European Heart Journal
doi:10.1093/eurheartj/ehv320



# 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation – Web Addenda

## 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: Marco Roffi* (Chairperson) (Switzerland), Carlo Patrono* (co-Chairperson) (Italy), Jean-Philippe Collet† (France), Christian Mueller† (Switzerland), Marco Valgimigli† (The Netherlands), Felicita Andreotti (Italy), Jeroen J. Bax (The Netherlands), Michael A. Borger (Germany), Carlos Brotons (Spain), Derek P. Chew (Australia), Baris Gencer (Switzerland), Gerd Hasenfuss (Germany), Keld Kjeldsen (Denmark), Patrizio Lancellotti (Belgium), Ulf Landmesser (Germany), Julinda Mehilli (Germany), Debabrata Mukherjee (USA), Robert F. Storey (UK), and Stephan Windecker (Switzerland)**

**Document Reviewers: Helmut Baumgartner (CPG Review Coordinator) (Germany), Oliver Gaemperli (CPG Review Coordinator) (Switzerland), Stephan Achenbach (Germany), Stefan Agewall (Norway), Lina Badimon (Spain), Colin Baigent (UK), Héctor Bueno (Spain), Raffaele Bugiardini (Italy), Scipione Carerj (Italy), Filip Casselman (Belgium), Thomas Cuisset (France), Çetin Erol (Turkey), Donna Fitzsimons (UK), Martin Halle (Germany), Christian Hamm (Germany), David Hildick-Smith (UK), Kurt Huber (Austria), Efstathios Iliodromitis (Greece), Stefan James (Sweden), Basil S. Lewis (Israel), Gregory Y. H. Lip (UK), Massimo F. Piepoli (Italy), Dimitrios Richter**

* Corresponding authors: Marco Roffi, Division of Cardiology, University Hospital, Rue Gabrielle Perret-Gentil 4, 1211 Geneva 14, Switzerland, Tel: +41 22 37 23 743, Fax: +41 22 37 27 229, E-mail: Marco.Roffi@hcuge.ch.

Carlo Patrono, Istituto di Farmacologia, Università Cattolica del Sacro Cuore, Largo F. Vito 1, IT-00168 Rome, Italy, Tel: +39 06 30154253, Fax: +39 06 3050159, E-mail: carlo.patrono@rm.unicatt.it.

† Section Coordinators affiliations listed in the Appendix in the full text document http://www.escardio.org/guidelines.

ESC Committee for Practice Guidelines (CPG) and National Cardiac Societies document reviewers listed in the Appendix in full text document http://www.escardio.org/guidelines

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

**Associations:** Acute Cardiovascular Care Association (ACCA), European Association for Cardiovascular Prevention & Rehabilitation (EACPR), European Association of Cardiovascular Imaging (EACVI), European Association of Percutaneous Cardiovascular Interventions (EAPCI), Heart Failure Association (HFA).

**Councils:** Council on Cardiovascular Nursing and Allied Professions (CCNAP), Council for Cardiology Practice (CCP), Council on Cardiovascular Primary Care (CCPC).

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

(Greece), Thomas Rosemann (Switzerland), Udo Sechtem (Germany), Ph. Gabriel Steg (France), Christian Vrints (Belgium), and Jose Luis Zamorano (Spain)

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

**Questions and answers companion manuscripts of these guidelines are available at: http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Acute-Coronary-Syndromes-ACS-in-patients-presenting-without-persistent-ST-segm**

**Keywords** Acute cardiac care • Acute coronary syndrome • Angioplasty • Anticoagulation • Apixaban • Aspirin • Atherothrombosis • Beta-blockers • Bivalirudin • Bypass surgery • Cangrelor • Chest pain unit • Clopidogrel • Dabigatran • Diabetes • Early invasive strategy • Enoxaparin • European Society of Cardiology • Fondaparinux • Glycoprotein IIb/IIIa inhibitors • Guidelines • Heparin • High-sensitivity troponin • Myocardial ischaemia • Nitrates • Non-ST-elevation myocardial infarction • Platelet inhibition • Prasugrel • Recommendations • Revascularization • Rhythm monitoring • Rivaroxaban • Statin • Stent • Ticagrelor • Unstable angina • Vorapaxar

**The table of contents of these guidelines can be found in the full text document this addenda refers to.**

## 2.1 Definitions, pathophysiology and epidemiology

### 2.1.3 Pathophysiology and epidemiology

Plaque rupture or erosion with overlying thrombosis is considered to be the main initiating mechanism of ACS. Inflammation is believed to play a key role in plaque disruption, although the stimuli that initiate the acute inflammatory process remain elusive.[14,15] Platelet activation and aggregation onto the exposed thrombogenic surface of a ruptured plaque is an early important event in the pathogenesis of ACS.[15,16] Activated platelets release inflammatory and mitogenic substances into the microenvironment, primarily altering the chemotactic, adhesive and proteolytic properties of the endothelium.[16] Healthy vascular endothelium releases prostacyclin and nitric oxide, both of which inhibit platelet activation and aggregation. It is likely that, when intact, these counterregulatory mechanisms of endothelial thromboresistance limit the extent and duration of platelet activation in response to vascular injury.[16] This hypothesis would explain why only a small fraction of disrupted plaques may elicit symptoms while the majority heal silently. The episodic nature of platelet activation, supported by transient increases in thromboxane biosynthesis, is consistent with the concept of coronary atherothrombosis as a dynamic process, in which repeated episodes of thrombus formation and fragmentation occur over a disrupted plaque.[16] Finally, focal or diffuse spasm of normal or atherosclerotic coronary arteries, predominantly caused by vasoconstrictor stimuli acting on hyperreactive vascular smooth muscle cells, may cause ACS.

While the incidence of STEMI has decreased appreciably over the last decade, the rate of NSTEMI has slightly increased.[17] Overall, NSTEMI patients appear to have lower short-term mortality compared with STEMI individuals, while at 1- or 2-years follow-up the mortality rates become comparable, likely due to differences in baseline characteristics, including older age and a greater prevalence of co-morbidities in the NSTEMI population.[18–20]

## 3.3 Diagnostic tools

### 3.3.3 'Rule-in' and 'rule-out' algorithms

**Table 5 Characteristics of the 0 h/3 h and the 0 h/1 h algorithms**

| | 0h/3 h algorithm | 0h/1 h algorithm |
|---|---|---|
| Negative predictive value for acute MI | 98–100% | 98–100% |
| Positive predictive value for acute MI | Unknown, depending on delta change and assay | 75–80% |
| Effectiveness[a] | ++ | +++ |
| Feasibility | ++ requires GRACE score | +++ |
| Challenges | Pain onset cannot be reliably quantified in many patients | Cut-off levels are assay-specific and different from the 99th percentile |
| Validation in large multicentre studies | + | +++ |
| Additional advantages | Already used clinically | Shorter time to decision |

GRACE = Global Registry of Acute Coronary Events; MI = myocardial infarction.
[a]Effectiveness is quantified by the percentage of consecutive chest pain patients clearly classified as rule-out or rule-in of acute MI (i.e., approximately 60% for the 0 h/3 h algorithm and approximately 75% for the 0 h/1 h algorithm).

## 5.1 Pharmacological treatment of ischaemia

### 5.1.4 Other drug classes

Diltiazem and verapamil show similar efficacy in relieving symptoms and appear in this respect equivalent to beta-blockers.[121,122] In the 1980s, one study comparing nifedipine and metoprolol in

unstable angina was stopped early because of an excess of reinfarctions in the nifedipine arm, while trials comparing verapamil with placebo have shown significant reductions in sudden death, reinfarction and total mortality, especially in patients with preserved LV function.[123,124] Ranolazine, a drug that prevents calcium overload in ischaemia, did not reduce major cardiac events compared with placebo in the Metabolic Efficiency With Ranolazine for Less Ischaemia in Non-ST-Elevation Acute Coronary Syndromes (MERLIN) trial among 3279 NSTE-ACS patients, but did reduce the rate of recurrent ischaemia.[125] Calcium channel blockers and ranolazine may be considered in patients who cannot be adequately revascularized and have residual angina on beta-blockers. All types of calcium channel blockers may be used in vasospastic angina.[63]

## 5.2 Platelet inhibition

### 5.2.4 Monitoring of $P2Y_{12}$ inhibitors

In the Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents (ADAPT-DES) study, a large platelet function investigation, close to 50% of 30-day post-PCI stent thrombosis was attributable to high platelet reactivity.[167] Although on-treatment platelet reactivity has been identified as an independent predictor of subsequent ischaemic events, tailoring of antiplatelet therapy based on platelet function testing was not associated with improved outcomes after PCI.[168–170] Platelet function testing is now being investigated to gauge $P2Y_{12}$ inhibition in elderly patients at risk for both bleeding and ischaemic events (NCT01538446). Genetic variability in clopidogrel absorption and metabolism is a key factor responsible for the highly variable generation of its active metabolite. The two-step hepatic CYP-dependent oxidative metabolism of the prodrug appears to be of particular importance. Pharmacogenomic analyses have identified loss-of-function variant alleles of CYP 2C19, and specifically the 2C19*2 allele, to be the predominant genetic determinants of the variability in the antiplatelet effect of clopidogrel. Carriers of this variant have been shown to have lower active metabolite levels, higher platelet reactivity and a higher rate of CV events.[145,171–173] Rapid and accurate point-of-care genetic tests to identify these alleles are available. There are pending questions about the role of such testing, such as patient selection and whether personalized treatment based on genotyping has a positive impact on clinical outcome and costs.[174] The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have issued warnings about diminished clopidogrel action when combined with proton pump inhibitors, especially omeprazole and esomeprazole, which reduce metabolic activation of clopidogrel. Pharmacodynamic studies, but not clinical outcome studies, support the use of newer proton pump inhibitors such as pantoprazole instead of omeprazole in order to avoid this negative drug–drug interaction.[175] At present, genetic testing cannot be recommended in routine clinical practice due to insufficient prospective data. In conclusion, platelet function or genetic testing may be considered in selected patients treated with clopidogrel, including those with a history of stent thrombosis, suspected non-compliance, as well as persistent high on-treatment platelet reactivity or high bleeding risk in the presence of stents in critical coronary segments (e.g. left main trunk).

