev Cardiol* 2018;**25**:1186–1197.
241. Wood AM, Kaptoge S, Butterworth AS, Willeit P, Warnakula S, Bolton T, Paige E, Paul DS, Sweeting M, Burgess S, Bell S, Astle W, Stevens D, Koulman A, Selmer RM, Verschuren WMM, Sato S, Njolstad I, Woodward M, Salomaa V, Nordestgaard BG, Yeap BB, Fletcher A, Melander O, Kuller LH, Balkau B, Marmot M, Koenig W, Casiglia E, Cooper C, Arndt V, Franco OH, Wennberg P, Gallacher J, de la Camara AG, Volzke H, Dahm CC, Dale CE, Bergmann MM, Crespo CJ, van der Schouw YT, Kaaks R, Simons LA, Lagiou P, Schoufour JD, Boer JMA, Key TJ, Rodriguez B, Moreno-Iribas C, Davidson KW, Taylor JO, Sacerdote C, Wallace RB, Quiros JR, Tumino R, Blazer DG, 2nd, Linneberg A, Daimon M, Panico S, Howard B, Skeie G, Strandberg T, Weiderpass E, Nietert PJ, Psaty BM, Kromhout D, Salamanca-Fernandez E, Kiechl S, Krumholz HM, Grioni S, Palli D, Huerta JM, Price J, Sundstrom J, Arriola L, Arima H, Travis RC, Panagiotakos DB, Karakatsani A, Trichopoulou A, Kuhn T, Grobbee DE, Barrett-Connor E, van Schoor N, Boeing H, Overvad K, Kauhanen J, Wareham N, Langenberg C, Forouhi N, Wennberg M, Despres JP, Cushman M, Cooper JA, Rodriguez CJ, Sakurai M, Shaw JE, Knuiman M, Voortman T, Meisinger C, Tjonneland A, Brenner H, Palmieri L, Dallongeville J, Brunner EJ, Assmann G, Trevisan M, Gillum RF, Ford I, Sattar N, Lazo M, Thompson SG, Ferrari P, Leon DA, Smith GD, Peto R, Jackson R, Banks E, Di Angelantonio E, Danesh J, Emerging Risk Factors Collaboration/EPIC-CVD/UK Biobank Alcohol Study Group. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet* 2018;**391**:1513–1523.
242. GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2018;**392**:1015–1035.
243. Piano MR. Alcohol's effects on the cardiovascular system. *Alcohol Res* 2017;**38**:219–241.
244. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L, INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**:937–952.
245. Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, Sweis RN, Lloyd-Jones DM. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. *JAMA Cardiol* 2018;**3**:280–287.
246. Pack QR, Rodriguez-Escudero JP, Thomas RJ, Ades PA, West CP, Somers VK, Lopez-Jimenez F. The prognostic importance of weight loss in coronary artery disease: a systematic review and meta-analysis. *Mayo Clin Proc* 2014;**89**:1368–1377.
247. Gardner CD, Trepanowski JF, Del Gobbo LC, Hauser ME, Rigdon J, Ioannidis JPA, Desai M, King AC. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial. *JAMA* 2018;**319**:667–679.
248. Bruning RS, Sturek M. Benefits of exercise training on coronary blood flow in coronary artery disease patients. *Prog Cardiovasc Dis* 2015;**57**:443–453.
249. Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. *Physiology (Bethesda)* 2013;**28**:330–358.
250. Cheng W, Zhang Z, Cheng W, Yang C, Diao L, Liu W. Associations of leisure-time physical activity with cardiovascular mortality: a systematic review and meta-analysis of 44 prospective cohort studies. *Eur J Prev Cardiol* 2018;**25**:1864–1872.
251. Vanhees L, De Sutter J, Gelada SN, Doyle F, Prescott E, Cornelissen V, Kouidi E, Dugmore D, Vanuzzo D, Borjesson M, Doherty P, EACPR. Importance of characteristics and modalities of physical activity and exercise in defining the benefits to cardiovascular health within the general population: recommendations from the EACPR (Part I). *Eur J Prev Cardiol* 2012;**19**:670–686.
