Antithrombotic therapy in patients with acute coronary syndrome complicated by cardiogenic shock or out-of-hospital cardiac arrest: a Joint Position Paper from the European Society of Cardiology (ESC) Working Group on Thrombosis, in association with the Acute Cardiovascular Care Association (ACCA) and European Association of Percutaneous Cardiovascular Interventions (EAPCI)

Diana A Gorog MB BS, MD, PhD, FESC,[1] Susanna Price MB BS, BSc, PhD, FESC,[2] Dirk Sibbing MHBA, FESC,[3] Andreas Baumbach MD, FESC,[4] Davide Capodanno MD, PhD,[5] Bruna Gigante MD, PhD,[6] Sigrun Halvorsen MD, PhD, FESC,[7] Kurt Huber MD, FESC,[8] Maddalena Lettino MD, FESC,[9] Sergio Leonardi MD, MHS,[10] Joao Morais MD, PhD, FESC,[11] Andrea Rubboli MD, FESC,[12] Jolanta M Siller-Matula MD, PhD,[13] Robert F Storey MD, DM, FESC,[14] Pascal Vranckx MD, PhD,[15] Bianca Rocca MD, PhD, FESC[16]

1. [a]Department of Medicine, National Heart & Lung Institute, Imperial College, London, United Kingdom and [b]Postgraduate Medical School, University of Hertfordshire, Hatfield, United Kingdom

2. [a]Intensive Care Unit, Royal Brompton Hospital, London, United Kingdom and and [b]Department of Medicine, National Heart & Lung Institute, Imperial College, London, United Kingdom

3. Ludwig-Maximilians-Universität, München and Medizinische Klinik und Poliklinik I, Campus Großhadern, München, Germany

4. Barts Heart Centre, William Harvey Research Institute, Bartshealth NHS Trust, Queen Mary University of London, West Smithfield, London, United Kingdom

5. Division of Cardiology, A.O.U. "Policlinico-Vittorio Emanuele", University of Catania, Catania, Italy

6. Department of Medicine, Unit of Cardiovascular Medicine, Karolinska Institutet, Stockholm, Sweden and [b]Department of Clinical Science, Danderyds Hospital, Danderyd, Sweden

7. Department of Cardiology, Oslo University Hospital Ulleval and University of Oslo, Oslo, Norway

8. 3rd Department of Medicine, Cardiology and Intensive Care Medicine, Wilhelminenhospital, Vienna, Austria and [b]Sigmund Freud University, Medical School, Vienna, Austria

9. Cardio-Thoracic and Vascular Department, San Gerardo Hospital, ASST-Monza, Monza, Italy

10.   Coronary Care Unit, University of Pavia and Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy.

11.   [a]Cardiology Division, Leiria Hospital Center, Pousos, Leiria, Portugal and [b]ciTechCare, Polytechnic of Leiria, Leiria, Portugal

12.   Department of Cardiovascular Diseases – AUSL Romagna, Division of Cardiology, Ospedale S. Maria delle Croci, Ravenna, Italy