### 5.2.6 Duration of dual antiplatelet therapy

See *Table 9*.

### 5.2.7 Glycoprotein IIb/IIIa inhibitors

*5.2.7.1 Upstream vs. procedural initiation*

The ACUITY timing trial tested deferred selective (only during PCI) vs. routine upstream administration of any GPIIb/IIIa inhibitor among 9207 patients with NSTE-ACS.[198] The deferred selective strategy resulted in a significantly lower rate of 30-day major non-CABG-related bleeds [4.9% vs. 6.1%; RR 0.80 (95% CI 0.67, 0.95), $P = 0.009$] with no significant difference in death, MI or unplanned revascularization [7.9% vs. 7.1%; RR 1.12 (95% CI 0.97, 1.29), $P = 0.13$]. The Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome (EARLY-ACS) trial randomized 9492 patients undergoing invasive management to early eptifibatide or placebo with provisional use of eptifibatide after angiography for PCI.[199] The primary endpoint was a composite of death, MI, recurrent ischaemia requiring urgent revascularization and 'thrombotic bailout' (thrombotic complication during PCI requiring the use of the bailout kit) at 96 h. Among PCI patients allocated to the delayed provisional eptifibatide arm, 39% received GPIIb/IIIa inhibitor therapy during the procedure. There was no significant reduction in the primary outcome in the early vs. delayed provisional eptifibatide groups [9.3% vs. 10.0%; OR 0.92 (95% CI 0.80, 1.06), $P = 0.23$]. Death or MI at 30 days was also similar [11.2% early vs. 12.3% delayed; OR 0.89 (95% CI 0.79, 1.01), $P = 0.08$]. Major bleeding rates were higher in the early eptifibatide arm using a variety of definitions [e.g. TIMI major bleeds at 120 h, 2.6% vs. 1.8%; OR 1.42 (95% CI 1.07, 1.89), $P = 0.015$]. With no demonstrated advantage of a routine upstream use of GPIIb/IIIa inhibitors in an invasive strategy, it is reasonable to withhold these agents until after angiography. In patients undergoing PCI and receiving prasugrel or ticagrelor, GPIIb/IIIa inhibitor use should be restricted to bailout of thrombotic complications.

*5.2.7.2 Combination with $P2Y_{12}$ inhibitors*

The combination of $P2Y_{12}$ and GPIIb/IIIa blockade leads to augmented inhibition of platelet activation and aggregation.[200,201] Limited data have assessed the benefits of adding a GPIIb/IIIa inhibitor to the combination of aspirin and a $P2Y_{12}$ inhibitor in the setting of NSTE-ACS. In the ISAR-REACT 2 trial, 2022 high-risk NSTE-ACS patients were randomized following pretreatment with aspirin and 600 mg of clopidogrel to either abciximab or placebo during PCI.[202] The 30-day composite endpoint of death, MI or urgent target vessel revascularization occurred significantly less frequently in abciximab- vs. placebo-treated patients [8.9% vs. 11.9%; RR 0.75 (95% CI 0.58, 0.97), $P = 0.03$]. In the EARLY-ACS study, randomization to early eptifibatide compared with delayed provisional eptifibatide among patients commenced on clopidogrel was associated with a reduction in 30-day death or MI [10.1% vs. 11.8%; OR 0.85 (95% CI 0.73, 0.99)] but an increase in in-hospital TIMI major bleeds [2.2% vs. 1.4%; OR 1.54 (95% CI 1.07, 2.24)].[200] In the TRITON and PLATO trials, GPIIb/IIIa inhibitors were used in 55% and 27% of patients, respectively. While the relative efficacy of prasugrel and ticagrelor appears consistent among patients receiving and not receiving GPIIb/IIIa inhibitors, no study has investigated the role of GPIIb/IIIa inhibitors in patients treated with these agents.[153,197]

**Table 9 Main features of published randomized studies investigating various durations of dual antiplatelet therapy following percutaneous coronary intervention (PCI)**

| Study (year) | N (%ACS) | DAPT duration (months) | Timing of randomization | Stent type | Primary endpoint | Bleeding events |
|---|---|---|---|---|---|---|
| RESET (2012)[187] | 2117 (55%) | 3 vs. 12 | PCI | ZES in the 3 months DAPT arm vs. SES in the 12 months DAPT arm | CV death, MI, ST, TVR, major or minor bleeds: 4.7% in aspirin vs. 4.7% in DAPT (difference 0.0%, 95% CI −2.5% to 2.5%, $P = 0.84$, $P_{non\text{-}inferiority} < 0.001$) (1 year after stenting) | TIMI major: 0.2% in aspirin vs. 0.6% in DAPT, difference –0.4% (95% CI −0.9 to 0.2, $P = 0.18$) |
| OPTIMIZE (2013)[188] | 3119 (32%) | 3 vs. 12 | PCI | E-ZES (100%) | Death, MI, stroke, major bleeds: 6% in aspirin vs. 5.8% in DAPT (HR 1.03, 95% CI 0.77–1.38, Log-rank $P = 0.84$, $P_{non\text{-}inferiority} = 0.002$) (1 year after stenting) | TIMI major: 0.6% in aspirin vs. 0.9% in DAPT (HR 0.71, 95% CI 0.32–1.60, $P = 0.41$) |
| EXCELLENT (2012)[189] | 1443 (52%) | 6 vs. 12 | PCI | 1:1 randomisation EES (75%) vs. SES (25%) | Target vessel failure 4.8% aspirin and 4.3% in DAPT group (HR 1.14, 95% CI 0.70–1.86, $P = 0.60$; absolute risk difference 0.5% points; upper limit of 1-sided 95% CI 2.4%; $P < 0.001$ for non-inferiority) (1 year after stenting) | TIMI major: 0.3% in aspirin vs. 0.6% in DAPT group (HR 0.50, 95% CI 0.09–2.73, $P = 0.42$) |
| PRODIGY (2012)[190] | 1970 (75%) | 6 vs. 24 | 1 month after PCI | 1:1:1:1 randomisation BMS (25%) vs. E-ZES (25%) vs. PES (25%) vs. EES (25%) | Death, MI, stroke: 10% in aspirin vs. 10.1% in DAPT group (HR 0.98, 95% CI 0.74–1.29, $P = 0.91$) (2 years after stenting) | BARC type 5, 3 or 2: 3.5% in aspirin vs. 7.4% in DAPT (HR 0.46, 95% CI 0.31–0.69, $P < 0.001$) |
| SECURITY (2014)[191] | 1399 (38%) | 6 vs. 12 | NR | E-ZES (41%); EES (20%); others (33%) | Cardiac death, MI, stroke, definite or probable ST or BARC type 3 or 5 bleeds at 12 months: 4.5% vs. 3.7% in aspirin vs. DAPT (risk difference 0.8%, 95% CI –2.4% to 1.7%, $P = 0.469$, $P_{non\text{-}inferiority} < 0.05$) (1 year after stenting) | BARC type 3 or 5: 0.6% in aspirin vs. 1.1% in the DAPT group (risk difference –0.5%, 95% CI –1.4% to 0.4%, $P = 0.283$) |
| ISAR-SAFE (2015)[192] | 4000 (40%) | 6 vs. 12 | 6 months after PCI | PES (2%), SES (8%), EES (48%), ZES (15%), BES (8%), BMS (0.3%) | Death, MI, ST, stroke and TIMI major bleeds at 9 months after randomization: 1.5% in aspirin vs. 1.6% in DAPT (HR 0.91, 95% CI 0.55–1.50, $P = 0.70$, $P_{non\text{-}inferiority} < 0.001$) (2 years after stenting) | TIMI major bleeds: 0.2% in aspirin vs. 0.3% in DAPT (HR 0.80, 95% CI 0.21–2.98, $P = 0.74$) |
| ITALIC/ ITALIC + (2015)[193] | 1850 (23%) | 6 vs. 24 | PCI | EES (100%) | Death, MI, urgent TVR, stroke and major bleeds: 1.6% in aspirin vs. 1.5% in DAPT (risk difference 0.11, 95% CI –1.04 to 1.26, $P = 0.85$, $P_{non\text{-}inferiority} = 0.0002$) (2 years after stenting) | Minor bleeds: 0.4% in DAPT vs. 0.5% in aspirin (HR 1.247, 95% CI 0.335–4.643, $P = 0.74$) |
| DES LATE (2014)[194] | 5045 (61%) | 12 vs. 24 | 12 months after PCI | SES (44%); PES (20%); ZES (19%) EES (11%); others (6%) | CV death, MI or stroke 2.4% in the aspirin vs. 2.6% in DAPT (HR 0.94, 95% CI 0.66–1.35, $P = 0.75$) (2 years after stenting) | TIMI major bleeds: 1.1% in aspirin vs. 1.4% in DAPT group (HR 0.71, 95% CI 0.42–1.20, $P = 0.20$) |
| ARTIC- INTERRUPTION (2014)[195] | 1259 (30%) | 12 vs. 24 | 12 months after PCI | First generation DES 4.3% | Death, MI, ST, stroke, or urgent revascularization: 4% in DAPT group compared with 4% with aspirin alone (HR 1.17, 95% CI 0.68–2.03, $P = 0.58$) (2 years after stenting) | STEEPLE major bleeds: 1% in DAPT versus < 0.5% in aspirin group (HR 0.15, 95% CI 0.02–1.20, $P = 0.07$) |
| DAPT (2014)[184] | 9961 (43%) | 12 vs. 30 | 12 months after PCI | PES 26%, SES 11%, EES 47%, ZES 12% | Death, MI or stroke 4.3% in DAPT vs. 5.9% in aspirin (HR 0.71, 95% CI 0.59–0.85, $P < 0.001$) (33 months after stenting) | GUSTO moderate or severe bleeds 2.5% in DAPT vs. 1.6% in aspirin (HR 1.61, 95% CI 1.21–2.16, $P = 0.001$) |