252. Vanhees L, Geladas N, Hansen D, Kouidi E, Niebauer J, Reiner Z, Cornelissen V, Adamopoulos S, Prescott E, Borjesson M, Bjarnason-Wehrens B, Bjornstad HH, Cohen-Solal A, Conraads V, Corrado D, De Sutter J, Doherty P, Doyle F, Dugmore D, Ellingsen O, Fagard R, Giada F, Gielen S, Hager A, Halle M, Heidbuchel H, Jegier A, Mazic S, McGee H, Mellwig KP, Mendes M, Mezzani A, Pattyn N, Pelliccia A, Piepoli M, Rauch B, Schmidt-Trucksass A, Takken T, van Buuren F, Vanuzzo D. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular risk factors: recommendations from the EACPR. Part II. *Eur J Prev Cardiol* 2012;**19**:1005–1033.
253. Vanhees L, Rauch B, Piepoli M, van Buuren F, Takken T, Borjesson M, Bjarnason-Wehrens B, Doherty P, Dugmore D, Halle M, Writing Group, EACPR. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular disease (Part III). *Eur J Prev Cardiol* 2012;**19**:1333–1356.
254. Lahtinen M, Toukola T, Junttila MJ, Piira OP, Lepojarvi S, Kaariainen M, Huikuri HV, Tulppo MP, Kiviniemi AM. Effect of changes in physical activity on risk for cardiac death in patients with coronary artery disease. *Am J Cardiol* 2018;**121**:143–148.
255. Stewart RAH, Held C, Hadziosmanovic N, Armstrong PW, Cannon CP, Granger CB, Hagstrom E, Hochman JS, Koenig W, Lonn E, Nicolau JC, Steg PG, Vedin O, Wallentin L, White HD, Investigators STABILITY. Physical activity and mortality in patients with stable coronary heart disease. *J Am Coll Cardiol* 2017;**70**:1689–1700.
256. Patel AV, Bernstein L, Deka A, Feigelson HS, Campbell PT, Gapstur SM, Colditz GA, Thun MJ. Leisure time spent sitting in relation to total mortality in a prospective cohort of US adults. *Am J Epidemiol* 2010;**172**:419–429.
257. Belardinelli R, Georgiou D, Cianci G, Purcaro A. 10-year exercise training in chronic heart failure: a randomized controlled trial. *J Am Coll Cardiol* 2012;**60**:1521–1528.
258. Rauch B, Davos CH, Doherty P, Saure D, Metzendorf MI, Salzwedel A, Voller H, Jensen K, Schmid JP, 'Cardiac Rehabilitation Section', European Association of Preventive Cardiology (EAPC), in cooperation with the Institute of Medical Biometry and Informatics (IMBI), Department of Medical Biometry, University of Heidelberg, and the Cochrane Metabolic and Endocrine Disorders Group, Institute of General Practice, Heinrich-Heine University, Düsseldorf, Germany. The prognostic effect of cardiac rehabilitation in the era of acute revascularisation and statin therapy: a systematic review and meta-analysis of randomized and non-randomized studies - The Cardiac Rehabilitation Outcome Study (CROS). *Eur J Prev Cardiol* 2016;**23**:1914–1939.
259. Lee J, Lee R, Stone AJ. Combined aerobic and resistance training for peak oxygen uptake, muscle strength, and hypertrophy after coronary artery disease: a systematic review and meta-analysis. *J Cardiovasc Transl Res* 2019;doi: 10.1007/s12265-019-09922-0.
260. Anderson L, Thompson DR, Oldridge N, Zwisler AD, Rees K, Martin N, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2016:CD001800.
261. de Vries H, Kemps HM, van Engen-Verheul MM, Kraaijenhagen RA, Peek N. Cardiac rehabilitation and survival in a large representative community cohort of Dutch patients. *Eur Heart J* 2015;**36**:1519–1528.