BARC = Bleeding Academic Research Consortium; BES = biolimus-eluting stent; BMS = bare metal stent; CI = confidence interval; CV = cardiovascular; DAPT = dual (oral) antiplatelet therapy; EES = everolimus eluting stent; GUSTO = global utilization of streptokinase and t-PA for occluded arteries; HR = hazard ratio; MI = myocardial infarction; N = number of patients; NR = not reported; PCI = index percutaneous coronary intervention; PES = paclitaxel eluting stent; SES = sirolimus eluting stent; ST = stent thrombosis; STEEPLE = Safety and Efficacy of Enoxaparin in PCI patients, an International Randomized Evaluation; TIMI = thrombolysis in myocardial infarction; TVR = target vessel revascularisation; ZES = zotarolimus eluting stent.

*5.2.7.3 Adjunctive anticoagulant therapy*

Several NSTE-ACS and PCI trials have shown that LMWH, predominantly enoxaparin, can be safely used with GPIIb/IIIa inhibitors. In a subgroup analysis of the OASIS-5 trial, GPIIb/IIIa inhibitors were used with aspirin, clopidogrel and either fondaparinux (in 1308 patients) or enoxaparin (in 1273 patients).[203] Overall, bleeding complications were lower with fondaparinux than with enoxaparin. Bivalirudin and UFH/LMWH were shown to have equivalent safety and efficacy when used with aspirin, clopidogrel and a GPIIb/IIIa inhibitor in the ACUITY trial.[204] The combination of bivalirudin and a GPIIb/IIIa inhibitor resulted in a similar rate of ischaemic events compared with bivalirudin alone and a higher rate of major bleeds, and is not recommended for routine use.[205]

### 5.2.8 Vorapaxar

Vorapaxar is an orally active selective inhibitor of the platelet thrombin receptor PAR-1. The Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial enrolled 12 944 NSTE-ACS patients randomized to vorapaxar 40 mg loading and 2.5 mg daily maintenance or placebo. Aspirin and clopidogrel were administered in 97% and 87% of patients, respectively. After a median follow-up of 502 days, the primary endpoint of CV death, MI, stroke, recurrent ischaemia and urgent revascularization did not differ significantly among the groups [vorapaxar 18.5% vs. placebo 19.9%; HR 0.92 (95% CI 0.85, 1.01), $P = 0.07$], while severe bleeding events were more frequent in the study drug group [vorapaxar 7.2% vs. placebo 5.2%; HR 1.35 (95% CI 1.16, 1.58), $P < 0.001$], with a marked increase in intracranial haemorrhage [HR 3.39 (95% CI 1.78, 6.45), $P < 0.001$].[206] In the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2P-TIMI 50) trial, including 26 449 patients with prior MI, stroke or peripheral vascular disease, randomization to vorapaxar was associated with a modest reduction in CV death, MI and stroke over 3 years [vorapaxar 9.3% vs. placebo 10.5%; HR 0.87 (95% CI 0.80, 0.94), $P < 0.001$].[207] Administration of the study drug was associated with an increase in intracranial haemorrhage, and the absolute increase in TIMI clinically significant bleeds [vorapaxar 15.8% vs. placebo 11.1%; HR 1.46 (95% CI 1.36, 1.57), $P < 0.001$] was greater than the absolute reduction in ischaemic events. In the subgroup of 17 779 patients with prior MI, rates of the primary endpoint over 3 years were 8.1% in the vorapaxar group vs. 9.7% in the placebo group [HR 0.80 (95% CI 0.72, 0.89), $P < 0.0001$]. TIMI clinically significant bleeding occurred in 15.1% and 10.4% of patients, respectively [HR 1.49 (95% CI 1.36, 1.63), $P < 0.0001$]. While approved by the FDA and EMA for reducing ischaemic events in patients with a history of MI, the benefit of vorapaxar in addition to aspirin and clopidogrel is modest and must be carefully weighed against the increase in bleeding events, including intracranial haemorrhage. Its use is contraindicated in patients with a history of cerebrovascular disease.

## 5.5 Management of acute bleeding events

### 5.5.1 General supportive measures

Recommendations for resuscitation of patients in early haemorrhagic shock or with ongoing bleeding events have evolved over time.[253] 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.[253] 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.[253]

### 5.5.2 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.[254,255] Furthermore, there have been no studies in CAD patients. While aspirin-inhibited platelet aggregation can be restored after 2–5 units of platelet transfusion, it is more difficult to restore ADP-dependent platelet function.[256] In prasugrel- or clopidogrel-treated patients, platelet transfusions may be effective in restoring platelet function 4–6 h after the last drug intake.[257] In patients on ticagrelor, it may take $\geq$24 h for drug clearance to allow transfused platelets to restore haemostatic competence.

### 5.5.3 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.[258] 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 of phenprocoumon will result in a far slower decline.[259,260] 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 compared vitamin K1 with placebo in patients with an INR of 4.5–10 in the absence of ongoing bleeding.[260–263] 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 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.[264] 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.[265] Overall, prothrombin complex concentrates may be associated with less thrombotic risk than recombinant activated factor

VII, and the latter should be used only if prothrombin complex concentrates are not available.[265] 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.[265] 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.

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

Specific antidotes for NOACs and rapid (routine) quantitative measurements of their anticoagulant properties are currently lacking. 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 a dialysis in this setting is challenging and the experience limited.[266] Intracerebral haemorrhage or bleeding involving a critical organ such as the eye warrants immediate attempts to neutralize the anticoagulant effect of the NOACs by the administration of prothrombin complex concentrates or activated prothrombin complex concentrates (i.e. with the addition of activated factor VII).[267] 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.[265] 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. A reconstructed recombinant factor Xa has been proposed as an antidote for factor Xa inhibitors, and other compounds are currently in early phases of development.[268]

#### 5.5.5 Non-access-related bleeding events

Non-access-related bleeding events in patients with ACS undergoing PCI represent roughly 40–60% of all bleeds.[269–272] A pooled analysis of the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events 2 (REPLACE-2), ACUITY and 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].[269,270] According to data collected from the PLATO trial, the most common locations of non-access-related major bleeds were, in decreasing order of frequency, gastrointestinal tract, nose, urinary tract, subcutaneous dermal and intracranial, representing together three-quarters of all non-access bleeding events.[272]

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 as compared with access site events.

#### 5.5.6 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%.[148,164,202,221,223,273] Among different definitions used to classify the severity of bleeding complications, the BARC 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 strongly correlates with the risk of death.[274,275] A pooled analysis of seven RCTs including a total of 14 180 patients (with both stable CAD and NSTE-ACS) showed that periprocedural bleeds were associated with a five-fold increase in 30-day mortality.[276,277] Bleeding was the strongest predictor of early mortality, whereas the increased risk for late mortality was mostly mediated by CV risk factors clustered in patients suffering a bleeding event.[276] Different from periprocedural MI, periprocedural bleeds increase the risk of death and ischaemic events even beyond 3 years after PCI in NSTEMI patients.[273,276]

These findings, together with the identification of a variety of non-modifiable independent predictors of periprocedural bleeds such as female gender, 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.[273,278,279] Access site bleeding complications comprise ~40–60% of the periprocedural bleeds.[269,280,281] 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; OR 2.03 (95% CI 1.49, 2.77)].[281] Modifications of the periprocedural antithrombotic regimen have been efficacious in reducing periprocedural bleeds.[223,282] The radial approach for coronary angiography and PCI has been shown to be superior to the femoral one in patients with ACS. Accordingly, the large-scale MATRIX RCT showed a significant reduction in major bleeds as well as all-cause mortality in patients allocated to the radial compared with the femoral approach (see section 5.6.5.2).[251] 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. Except for a significantly shorter time to haemostasis, no benefit was observed with vascular closure devices.[283] 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.[280] 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 5.4.1 of the main text).

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

Reported bleeding rates during CABG in NSTE-ACS patients range from 64 to 80% depending on the definition used and the time elapsed between DAPT discontinuation and surgery.[284,285] Bleeding events as well as blood transfusions during CABG have been

associated with an increased rate of morbidity and mortality.[286,287] Several risk factors for CABG-associated bleeding events have been identified, including antithrombotic therapy, preoperative anaemia, female sex, age, small body size, renal or hepatic dysfunction, urgent or emergent procedures, redo surgery and hereditary or acquired platelet dysfunction.[288,289] Timing of DAPT cessation in NSTE-ACS patients undergoing CABG is detailed in sections 5.6.6.1. and 5.6.6.2. Severe CABG-associated bleeds in patients on DAPT should be managed with platelet concentrates. Recombinant factor VIIa should be used only 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.[290] 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.[291]

#### 5.5.8 Transfusion therapy

Red blood cell transfusions are administered in up to 10% of patients presenting with ACS.[292] 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%.[293] Women, the elderly, as well as 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.[292–294] Irrespective of bleeding complications, the need for blood transfusion is associated with an approximately four-fold increase in early mortality and three-fold increase in death or MI in ACS patients.[292–294] An increase in platelet reactivity following transfusions may account for the excess of ischaemic events.[295]

The nadir haemoglobin cut-off value mandating transfusion is not standardized and varies among hospitals.[293,296–298] In the majority of studies investigating different transfusion protocols, a liberal blood transfusion strategy was defined as any red blood cell transfusion at a haemoglobin level $<9.0$ g/dL, while a restrictive blood transfusion strategy was defined as any transfusion at a haemoglobin level $<7.0$ g/dL.[296–299] A meta-analysis of 10 studies totalling 203 665 patients (9 observational studies and 1 RCT with 45 patients) with ACS (both STEMI and NSTEMI-ACS) 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.[298] 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 $>25\%$.[293,298] Observations from the CRUSADE initiative in 44 242 patients with NSTE-ACS showed that among patients with haematocrit $\leq 24\%$, 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.[300] A meta-analysis of 31, largely unblinded, RCTs totalling 9813 patients (only a small minority with NSTE ACS) found no significant difference in primary clinical outcomes for a liberal vs. a restrictive blood transfusion strategy.[301] The most recent RCT was conducted in 2007 largely stable patients after cardiac surgery.[302] 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 the inconsistent results of the studies 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 outcomes of ACS patients with anaemia has not been investigated. However, the accumulated evidence on 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.[297]

## 5.6 Invasive coronary angiography and revascularization

#### 5.6.4 Conservative treatment

*5.6.4.2 In patients with normal coronary angiogram*

**Tako–Tsubo cardiomyopathy**, also called apical ballooning, is an emotional stress–related cardiomyopathy of undetermined aetiology characterized by chest pain, elevated cardiac enzymes, normal coronary angiography and an acute transient LV (more frequently apical) dysfunction that mimics MI. Although usually the wall motion abnormalities do not match a territory of coronary perfusion, a coronary aetiology must be excluded by coronary angiogram. An incidence of 2% in patients admitted for ACS has been reported, but this may represent an underestimation.[338,339] An incidence of 5.9% was documented among post-menopausal women admitted with suspected ACS.[340] Three-quarters of patients with Tako–Tsubo cardiomyopathy have higher serum catecholamine levels, and a vascular dysfunction leading to microvascular spasm has been proposed as an underlying mechanism.[341] There is a lack of consensus on the diagnostic criteria as well as therapy.[342]

**Coronary thromboembolism** is implicated in rare cases of NSTE-ACS with normal or near-normal coronary arteriograms. The angiographic differentiation from coronary atherothrombosis is in many instances difficult, if not impossible. Underlying conditions may include systemic diseases leading to arterial thrombosis and cardioembolism (in particular associated with atrial fibrillation or atrial flutter), as well as systemic embolism related to, among others, patent foramen ovale.

**Coronary spasm** is a frequently unrecognized cause of chest pain not precipitated by physical exertion or emotional stress. Focal occlusive coronary spasm leads to transient ST elevation on ECG, while diffuse subtotal vasospasm as well as microvascular spasm have been associated with ST depression and resting angina.[343] Spasms may occur at sites of minimal or severe focal stenoses. Patients tend to be younger and are often heavy smokers. Symptoms are often severe and may be accompanied by syncope or troponin elevation. Attacks tend to be more frequent during the night.

Spasms may be spontaneous or provoked by acetylcholine, cold pressor test or hyperventilation. Calcium antagonists, alone or in combination with nitrates, have been shown to be effective in preventing coronary spasm.[127] This condition has been extensively covered in the 2013 ESC guidelines on the management of stable CAD.[63]

**Coronary microvascular disease** is a syndrome characterized by typical anginal symptoms precipitated by exercise, ST depression on ECG suggesting subendocardial ischaemia during exercise stress test and non-obstructed coronary arteries on angiography. Resting angina, with or without troponin elevation, may occur due to severe and prolonged spasm of the microvasculature.[344] The chest pain may increase in frequency or intensity over time or may occur at rest with typical features of unstable angina. The underlying pathophysiology remains largely unknown, though impaired endothelial-dependent arterial vasodilatation, decreased nitric oxide production and increased sensitivity to sympathetic stimulation have been described. There is growing evidence that patients suffering from microvascular angina often have an increased response to pain. The most important therapy is reassurance and symptom relief, for which nitrates, beta-blockers and calcium antagonists have been found to be effective. This condition has been extensively covered in the 2013 ESC guidelines on the management of stable CAD.[63]

### 5.6.6 Coronary artery bypass surgery

*5.6.6.1 Timing of surgery and antithrombotic drug discontinuation*

Early myocardial revascularization for acute MI results in a reduction in myocardial necrosis, myocardial oedema and the no-reflow phenomenon. Due to the unavoidable delays associated with CABG surgery and the adverse effects of cardiopulmonary bypass and cardioplegic arrest, PCI is the procedure of choice for NSTE-ACS patients requiring immediate myocardial revascularization (i.e. in the presence of ongoing ischaemia, haemodynamic instability, pulmonary oedema or recurrent ventricular arrhythmias). In this setting, emergent CABG is performed only in patients in whom PCI is unsuccessful or not feasible. In the absence of randomized data, optimal timing for non-emergent CABG in stabilized NSTE-ACS patients should be determined individually. The risk of ischaemic events while awaiting surgery, related also possibly to suboptimal antiplatelet therapy, needs to be weighed against the risk of increased perioperative bleeding complications associated with platelet inhibitors and the deleterious effect of cardiopulmonary bypass and cardioplegic arrest on ischaemic myocardium. Patients who are at high risk for recurrent ischaemic events (i.e. patients with critical coronary anatomy or recurrent ischaemia) should be operated on as soon as possible without waiting for the full recovery of platelet function following discontinuation of DAPT. For all other patients, CABG appears to be most beneficial when surgery is performed after several days of medical stabilization and discontinuation of DAPT.

A review of California discharge data compared patients who underwent early ($<3$ days, $n = 4676$) vs. delayed ($\geq 3$ days, $n = 4800$) post-MI CABG.[362] Early CABG patients had a higher mortality rate than delayed CABG patients [unadjusted mortality 5.6% vs. 3.8%; propensity-adjusted OR 1.40 (95% CI 1.12, 1.74), $P < 0.001$], with the highest mortality observed in patients who were operated on the same day as the MI (8.2%). However, no differentiation was made between NSTEMI and STEMI, and higher-risk patients were likely treated more rapidly. In contrast, a retrospective study of NSTE-ACS patients ($n = 1454$) undergoing CABG failed to find any significant association between 30-day mortality rates and time to surgery.[363] However, patients undergoing CABG within 2 days of admission were excluded from this analysis. The timing of surgical intervention for NSTE-ACS was also assessed in the Acute Coronary Treatment and Intervention Outcomes Network Registry–Get with the Guidelines (ACTION Registry-GWTG) study.[364] Patients were divided into those operated on early ($\leq 48$ h of admission, $n = 825$) and late ($>48$ h, $n = 1822$) after admission for NSTE-MI. Despite a higher risk profile in patients operated on at a later time, no significant differences could be identified between groups with regards to in-hospital mortality (3.6% early vs. 3.8% late, $P = 0.56$) or the composite endpoint of death, MI, congestive heart failure or cardiogenic shock (12.6% early vs. 12.4% late, $P = 0.42$).

In patients without signs of recurrent or ongoing ischaemia, CABG should be delayed for 5 days following interruption of ticagrelor or clopidogrel therapy and 7 days following interruption of prasugrel therapy (see section 5.6.6.1). Aspirin should be continued through surgery except in patients with markedly increased bleeding risk (e.g. redo CABG or complex combined procedures) or in patients who refuse blood transfusion; in such patients it may be advisable to stop aspirin 3–5 days preoperatively. NSTE-ACS patients who are stable but at markedly increased risk for ischaemic events in the absence of DAPT (e.g. with recently implanted DES) may undergo bridging therapy with small molecule GPIIb/IIIa inhibitors (i.e. eptifibatide or tirofiban) after discontinuation of $P2Y_{12}$ inhibitors, though this strategy has been mainly studied for stent thrombosis prevention related to non-cardiac surgery.[181] Alternatively, bridging may be performed with cangrelor. Aspirin (75–100 mg/day) should be resumed within 6 h after CABG in all patients or can be substituted with clopidogrel (300 mg loading dose followed by 75 mg/day) in cases of aspirin intolerance.[182] In patients with recent DES implantation, resumption of $P2Y_{12}$ inhibitors should be considered as soon as postoperative bleeding allows.