262. Piepoli MF, Corra U, Adamopoulos S, Benzer W, Bjarnason-Wehrens B, Cupples M, Dendale P, Doherty P, Gaita D, Hofer S, McGee H, Mendes M, Niebauer J, Pogosova N, Garcia-Porrero E, Rauch B, Schmid JP, Giannuzzi P. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology. *Eur J Prev Cardiol* 2014;**21**:664–681.
263. Benzer W, Rauch B, Schmid JP, Zwisler AD, Dendale P, Davos CH, Kouidi E, Simon A, Abreu A, Pogosova N, Gaita D, Miletic B, Bonner G, Ouarrak T, McGee H, EuroCaReD study group. Exercise-based cardiac rehabilitation in twelve European countries results of the European cardiac rehabilitation registry. *Int J Cardiol* 2017;**228**:58–67.
264. Ormel J, Von Korff M, Burger H, Scott K, Demyttenaere K, Huang YQ, Posada-Villa J, Pierre Lepine J, Angermeyer MC, Levinson D, de Girolamo G, Kawakami N, Karam E, Medina-Mora ME, Gureje O, Williams D, Haro JM, Bromet EJ, Alonso J, Kessler R. Mental disorders among persons with heart disease -

results from World Mental Health surveys. *Gen Hosp Psychiatry* 2007;**29**:325–334.
265. Rudisch B, Nemeroff CB. Epidemiology of comorbid coronary artery disease and depression. *Biol Psychiatry* 2003;**54**:227–240.
266. Richards SH, Anderson L, Jenkinson CE, Whalley B, Rees K, Davies P, Bennett P, Liu Z, West R, Thompson DR, Taylor RS. Psychological interventions for coronary heart disease. *Cochrane Database Syst Rev* 2017;**4**:CD002902.
267. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J* 2011;**32**:1484–1492.
268. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with coronary artery disease. *Cochrane Database Syst Rev* 2011:CD008012.
269. Richards SH, Anderson L, Jenkinson CE, Whalley B, Rees K, Davies P, Bennett P, Liu Z, West R, Thompson DR, Taylor RS. Psychological interventions for coronary heart disease: Cochrane systematic review and meta-analysis. *Eur J Prev Cardiol* 2018;**25**:247–259.
270. Rutledge T, Redwine LS, Linke SE, Mills PJ. A meta-analysis of mental health treatments and cardiac rehabilitation for improving clinical outcomes and depression among patients with coronary heart disease. *Psychosom Med* 2013;**75**:335–349.
271. Liu C, Chen R, Sera F, Vicedo-Cabrera AM, Guo Y, Tong S, Coelho M, Saldiva PHN, Lavigne E, Matus P, Valdes Ortega N, Osorio Garcia S, Pascal M, Stafoggia M, Scortichini M, Hashizume M, Honda Y, Hurtado-Diaz M, Cruz J, Nunes B, Teixeira JP, Kim H, Tobias A, Iniguez C, Forsberg B, Astrom C, Ragettli MS, Guo YL, Chen BY, Bell ML, Wright CY, Scovronick N, Garland RM, Milojevic A, Kysely J, Urban A, Orru H, Indermitte E, Jaakkola JJK, Ryti NRI, Katsouyanni K, Analitis A, Zanobetti A, Schwartz J, Chen J, Wu T, Cohen A, Gasparrini A, Kan H. Ambient particulate air pollution and daily mortality in 652 cities. *N Engl J Med* 2019;**381**:705–715.
272. Brook RD, Newby DE, Rajagopalan S. Air pollution and cardiometabolic disease: an update and call for clinical trials. *Am J Hypertens* 2017;**31**:1–10.
273. Claeys MJ, Rajagopalan S, Nawrot TS, Brook RD. Climate and environmental triggers of acute myocardial infarction. *Eur Heart J* 2017;**38**:955–960.
274. Lechner K, von Schacky C, McKenzie AL, Worm N, Nixdorff U, Lechner B, Krankel N, Halle M, Krauss RM, Scherr J. Lifestyle factors and high-risk atherosclerosis: pathways and mechanisms beyond traditional risk factors. *Eur J Prev Cardiol* 2020;**27**:394–406.