In summary, in unstable NSTE-ACS patients with ongoing ischaemia or haemodynamic instability with an indication for CABG, emergency surgery should be performed regardless of antiplatelet therapy, while urgent surgery (usually the following day) should be reserved for stable patients with critical anatomy or high-risk features. All other stable patients requiring CABG should undergo planned surgery after an appropriate period of DAPT discontinuation.

*5.6.6.3 Technical aspects and outcomes*

Anticoagulation status should be assessed in all NSTE-ACS patients, including information on the timing and dose of the most recently administered antithrombotic agents. The perioperative approach and management of stabilized NSTE-ACS patients is similar to those undergoing elective CABG for stable CAD. NSTE-ACS patients undergoing emergent CABG may require changes in surgical management because of the increased risk of myocardial ischaemia and bleeding complications. Specifically, patients should be monitored closely during anaesthetic induction because of the risk of

haemodynamic instability. Haemodynamically unstable patients may require institution of cardiopulmonary bypass prior to conduit harvesting. In these patients, the myocardium supplied by the culprit lesion should be revascularized as early as possible. Beating heart surgery with or without cardiopulmonary bypass is associated with more rapid reperfusion of the culprit lesion and may be preferred in high-risk patients.[373] Time-consuming harvesting of conduits (e.g. bilateral internal thoracic artery grafts) should be discouraged in the presence of haemodynamic instability. Similarly, in patients requiring vasopressors, the use of radial artery bypass grafts is not recommended because of the risk of perioperative spasm. The risk of excessive bleeds may be minimized with off-pump CABG due to a reduced heparin requirement, although haemodynamic instability may preclude this option. Other options for reducing bleeding complications include the use of minimized cardiopulmonary bypass circuits in order to limit haemodilution, blood salvaging techniques and platelet transfusion.

Off-pump CABG may be performed in haemodynamically stable NSTE-ACS patients, although the benefits for this patient population are not well defined. A substudy of the ACUITY trial compared the outcomes in moderate- or high-risk ACS patients who underwent conventional CABG ($n = 1154$) to off-pump surgery ($n = 221$).[374] Off-pump patients had a lower rate of bleeding events and perioperative MI but a higher rate of early coronary reintervention. A similar rate of major morbidity and mortality was observed 1 year postoperatively, with the exception of a lower rate of NSTEMI in the off-pump group. A meta-analysis of eight studies (including one RCT) comparing off-pump ($n = 817$) to conventional CABG ($n = 2184$) failed to demonstrate a clear benefit for off-pump surgery in NSTE-ACS patients.[375] Off-pump surgery was associated with a higher rate of incomplete revascularization than conventional CABG, with no difference in early or midterm mortality rates observed between groups.

An intra-aortic balloon pump may be implanted prior to surgery in patients with ongoing ischaemia despite maximal medical therapy and in those with mechanical complications of MI (i.e. ventricular septal defect or mitral regurgitation due to papillary muscle rupture). Intra- or postoperative insertion of an intra-aortic balloon pump should also be considered in patients requiring major inotropic support. The management of patients who cannot be successfully weaned from cardiopulmonary bypass should be individualized. Insertion of an extra-corporeal membrane oxygenator may allow assessment of the neurological status in patients who previously required cardiopulmonary resuscitation and also make it possible to determine the suitability for LV assist device implantation and/or heart transplantation.

Precise estimates of periprocedural morbidity and mortality rates are difficult to ascertain since most surgical ACS series do not differentiate between NSTE-ACS and STEMI. A retrospective, multicentre study described a perioperative mortality rate of 3.2% in 6260 patients (proportion of NSTE-ACS not detailed) undergoing urgent or emergent CABG.[376] In a single centre, propensity-matched comparison of patients undergoing urgent CABG for NSTE-ACS vs. elective CABG for stable CAD ($n = 342$ in each group), NSTE-ACS patients had a higher risk of in-hospital mortality (adjusted mortality 2.6% vs. 0.3%, $P = 0.026$).[361]

## 5.7 Gender specificities

Compared with men, women presenting with NSTE-ACS are up to 30% less likely to be referred for cardiac testing and catheterization.[391–393] Several factors might explain this observation. First, women with NSTE-ACS are older and more frequently have associated conditions such as obesity, chronic kidney disease, cerebrovascular disease and diabetes mellitus.[23,392,394,395] Second, they present more often with shortness of breath, fatigue or with jaw and neck discomfort and less frequently with typical chest pain.[23,24,393] In addition, clinicians perceive women to be at lower risk.[396] Furthermore, in the setting of NSTE-ACS, cardiac troponins are less likely to be elevated and ECG is more frequently non-diagnostic in women than men.[397–400] These factors may lead to a preferential referral of women with suspected NSTE-ACS to hospitals without cardiac catheterization facilities, adding delay to diagnosis and treatment.[401]

There is no convincing evidence for a gender-related difference in the efficacy and safety of currently available antithrombotic drugs. Moreover, women derive a benefit from an early invasive strategy similar to that of men.[323,395] Compared with men, women with NSTE-ACS, particularly those <60 years of age, have a two-fold higher risk of in-hospital death, which subsequently gradually attenuates, leading to essentially identical unadjusted outcomes at 1 year for both genders.[324,402–404] Comparable outcomes at 1 year were confirmed in a registry analysis of 46 455 consecutive NSTE-ACS patients (32% women) reporting no difference in mortality at 1 year between men and women in crude analyses and after adjustment for propensity score and discharge medication.[395] In addition, the MATRIX study showed a similar advantage among women and men of the radial approach over the femoral one.[251] Women seem to have a lower risk of restenosis than men after implantation of a BMS or DES.[405] Data from different ACS registries such as CRUSADE and the Get With the Guidelines (GWTG) initiatives in the USA and MINAP in the UK suggest that the early hazard of women is related to less frequent use of evidence-based care.[403,406,407] Therefore strategies to promote guideline implementation in women with NSTE-ACS and awareness of gender equality in CV risk should be implemented.

## 5.8 Special populations and conditions

### 5.8.1 The elderly and frail patients

Elderly patients comprise a growing segment of the population presenting with NSTE-ACS. Although the age cut-off of 65 years has been commonly applied to define this patient group, higher cut-offs, i.e. 75 years or even 80 years, have been proposed.[408,409] While in European NSTE-ACS registries the proportion of patients >75 years of age was 27–34%,[408,410] those patients were underrepresented in RCTs (i.e. 13% in the TRITON-TIMI 38 study and 15% in the PLATO study).[148,153] In addition, due to a selection bias, elderly individuals enrolled in RCTs may not be representative of the population treated in everyday clinical practice.[409] The clinical presentation of NSTE-ACS is more often atypical in the elderly than in younger patients. Among the atypical presentations, dyspnoea is the leading symptom, while syncope, malaise and confusion are less frequently encountered.[411] On ECG, ST deviation is less frequently present in the elderly than in younger patients.[410] High-sensitivity

cardiac troponin assays have an excellent diagnostic performance in diagnosing early MI in the elderly. However, the specificity of the test is lower than in younger patients, and elevated troponin levels are more commonly associated with conditions other than ACS.[412] Age is a major predictor of in-hospital and 6-month mortality in NSTE-ACS patients.[410,413] In the context of revascularization, both PCI and CABG, procedure-related complications are more frequent in the elderly, including MI, heart failure, stroke, renal failure and bleeds.[410,414]

Elderly patients are less likely to receive evidence-based therapies and undergo an invasive strategy compared with younger patients. In the GRACE registry, coronary angiography was performed in 67% of patients <70 years of age compared with 33% in patients >80 years.[415] In the Australian national ACS registry, diagnostic angiography was performed in 70% of patients <75 years of age vs. 49% of patients >75 years.[416] In the CRUSADE experience, coronary revascularization was performed in 40.1% of patients 75–89 years of age vs. 12.6% in those ≥90 years.[414] In the Euroheart ACS survey ($n = 10\,253$), the PCI rate during index admission decreased progressively from 71% in men <55 years of age to 61% in those 75–84 years.[410]

Despite the lower rate of revascularization in the elderly, its benefit appears to be maintained at older age, as suggested by a subgroup analysis of the Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI 18) trial.[417] Consistent with this observation, a propensity-adjusted analysis of the German Acute Coronary Syndromes registry suggested that among patients ≥75 years of age, the invasive strategy improved in-hospital mortality [6.0% vs. 12.5%; adjusted OR 0.55 (95% CI 0.35, 0.86), $P < 0.001$] and non-fatal MI rate [9.6% vs. 17.3%; adjusted OR 0.51 (95% CI 0.35, 0.75), $P < 0.001$], as well as the 1-year mortality rate [OR 0.56 (95% CI 0.38, 0.81)].[408] Available data on the impact of an early invasive strategy in the elderly are largely derived from subgroup analyses of registries or RCTs. The Italian Elderly ACS trial randomized 313 patients ≥75 years of age hospitalized for ACS to a routine early invasive strategy with coronary angiography and, if appropriate, revascularization within 72 h or to an initial conservative strategy (angiography only for recurrent ischaemia).[418] The primary composite endpoint of death, MI, stroke, repeat hospitalization for CV causes or severe bleeding at 1 year was not significantly different between the invasive and the conservative groups [27.9% vs. 34.6%; HR 0.87 (95% CI 0.49, 1.56)], although these results cannot exclude a clinically important difference one way or the other.

One of the reasons for suboptimal administration of evidence-based medications in the elderly is that patients may more frequently have contraindications to medications. Accordingly, in an analysis of nonagenarians presenting with NSTE-ACS, 10–15% of patients were deemed to have contraindications for aspirin, beta-blockers and statins, while the proportion reached 20% for angiotensin-converting enzyme (ACE) inhibitors.[414] Nevertheless, registry data suggest that even in the very elderly, adherence to recommended therapies within 24 h of admission for NSTE-ACS reduces in-hospital mortality (11.1% vs. 18.9% for age >90 years and 6.0% vs. 14.7% for age 75–89 years for adherence vs. no adherence; $P < 0.001$).[414] The benefit was observed despite the increased risk of side effects from pharmacological treatment and, specifically, the increased risk of bleeding events associated with antithrombotic therapy in the elderly.[414,419] Of note, the choice of antithrombotic agent and dosage should be carefully adapted to renal function, as well as specific contraindications. Decisions on how to manage the individual elderly patient should be based on ischaemic and bleeding risk assessment, estimated life expectancy, co-morbidities, quality of life, patient values and preferences and the estimated risks and benefits of revascularization.[409]

Beyond biological age, cognitive and functional impairment, physical dependence and frailty should be considered in the evaluation of patients with NSTE-ACS, similar to what has been done in the assessment of candidates for transcatheter aortic valve implantation.[420] Frailty has been identified as a strong independent predictor of in-hospital and 30-day mortality in elderly patients presenting with NSTE-ACS.[421]

### 5.8.2 Diabetes mellitus

While 20–30% of European patients with NSTE-ACS have known diabetes mellitus, a similar proportion may have undiagnosed diabetes or impaired glucose tolerance.[422–425] In the setting of NSTE-ACS, diabetic patients are older, more frequently have pre-existing CV disease, hypertension and renal failure and are more likely to present with atypical symptoms.[411,426] During hospitalization, patients with diabetes mellitus are more prone to develop ACS-related complications, such as heart failure, stroke, reinfarction, renal failure and bleeds.[106,426] A pooled analysis of 15 459 patients with NSTE-ACS showed that diabetes was independently associated with an increased risk of 30-day [2.1% vs. 1.1%; OR 1.78 (95% CI 1.24, 2.56), $P < 0.001$] and 1-year mortality [7.2% vs. 3.1%; adjusted HR 1.65 (95% CI 1.30, 2.10), $P < 0.001$].[427] Compared with non-diabetic subjects, diabetic patients have a blunted antiplatelet response to conventional dosing regimens of clopidogrel and aspirin and less favourable outcomes following both PCI and CABG.[428,429]

In the setting of ACS, both patients with undiagnosed diabetes mellitus and those with newly detected glucose intolerance have an increased 30-day mortality compared with non-diabetic individuals.[422,430] Controversies exist as to the extent to which glycaemic control should be undertaken in diabetic patients with NSTE-ACS, as the deleterious impact of hypoglycaemia on CV outcomes has been increasingly recognized.[431] According to the 2013 ESC/European Association for the Study of Diabetes Guidelines, glucose-lowering therapies should be considered in NSTE-ACS patients with significant hyperglycaemia [glucose concentration >10 mmol/L (>180–200 mg/dL)] and the glucose targets adapted to possible co-morbidities to avoid severe hypoglycaemia [<5 mmol/L (<90 mg/dL)].[432–434] As a general rule, with more advanced CV disease, older age, longer diabetes duration and more co-morbidities, less stringent glucose control should be applied in the acute phase and at follow-up.

The optimal revascularization modality in diabetic patients with multivessel disease presenting with NSTE-ACS remains uncertain because no RCT has compared different strategies in this setting. The best available evidence is derived from trials comparing PCI and CABG in patients with multivessel CAD and stable symptoms.[379,435,436] The choice of revascularization modality in the individual diabetic patient should be based on multiple parameters,

including clinical presentation (e.g. ongoing ischaemia or haemodynamic/electrical instability), pattern and complexity of coronary disease, accessibility of the coronary lesions for PCI, suitability of the distal segments for bypass grafting, ischaemic burden, LV function and co-morbidities. Finally, clinical scores to assess coronary lesion complexity (i.e. SYNTAX) as well as predicted surgical mortality [e.g. assessed with EuroSCORE II and Society of Thoracic Surgeons (STS) scores] should be integrated in the decision process.[437] All patients with diabetes and complex multivessel disease should be discussed within a Heart Team.[380] Overall, the threshold for CABG should be lower in patients with diabetes than in individuals without diabetes mellitus, and in low surgical risk patients with multivessel CAD, CABG should be favoured over PCI, especially in the setting of complex disease.[379,435,436] In diabetic patients with ongoing ischaemia or haemodynamic instability, immediate coronary angiography is indicated and the best revascularization should be chosen on a case-by-case basis after discussion within the Heart Team, acknowledging the increased risk of performing cardiac surgery in the setting of ongoing ischaemia. DESs have dramatically reduced the need for repeat revascularization in diabetic patients and are recommended as the first choice.[240,241]

With respect to antithrombotic treatment, diabetic patients should be treated with the same agents and dosing regimen as non-diabetic individuals. The newer $P2Y_{12}$ inhibitors prasugrel and ticagrelor were found to be superior to clopidogrel in diabetic patients with ACS in the TRITON-TIMI 38 and PLATO trials, respectively.[438,439] While GPIIb/IIIa inhibitors have been shown to reduce mortality in diabetic patients with NSTE-ACS in the pre-clopidogrel era, their role in the context of DAPT needs to be elucidated.[440] Monitoring of contrast-induced nephropathy is especially important in diabetic patients after PCI (see section 5.8.3). There are insufficient data to support the frequent practice of stopping metformin 24–48 h prior to angiography or PCI in all patients, as the risk of lactate acidosis is negligible. Renal function should be carefully monitored after PCI in all patients on metformin. If renal function deteriorates in patients on metformin undergoing coronary angiography/PCI, it is recommended to withhold treatment for 48 h or until renal function has returned to its initial level.

### 5.8.3 Chronic kidney disease

It is recommended to assess kidney function in all NSTE-ACS patients using the eGFR, with special attention paid to elderly people, women and patients with low body weight. While chronic kidney disease (CKD) patients have a worse prognosis in the setting of NSTE-ACS than individuals with normal renal function, they less frequently receive evidence-based treatments such as antithrombotic agents and early invasive strategy.[446,447] The diagnosis of NSTE-ACS in patients with CKD may be more challenging, as both mild elevations in cardiac troponin and ECG abnormalities (e.g. associated with electrolyte disturbances or hypertensive heart disease) are frequent. Therefore new ECG changes should be differentiated from pre-existing abnormalities and absolute changes in cardiac troponin (i.e. increase and/or decrease) should be assessed in order to differentiate MI from conditions associated with chronic cardiomyocyte damage.

In the majority of cases, elevations in cardiac troponin should not be primarily attributed to impaired clearance and considered harmless, as cardiac conditions such as chronic coronary or hypertensive heart disease appear to be the most important contributor to troponin elevation in this setting.[41] Only in patients with severe renal dysfunction (e.g. eGFR $<30$ mL/min/1.73m$^2$) may troponin elevation be solely the result of impaired renal clearance. High-sensitivity cardiac troponin assays maintain high diagnostic accuracy, and therefore clinical utility, in patients with renal dysfunction. Among patients with renal dysfunction and elevated baseline cardiac troponin levels ($\geq$99th percentile), acute MI will be the most common diagnosis (range 45–80% depending on the assay used).[59]

The impact of an invasive strategy or antithrombotic treatment in NSTE-ACS patients with renal insufficiency has not been prospectively assessed. The SWEDEHEART registry examined the utilization and impact of an invasive strategy within 14 days of admission in 23 262 NSTEMI patients and documented that the more impaired the renal function, the lower the proportion of patients who underwent an invasive strategy: eGFR $\geq$90 mL/min/1.73m$^2$, 62%; eGFR 60–89 mL/min/1.73m$^2$, 55%; eGFR 30–59 mL/min/1.73m$^2$, 36%; eGFR 15–29 mL/min/1.73m$^2$, 14%; and eGFR $<15$ mL/min/1.73m$^2$ or dialysis, 15% ($P < 0.001$).[448] A Cox regression model with propensity score adjustment for the likelihood of invasive therapy and discharge medication was used to assess the association between early revascularization and 1-year mortality across renal function stages. After adjustment, the overall 1-year mortality was 36% lower [HR 0.64 (95% CI 0.56, 0.73), $P < 0.001$] with an invasive strategy; however, the benefit declined with greater reductions in renal function, with no impact on mortality among patients with eGFR $<15$ mL/min/1.73m$^2$ and in those receiving dialysis [HR 1.61 (95% CI 0.84, 3.09), $P = 0.15$]. In patients undergoing coronary angiography, hydration with isotonic saline (i.e. 12 h before and 24 h following) as well as close attention to minimize the total contrast load ($<4$ mL contrast/kg body weight and $<3.7$ times the eGFR value in millilitres) are recommended.[380]

The choice and dose of antithrombotic drugs need to be carefully considered in CKD. While most anticoagulants may need dose adjustment in renal insufficiency, this is not the case for oral antiplatelet agents.[449] Safety and efficacy data for the use of $P2Y_{12}$ inhibitors in stage 5 CKD patients (i.e. eGFR $<15$ mL/min/1.73m$^2$) are insufficient. Therefore in this setting, $P2Y_{12}$ inhibitors should be reserved for selected high-risk indications (i.e. coronary stent thrombosis prevention), with bleeding risk carefully weighed. In this context there is more safety experience with clopidogrel than ticagrelor or prasugrel.