275. Munzel T, Schmidt FP, Steven S, Herzog J, Daiber A, Sorensen M. Environmental noise and the cardiovascular system. *J Am Coll Cardiol* 2018;**71**:688–697.
276. Steinke EE, Jaarsma T, Barnason SA, Byrne M, Doherty S, Dougherty CM, Fridlund B, Kautz DD, Martensson J, Mosack V, Moser DK, Council on Cardiovascular and Stroke Nursing of the American Heart Association and the ESC Council on Cardiovascular Nursing and Allied Professions (CCNAP). Sexual counselling for individuals with cardiovascular disease and their partners: a consensus document from the American Heart Association and the ESC Council on Cardiovascular Nursing and Allied Professions (CCNAP). *Eur Heart J* 2013;**34**:3217–3235.
277. Bispo GS, de Lima Lopes J, de Barros AL. Cardiovascular changes resulting from sexual activity and sexual dysfunction after myocardial infarction: integrative review. *J Clin Nurs* 2013;**22**:3522–3531.
278. Levine GN, Steinke EE, Bakaeen FG, Bozkurt B, Cheitlin MD, Conti JB, Foster E, Jaarsma T, Kloner RA, Lange RA, Lindau ST, Maron BJ, Moser DK, Ohman EM, Seftel AD, Stewart WJ, American Heart Association Council on Clinical Cardiology, Council on Cardiovascular Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Quality of Care and Outcomes Research. Sexual activity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2012;**125**:1058–1072.
279. Stein R, Sardinha A, Araujo CG. Sexual activity and heart patients: a contemporary perspective. *Can J Cardiol* 2016;**32**:410–420.
280. Steinke EE, Mosack V, Hill TJ. Change in sexual activity after a cardiac event: the role of medications, comorbidity, and psychosocial factors. *Appl Nurs Res* 2015;**28**:244–250.
281. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, Stricker B, Mendis S, Hofman A, Mant J, Franco OH. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J* 2013;**34**:2940–2948.
282. Gnjidic D, Bennett A, Le Couteur DG, Blyth FM, Cumming RG, Waite L, Handelsman D, Naganathan V, Matthews S, Hilmer SN. Ischemic heart disease, prescription of optimal medical therapy and geriatric syndromes in community-dwelling older men: a population-based study. *Int J Cardiol* 2015;**192**:49–55.
283. Mohammed S, Arabi A, El-Menyar A, Abdulkarim S, AlJundi A, Alqahtani A, Arafa S, Al Suwaidi J. Impact of polypharmacy on adherence to evidence-based medication in patients who underwent percutaneous coronary intervention. *Curr Vasc Pharmacol* 2016;**14**:388–393.
284. Wimmer BC, Cross AJ, Jokanovic N, Wiese MD, George J, Johnell K, Diug B, Bell JS. Clinical outcomes associated with medication regimen complexity in older people: a systematic review. *J Am Geriatr Soc* 2017;**65**:747–753.
285. Demonceau J, Ruppar T, Kristanto P, Hughes DA, Fargher E, Kardas P, De Geest S, Dobbels F, Lewek P, Urquhart J, Vrijens B, ABC project team. Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: a systematic literature review and meta-analysis. *Drugs* 2013;**73**:545–562.
286. Engelbertsen D, Vallejo J, Quach TD, Fredrikson GN, Alm R, Hedblad B, Bjorkbacka H, Rothstein TL, Nilsson J, Bengtsson E. Low levels of IgM antibodies against an advanced glycation endproduct-modified apolipoprotein B100 peptide predict cardiovascular events in nondiabetic subjects. *J Immunol* 2015;**195**:3020–3025.
287. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, Agoritsas T, Mistry N, Iorio A, Jack S, Sivaramalingam B, Iserman E, Mustafa RA, Jedraszewski D, Cotoi C, Haynes RB. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2014:CD000011.
288. Koertge J, Weidner G, Elliott-Eller M, Scherwitz L, Merritt-Worden TA, Marlin R, Lipsenthal L, Guarneri M, Finkel R, Saunders DE, Jr., McCormac P, Scheer JM, Collins RE, Ornish D. Improvement in medical risk factors and quality of life in women and men with coronary artery disease in the Multicenter Lifestyle Demonstration Project. *Am J Cardiol* 2003;**91**:1316–1322.
289. Patel A, Cass A, Peiris D, Usherwood T, Brown A, Jan S, Neal B, Hillis GS, Rafter N, Tonkin A, Webster R, Billot L, Bompoint S, Burch C, Burke H, Hayman N, Molanus B, Reid CM, Shiel L, Togni S, Rodgers A, Kanyini Guidelines Adherence with the Polypill (Kanyini GAP) Collaboration. A pragmatic randomized trial of a polypill-based strategy to improve use of indicated preventive treatments in people at high cardiovascular disease risk. *Eur J Prev Cardiol* 2015;**22**:920–930.
290. Castellano JM, Fuster V, Jennings C, Prescott E, Bueno H. Role of the polypill for secondary prevention in ischaemic heart disease. *Eur J Prev Cardiol* 2017;**24**:44–51.
291. Hebsur S, Vakil E, Oetgen WJ, Kumar PN, Lazarous DF. Influenza and coronary artery disease: exploring a clinical association with myocardial infarction and analyzing the utility of vaccination in prevention of myocardial infarction. *Rev Cardiovasc Med* 2014;**15**:168–175.
292. MacIntyre CR, Mahimbo A, Moa AM, Barnes M. Influenza vaccine as a coronary intervention for prevention of myocardial infarction. *Heart* 2016;**102**:1953–1956.
293. Kadoglou NPE, Bracke F, Simmers T, Tsiodras S, Parissis J. Influenza infection and heart failure-vaccination may change heart failure prognosis? *Heart Fail Rev* 2017;**22**:329–336.
294. Clar C, Oseni Z, Flowers N, Keshtkar-Jahromi M, Rees K. Influenza vaccines for preventing cardiovascular disease. *Cochrane Database Syst Rev* 2015:CD005050.
295. Mohseni H, Kiran A, Khorshidi R, Rahimi K. Influenza vaccination and risk of hospitalization in patients with heart failure: a self-controlled case series study. *Eur Heart J* 2017;**38**:326–333.
296. Paules CI, Subbarao K. Influenza vaccination and prevention of cardiovascular disease mortality - authors' reply. *Lancet* 2018;**391**:427–428.
297. Andersson C, Shilane D, Go AS, Chang TI, Kazi D, Solomon MD, Boothroyd DB, Hlatky MA. Beta-blocker therapy and cardiac events among patients with newly diagnosed coronary heart disease. *J Am Coll Cardiol* 2014;**64**:247–252.
298. Bangalore S, Bhatt DL, Steg PG, Weber MA, Boden WE, Hamm CW, Montalescot G, Hsu A, Fox KA, Lincoff AM. Beta-blockers and cardiovascular events in patients with and without myocardial infarction: post hoc analysis from the CHARISMA trial. *Circ Cardiovasc Qual Outcomes* 2014;**7**:872–881.
299. Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999;**318**:1730–1737.
300. Hwang D, Lee JM, Kim HK, Choi KH, Rhee TM, Park J, Park TK, Yang JH, Song YB, Choi JH, Hahn JY, Choi SH, Koo BK, Kim YJ, Chae SC, Cho MC, Kim CJ, Gwon HC, Jeong MH, Kim HS, KAMIR Investigators. Prognostic impact of beta-blocker dose after acute myocardial infarction. *Circ J* 2019;**83**:410–417.
301. Leizorovicz A, Lechat P, Cucherat M, Bugnard F. Bisoprolol for the treatment of chronic heart failure: a meta-analysis on individual data of two placebo-controlled studies—CIBIS and CIBIS II. Cardiac Insufficiency Bisoprolol Study. *Am Heart J* 2002;**143**:301–307.
302. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996;**334**:1349–1355.
303. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C, Scherhag A, Skene A, Carvedilol Or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003;**362**:7–13.

304. Dahl Aarvik M, Sandven I, Dondo TB, Gale CP, Ruddox V, Munkhaugen J, Atar D, Otterstad JE. Effect of oral beta-blocker treatment on mortality in contemporary post-myocardial infarction patients: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother* 2019;**5**:12–20.