Numerous antithrombotic agents are available for parenteral use, including eptifibatide, tirofiban, bivalirudin, enoxaparin and fondaparinux, and require different degrees of adjustment for renal function (*Tables 8*, *10* and *11* in the main text and section 5.8.3.1). No dose adjustment based on renal function is required for abciximab. However, because the potential risk of bleeding complications is increased in patients with stage 4 CKD (eGFR 15–29 mL/min/1.73m$^2$), the use of abciximab in CKD patients should be considered only after careful evaluation of the risks and benefits. Dose reductions of NOACs should also be considered in CKD patients.

#### *5.8.3.1 Dose adjustment of antithrombotic agents*

In patients with stage 3 or 4 CKD (eGFR 15–59 mL/min/1.73m$^2$), the clearance of eptifibatide is reduced by 50% and steady-state

plasma levels are approximately double. The maintenance dose of eptifibatide should therefore be reduced from 2.0 to 1.0 μg/kg/min in patients with an eGFR <50 mL/min/1.73m$^2$; eptifibatide is contraindicated in patients with severe renal impairment. In patients with stage 4 CKD (eGFR 15–29 mL/min/1.73m$^2$), the infusion rate of tirofiban should be adjusted from 0.1 to 0.05 μg/kg/min. UFH does not require dose adjustment in patients with stage 4 or 5 CKD (eGFR <29 mL/min/1.73m$^2$). Conversely, enoxaparin is eliminated predominantly via the renal pathway. As a consequence, it is recommended to extend the dosing interval of the maintenance dose of enoxaparin (1.0 mg/kg) from 12 h to 24 h in patients with stage 4 CKD (eGFR 15–29 mL/min/1.73m$^2$). In the case of fondaparinux, no dose reduction is required for patients with stage 2 or 3 CKD (GFR 30–89 mL/min/1.73m$^2$), whereas it should be avoided in patients with an eGFR <20 mL/min/1.73m$^2$. The infusion dose of bivalirudin may need to be reduced in patients with advanced CKD. Dose adjustment from 1.75 to 1.0 or 0.25 mg/kg/h should be considered in patients with stage 4 or 5 CKD, respectively. Long-term anticoagulation with warfarin requires careful dosing and more frequent INR monitoring in CKD patients.[450]

With regard to NOACs, it is advisable to assess renal function before starting therapy with dabigatran and to test it regularly in patients >75 years of age or with an eGFR <50 mL/min/1.73m$^2$. Since dabigatran is cleared primarily by the kidneys, leading to accumulation and hence potentially more bleeding complications, patients with CKD could theoretically benefit from a lower dose. The concomitant use of dabigatran and GPIIb/IIIa inhibitors should be avoided in patients with stage 4 CKD.[451] A dose modification of rivaroxaban from 20 to 15 mg once daily is required in patients with an eGFR <50 mL/min/1.73m$^2$, whereas it is not recommended in patients with stage 5 CKD.[452] With respect to apixaban, patients with severe renal impairment (eGFR 15–29 mL/min/1.73m$^2$) or 2 or more among serum creatinine ≥133 μmol/L (1.5 mg/dL), age ≥80 years or body weight ≤60 kg should receive apixaban at a lower dose of 2.5 mg twice daily. In patients with stage 5 CKD or undergoing dialysis, apixaban should not be administered.

### 5.8.4 Left ventricular dysfunction and heart failure

Heart failure is one of the most frequent and deadly complications of NSTE-ACS, especially in elderly patients, although its incidence may be declining.[84,467] Both depressed LVEF and clinical heart failure are independent predictors of mortality and other major adverse cardiac events in NSTE-ACS. Since CAD is the most frequent cause of heart failure with reduced LVEF, and hospitalizations from heart failure are increasing, the number of patients with pre-existing LV dysfunction/heart failure that presents with NSTE-ACS is expected to increase.[468] In the setting of NSTE-ACS, both heart failure at presentation and heart failure during hospitalization are associated with a worse prognosis.[84] The diagnosis of NSTE-ACS may be challenging in patients with heart failure since overt acute cardiac decompensation may itself cause chest discomfort and troponin elevation may be common even in the absence of associated obstructive CAD. In addition, the ECG in patients with heart failure may not be interpretable (bundle branch block or paced rhythm). Therefore coronary angiography may at times be needed to establish the diagnosis of NSTE-ACS. The revascularization strategy should be based on the coronary anatomy, LV function, co-morbidities and estimated surgical risk according to a Heart Team consensus and based on current recommendations.[380] Echocardiography should be performed before cardiac catheterization to gather information on LVEF, wall motion abnormalities, associated valvular heart disease and volume loading. In patients with reduced LVEF, the risk of any coronary revascularization is increased; this risk is also increased because of the commonly associated renal dysfunction. Nevertheless, an invasive assessment should not be withheld in these patients. In the absence of ongoing myocardial ischaemia or haemodynamic instability mandating urgent angiography, the timing of the invasive assessment should be carefully assessed on a case-by-case basis.

With respect to detailed medical management of acute heart failure, we refer the reader to dedicated guidelines.[469] The Intra-Aortic Balloon Pump in Cardiogenic Shock II (IABP-Shock II) trial, performed in patients with acute MI and cardiogenic shock revascularized or scheduled for revascularization but with no mechanical complications or >12 h duration, showed that counterpulsation did not reduce 30-day and 12-month mortality compared with standard treatment. Accordingly, this support should be considered for patients with mechanical complications of MI.[470] In selected patients with no contraindication for cardiac transplantation, a percutaneous LV assist device may be considered as a bridge to cardiac transplantation. In patients not eligible for transplant, the assist device may be considered as a bridge to recovery or with the goal of long-term support (destination therapy).[471–473] More on ventricular assist devices can be found in the 2014 ESC/European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization.[380]

Patients with NSTE-ACS and heart failure less frequently receive evidence-based therapies than individuals without heart failure, including beta-blockers and ACE inhibitors or angiotensin receptor blockers (ARBs), coronary angiography and revascularization.[84,467] Recommendations derived from post-MI studies may be extrapolated to NSTE-ACS patients with heart failure and are found in the respective guidelines.[469] The angiotensin–neprilysin inhibitor LCZ696, consisting of the neprilysin inhibitor sarcubitril and the angiotensin receptor blocker valsartan, has been investigated against the ACE inhibitor enalapril in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial, which enrolled 8442 patients with New York Heart Association (NYHA) class II–IV heart failure and LVEF ≤40%.[474] Among them, 60% and 43% had ischaemic cardiomyopathy and previous MI, respectively. The primary endpoint, i.e. death from CV causes or hospitalization for heart failure, was significantly reduced by 20% in the LCZ696 group [21.8% vs. 26.5%; HR 0.80 (95% CI 0.73, 0.87), $P < 0.001$].[474] The very promising results of this trial need to be replicated in the post-NSTE-ACS setting in order to recommend LCZ696 instead of an ACE inhibitor or an ARB in NSTE-ACS patients with moderate to severe heart failure and LVEF ≤40%.

### 5.8.5 Atrial fibrillation

Atrial fibrillation in its permanent or paroxysmal form is frequent in NSTE-ACS patients. This may rarely result from ischaemia, while elevation of ventricular filling pressures and atrial overload are the most common triggers of atrial fibrilllation in this setting. The development

of this arrhythmia occurs in 2–21% of patients with NSTE-ACS. For details, see the current heart failure and atrial fibrillation guidelines.[469,493] Atrial fibrillation increases the risk of worsening ischaemia, of developing heart failure and of thromboembolic complications. Atrial fibrillation complicating ACS is associated with increased in-hospital and long-term mortality.[493,494] Depending on the duration of atrial fibrillation, heart rate, haemodynamics and functional status of the patient, different therapeutic actions are required, ranging from rate control to urgent electrical cardioversion.

A particular diagnostic challenge results from the fact that patients with atrial fibrillation with rapid ventricular response may present with increased troponin levels as well as chest discomfort.[495] In a large-scale atrial fibrillation trial, 9.2% of patients had elevated high-sensitivity troponin I levels (>99th percentile), and this proportion may be higher in the setting of acute-onset atrial fibrillation.[495,496] Cardiac troponin dynamics in patients with atrial fibrillation and rapid ventricular rate may mimic type 1 MI. While in the presence of very high levels of troponin the likelihood of type 1 MI is high and coronary angiography is justified, in the majority of cases of atrial fibrillation and troponin elevation, ischaemia detection should be considered first. The management of anticoagulation and antiplatelet therapy is detailed in section 5.4 in the main text.

### 5.8.6 Anaemia

Anaemia is common in patients hospitalized for ACS and its prevalence ranges from 6.4 to 45%.[499] Persistent or worsening anaemia in patients with ACS is strongly associated with increased mortality, recurrent MI and major bleeds.[500] However, it is uncertain if anaemia itself is the determinant for poorer outcome or is a marker of co-morbid conditions such as renal insufficiency, poor nutrition, drug-induced gastrointestinal bleeds or malignancy. In the setting of ACS, it is critical to identify the cause of anaemia, and particularly occult bleeds, because of the need for antithrombotic therapy. The indication for coronary angiography, access site choice (radial approach favoured) as well as the need for revascularization must be carefully considered to avoid further blood loss.[501,502] The choice of antithrombotic agents needs to carefully weigh ischaemic and bleeding risks, favouring the use of shorter half-life or reversible agents. In the setting of anaemia related to an unknown/untreatable source, the use of a DES should be restricted due to the need for prolonged DAPT. Blood transfusion is discussed in section 5.5.8.

### 5.8.7 Thrombocytopenia

Thrombocytopenia is an independent predictor of poor outcomes, including death, major bleeds and life-threatening prothrombotic states.[503–506] Significant thrombocytopenia is defined as a platelet count <100 000/μL or a relative drop of >50% from baseline. Possible causes range from haemodilution and *in vitro* artefacts to increased platelet consumption/sequestration/destruction or decreased platelet production.[507] Blood sampling should be in non-ethylenediaminetetraacetic acid (EDTA) tubes, as EDTA can lead to platelet clumping and pseudo-thrombocytopenia.[507,508]

#### *5.8.7.1 Thrombocytopenia related to GPIIb/IIIa inhibitors*

In a pooled analysis of patients undergoing PCI, mild thrombocytopenia (defined as a platelet count of 50 000–100 000/μL) was reported in 4.2% of abciximab vs. 2.0% of placebo-treated patients [OR 2.13 (95% CI 1.52, 3.04), $P < 0.001$], whereas severe thrombocytopenia (defined as a platelet count of 20 000–50 000/μL) was reported in 1.0% (abciximab) vs. 0.4% (placebo) of patients [OR 2.48 (95% CI 1.18, 5.85), $P < 0.01$].[509] In a meta-analysis of 23 RCTs, there was a 51% proportional increase in the incidence of any thrombocytopenia with tirofiban treatment vs. placebo [OR 1.51 (95% CI 1.06, 2.16), $P = 0.02$].[510] In one large RCT, thrombocytopenia <100 000/μL was not found more frequently with eptifibatide vs. placebo (4.9% vs. 4.9%, $P = 0.98$),[503] but case series support a link between the two.[511,512] In a head-to-head comparison of abciximab vs. tirofiban, thrombocytopenia was reported in 2.4% and 0.5% of patients, respectively ($P < 0.001$);[504] in a subsequent meta-analysis of nine RCTs, the incidence of thrombocytopenia was 0.3% (tirofiban) vs. 2.4% (abciximab) [OR 0.28 (95% CI 0.08, 0.94), $P = 0.04$].[510]

Patients treated with GPIIb/IIIa inhibitors should undergo a platelet count at 8–12 h of first drug administration, or in case of bleeding complications, and again after 24 h; if abciximab is administered, then an additional platelet count within 4 h of first drug administration is appropriate. The infusion of GPIIb/IIIa inhibitors should be stopped if the platelet count falls to <100 000/μL or drops by >50% from baseline. Platelet transfusions are recommended when there is active bleeding associated with profound thrombocytopenia, but transfusions may be ineffective while reversibly binding inhibitors (eptifibatide or tirofiban) are still circulating ($t_{1/2}$ ~2 h for both drugs).[507] Prophylactic platelet transfusions may be considered for platelet counts <5000–10 000/μL.[513] In patients with major ongoing 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.[511] Patients experiencing thrombocytopenia following GPIIb/IIIa inhibitor administration should be counselled to avoid subsequent exposures.

#### *5.8.7.2 Heparin-induced thrombocytopenia*

In contrast to the non-immune, mild thrombocytopenia (i.e. platelet count >100 000/μL) that presents within 48–72 h of the onset of therapy in 10–20% of patients treated with UFH, and that generally resolves without complications despite continued UFH use, immune HIT is a potentially fatal prothrombotic disorder that occurs in ~0.5–3% of patients receiving this agent.[505] HIT must be suspected when the platelet count drops to <100 000/μL (although usually not <10 000–20 000/μL).[508,512,514] Typically the onset occurs 5–10 days after a first UFH exposure or sooner—within hours—after a subsequent exposure in the first 100 days from diagnosis.[515] In the absence of heparin-dependent antibodies, re-exposures occurring thereafter do not necessarily cause a relapse of the syndrome.[515] The underlying mechanism involves IgG antibodies against heparin-bound platelet factor 4 that cause intense platelet activation, release of procoagulant microparticles and an elevated risk of potentially fatal venous and arterial thrombosis (~50% of untreated patients).[514] As soon as HIT is suspected, immediate discontinuation of UFH, LMWH or other heparin products (including flushes, coated catheters, etc.) is mandatory and alternative antithrombin therapy with non-heparin anticoagulants must be introduced. The i.v. direct thrombin inhibitor argatroban is approved for this indication. Intravenous danaparoid is approved

in Europe, Canada, Japan and Australia. Fondaparinux and bivalirudin are potentially useful but not approved for HIT. Platelet transfusions may aggravate the process, given the underlying platelet activation.

#### 5.8.8 Patients requiring chronic analgesic or anti-inflammatory treatment

Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors (coxibs; i.e. celecoxib and etoricoxib in Europe), are often used for the symptomatic treatment of osteoarticular disorders, including osteoarthritis. All NSAIDs are inhibitors of COX-2, with variable COX-1 inhibition depending on individual COX isozyme selectivity.[516] Besides gastrointestinal toxicity (largely due to COX-1 inhibition), NSAIDs also share untoward COX-2-dependent CV effects.[517] These include (1) increased blood pressure and interference with the blood pressure lowering effect of antihypertensive drugs; (2) increased risk of major CV events, largely driven by a doubling of the risk of MI; and (3) increased risk of hospitalization due to heart failure.[518] While (1) and (3) are shared by all NSAIDs, the increased risk of coronary events has been convincingly established for coxibs, diclofenac and ibuprofen, but not for high-dose naproxen.[518] The size of this increased risk is proportional to a patient's baseline risk and appears to be related to the daily dose of the COX-2 inhibitor. Evidence of increased risk appears early, as suggested by short-term trials of coxib therapy among patients undergoing CABG, and is not attenuated by concomitant aspirin use.[517] Based on these findings, the EMA has deemed the use of coxibs, diclofenac and high-dose ibuprofen in patients at high CV risk as contraindicated. Other NSAIDs, including naproxen, should be used with caution in high-risk patients since they are likely to share the same mechanism-based untoward effects. Moreover, both ibuprofen and naproxen can interfere with the antiplatelet effect of low-dose aspirin.[517]

#### 5.8.9 Non-cardiac surgery

Optimal CV assessment and management of patients undergoing non-cardiac surgery has been the focus of recent guidelines while discontinuation of antiplatelet therapy in patients with coronary stents is discussed in section 5.2.6 in the main text.[179] Perioperative NSTE-ACS may occur in 5–11% of patients.[519,520] Type 1 MI (i.e. related to a coronary cause such as plaque rupture or thrombotic occlusion) accounts for a minority of troponin elevations postoperatively, while the main cause of perioperative myonecrosis consists of type 2 MI (i.e. secondary to an oxygen supply and demand mismatch).[519] As most of the patients with a perioperative MI do not experience ischaemic symptoms, and symptomatic and asymptomatic events seem to have an equally poor prognosis, routine monitoring of troponin levels after surgery in at-risk patients should be considered.[519,520] In-hospital mortality associated with perioperative MI ranges from 12% to 25%.[519] In the PeriOperative ISchemic Evaluation (POISE) study, the 30-day mortality rate was 11.6% in patients with perioperative MI compared with 2.2% in those without MI.[519] In the absence of contraindications related to the pathology requiring surgery or surgery itself, patients with NSTE-ACS after non-cardiac surgery should receive standard management in addition to aetiology-specific treatments (e.g. correction of anaemia, hypovolaemia, infection). Since limitations on antiplatelet and anticoagulant therapies may be imposed by the surgery or the underlying pathology, antithrombotic therapy should be individualized in agreement with the surgical team based on risk–benefit estimation. In NSTEMI patients in whom the risks of bleeding complications with antithrombotic drugs may outweigh the benefits, pharmacological treatment consists of beta-blockers and nitrates. In patients with haemodynamic instability of suspected ischaemic origin, immediate coronary angiography is indicated. Coronary angiography may be useful even in patients with a (temporary) contraindication to antiplatelet or anticoagulant therapy to estimate the ischaemic risk and assess the optimal timing of revascularization as well as the revascularization modality.