305. Bangalore S, Steg G, Deedwania P, Crowley K, Eagle KA, Goto S, Ohman EM, Cannon CP, Smith SC, Zeymer U, Hoffman EB, Messerli FH, Bhatt DL, REACH Registry Investigators. Beta-blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA* 2012;**308**:1340–1349.
306. Motivala AA, Parikh V, Roe M, Dai D, Abbott JD, Prasad A, Mukherjee D. Predictors, trends, and outcomes (among older patients >/=65 years of age) associated with beta-blocker use in patients with stable angina undergoing elective percutaneous coronary intervention: insights from the NCDR registry. *JACC Cardiovasc Interv* 2016;**9**:1639–1648.
307. Zhang H, Yuan X, Zhang H, Chen S, Zhao Y, Hua K, Rao C, Wang W, Sun H, Hu S, Zheng Z. Efficacy of long-term beta-blocker therapy for secondary prevention of long-term outcomes after coronary artery bypass grafting surgery. *Circulation* 2015;**131**:2194–2201.
308. Bangalore S, Makani H, Radford M, Thakur K, Toklu B, Katz SD, DiNicolantonio JJ, Devereaux PJ, Alexander KP, Wetterslev J, Messerli FH. Clinical outcomes with beta-blockers for myocardial infarction: a meta-analysis of randomized trials. *Am J Med* 2014;**127**:939–953.
309. Hong J, Barry AR. Long-term beta-blocker therapy after myocardial infarction in the reperfusion era: a systematic review. *Pharmacotherapy* 2018;**38**:546–554.
310. Puymirat E, Riant E, Aissaoui N, Soria A, Ducrocq G, Coste P, Cottin Y, Aupetit JF, Bonnefoy E, Blanchard D, Cattan S, Steg G, Schiele F, Ferrieres J, Juilliere Y, Simon T, Danchin N. Beta blockers and mortality after myocardial infarction in patients without heart failure: multicentre prospective cohort study. *BMJ* 2016;**354**:i4801.
311. Tsujimoto T, Kajio H, Shapiro MF, Sugiyama T. Risk of all-cause mortality in diabetic patients taking beta-blockers. *Mayo Clin Proc* 2018;**93**:409–418.
312. Neumann A, Maura G, Weill A, Alla F, Danchin N. Clinical events after discontinuation of beta-blockers in patients without heart failure optimally treated after acute myocardial infarction: a cohort study on the French healthcare databases. *Circ Cardiovasc Qual Outcomes* 2018;**11**:e004356.
313. Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. *Eur Heart J* 2005;**26**:967–974.
314. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005;**352**:1951–1958.
315. Fox KM, Mulcahy D, Findlay I, Ford I, Dargie HJ. The Total Ischaemic Burden European Trial (TIBET). Effects of atenolol, nifedipine SR and their combination on the exercise test and the total ischaemic burden in 608 patients with stable angina. The TIBET Study Group. *Eur Heart J* 1996;**17**:96–103.
316. Kawanishi DT, Reid CL, Morrison EC, Rahimtoola SH. Response of angina and ischemia to long-term treatment in patients with chronic stable angina: a double-blind randomized individualized dosing trial of nifedipine, propranolol and their combination. *J Am Coll Cardiol* 1992;**19**:409–417.
317. Shu de F, Dong BR, Lin XF, Wu TX, Liu GJ. Long-term beta blockers for stable angina: systematic review and meta-analysis. *Eur J Prev Cardiol* 2012;**19**:330–341.
318. Wallace WA, Wellington KL, Chess MA, Liang CS. Comparison of nifedipine gastrointestinal therapeutic system and atenolol on antianginal efficacies and exercise hemodynamic responses in stable angina pectoris. *Am J Cardiol* 1994;**73**:23–28.
319. Hawkins NM, Virani S, Ceconi C. Heart failure and chronic obstructive pulmonary disease: the challenges facing physicians and health services. *Eur Heart J* 2013;**34**:2795–2803.
320. 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.
321. Rutten FH, Cramer MJ, Lammers JW, Grobbee DE, Hoes AW. Heart failure and chronic obstructive pulmonary disease: an ignored combination? *Eur J Heart Fail* 2006;**8**:706–711.
322. Rutten FH, Moons KG, Cramer MJ, Grobbee DE, Zuithoff NP, Lammers JW, Hoes AW. Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. *BMJ* 2005;**331**:1379.
323. Reddel HK, Bateman ED, Becker A, Boulet LP, Cruz AA, Drazen JM, Haahtela T, Hurd SS, Inoue H, de Jongste JC, Lemanske RF, Jr., Levy ML, O'Byrne PM, Paggiaro P, Pedersen SE, Pizzichini E, Soto-Quiroz M, Szefler SJ, Wong GW, FitzGerald JM. A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J* 2015;**46**:622–639.
324. Zeitouni M, Kerneis M, Lattuca B, Guedeney P, Cayla G, Collet JP, Montalescot G, Silvain J. Do patients need lifelong beta-blockers after an uncomplicated myocardial infarction? *Am J Cardiovasc Drugs* 2019;**19**:431–438.
325. Agewall S, Cattaneo M, Collet JP, Andreotti F, Lip GY, Verheugt FW, Huber K, Grove EL, Morais J, Husted S, Wassmann S, Rosano G, Atar D, Pathak A, Kjeldsen K, Storey RF, ESC Working Group on Cardiovascular Pharmacology and Drug Therapy and ESC Working Group on Thrombosis. Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy. *Eur Heart J* 2013;**34**:1708–1713, 1713a–1713b.
326. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, Torp-Pedersen C, Ball S, Pogue J, Moye L, Braunwald E. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000;**355**:1575–1581.
327. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302.
328. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Jr., Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Hawkins CM. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;**327**:669–677.
329. Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145–153.
330. Patel A, ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;**370**:829–840.
331. WTO takes a first step. *Lancet* 2003;**362**:753.
332. Braunwald E, Domanski MJ, Fowler SE, Geller NL, Gersh BJ, Hsia J, Pfeffer MA, Rice MM, Rosenberg YD, Rouleau JL, PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;**351**:2058–2068.
333. Bangalore S, Fakheri R, Wandel S, Toklu B, Wandel J, Messerli FH. Renin angiotensin system inhibitors for patients with stable coronary artery disease without heart failure: systematic review and meta-analysis of randomized trials. *BMJ* 2017;**356**:j4.
334. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004.
335. Carillo S, Zhang Y, Fay R, Angioi M, Vincent J, Sutradhor SC, Ahmed A, Pitt B, Zannad F. Heart failure with systolic dysfunction complicating acute myocardial infarction - differential outcomes but similar eplerenone efficacy by ST-segment or non-ST-segment elevation: a post hoc substudy of the EPHESUS trial. *Arch Cardiovasc Dis* 2014;**107**:149–157.
336. O'Keefe JH, Abuissa H, Pitt B. Eplerenone improves prognosis in postmyocardial infarction diabetic patients with heart failure: results from EPHESUS. *Diabetes Obes Metab* 2008;**10**:492–497.
337. Pitt B, White H, Nicolau J, Martinez F, Gheorghiade M, Aschermann M, van Veldhuisen DJ, Zannad F, Krum H, Mukherjee R, Vincent J, EPHESUS Investigators. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol* 2005;**46**:425–431.
338. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B, EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21.
339. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I, ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;**39**:3021–3104.
340. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, Trevisan M, Black HR, Heckbert SR, Detrano R, Strickland OL, Wong ND, Crouse JR, Stein E, Cushman M, Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;**349**:523–534.
341. Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, Collet J-P, Corrado D, Drezner JA, Halle M, Hansen D, Heidbuchel H, Myers J, Niebauer J, Papadakis P, Piepoli MF, Prescott E, Roos-Hesselink JW, Stuart AG, Taylor RS, Thompson PD, Tiberi M, Vanhees L, Wilhelm M. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2020; doi:10.1093/eurheartj/ehaa605.