13.   Department of Cardiology, Medical University of Vienna, Vienna, Austria

14.   Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom

15.   Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Hasselt, Belgium

16.   Department of Pharmacology**,** Catholic University School of Medicine**,** Rome, Italy

Abbreviations

ACS = acute coronary syndrome

ACT = activated clotting time

AF = atrial fibrillation

AMI = acute myocardial infarction

aPTT = activated partial thromboplastin time

CS = cardiogenic shock

CVVH = continuous venovenous hemofiltration

DDI = drug-drug interaction

DTI = direct thrombin inhibitor

ECLS = extracorporeal life support

ECMO = extracorporeal membrane oxygenation

GPI = glycoprotein IIb/IIIa inhibitor

HIT = heparin-induced thrombocytopenia

IABP = intra-aortic balloon pump

LMWH = low molecular weight heparin

LoE = level of evidence

LVAD = left ventricular assist device

NSTE-ACS = non-ST-elevation acute coronary syndrome

OAC = oral anticoagulant

OHCA = out-of-hospital cardiac arrest

PCI = percutaneous coronary intervention

PD = pharmacodynamic

pPCI = primary percutaneous coronary intervention

PK = pharmacokinetic

RCA = regional anticoagulation with citrate-buffered replacement solution

RCT = randomized controlled trial

RRT = renal replacement therapy

ST = stent thrombosis

STEMI = ST-segment-elevation myocardial infarction

TTM = targeted temperature management

TRA = transradial access

UFH = unfractionated heparin

Vd = volume of distribution

VKA = vitamin K antagonist

1. Introduction

The administration of timely and effective antithrombotic therapy is critical to improving outcome, including survival, in patients with acute coronary syndrome (ACS).[1] Achieving effective platelet inhibition and anticoagulation, with minimal risk, is particularly important in high-risk ACS patients, especially those with cardiogenic shock (CS) or those successfully resuscitated following out-of-hospital cardiac arrest (OHCA), who have a 30-50% risk of death or recurrent ischaemic event over the subsequent 30 days.[2,3] There are unique challenges to achieving effective and safe antithrombotic treatment in this cohort of patients that are not encountered in most other ACS patients. This position paper, led by the ESC Working Group on Thrombosis, in association with the Acute Cardiovascular Care Association (ACCA) and European Association of Percutaneous Coronary Interventions (EAPCI), examines issues related to this topic and provides consensus statements, based on best available evidence and expert opinion, on optimising treatment in these high-risk patients.

2. Definition of patient population

This consensus document focuses on patients presenting with CS or immediately post-OHCA, of presumed ischaemic aetiology.

Approximately 70% of survivors of OHCA have underlying coronary artery disease, with coronary occlusion or an unstable atherosclerotic plaque reported in 20-30% of cases, even in

the absence of ST-segment deviation on the ECG.[5] Almost all survivors of OHCA have CS

for at least a short time after return of spontaneous circulation and many undergo urgent or

emergency coronary angiography and percutaneous coronary intervention (PCI).

Haemodynamically, CS is generally defined as a fall in systolic blood pressure <90 mmHg for

at least 30 minutes in the absence of hypovolemia, with a cardiac index <1.8 $l/min/m^2$

without support or 2.0-2.2 $l/min/m^2$ with support, and in the presence of a raised pulmonary

capillary wedge pressure (>15 mm Hg).[2,3,6] Because haemodynamic measurements are rarely

available in the emergency setting, CS is conventionally defined as persistent hypotension

(systolic blood pressure <90 mm Hg) in the absence of hypovolemia, with clinical evidence of

hypoperfusion (which can include cool/clammy extremities, oliguria, altered mental status)

that is presumed to be due to cardiac dysfunction.[7] With regards to the recent Society for

Cardiovascular Angiography and Interventions (SCAI) definitions, we refer to stages C to E.[6]

2. Systematic Review

We performed a systematic review through search of PubMed/MEDLINE, Ovid/Embase, and

Cochrane databases up to 1 September, 2019 (Supplementary Figure 1). Two reviewers

performed a systematic review for each antithrombotic medication, and disagreements were

resolved in a panel discussion with an independent reviewer. Study selection involved

screening of titles and abstracts followed by full-text evaluation of potentially eligible studies.

We used an initial screening strategy of keywords related to shock, cardiac arrest, acute

coronary syndrome and acute myocardial infarction (AMI), and these were combined with

keywords antiplatelet, anticoagulant, or antithrombotic. We then performed a secondary

search of individual drugs (aspirin, clopidogrel, ticagrelor, prasugrel, cangrelor, abciximab,

tirofiban, eptifibatide, bivalirudin, heparin, and oral anticoagulants [OACs] including vitamin

K antagonists [VKAs] and non-VKA OACs) in combination with conditions with which

shock and cardiac arrest are associated (ACS, STEMI, AMI, primary PCI [pPCI], targeted

temperature management [TTM], therapeutic hypothermia, and atrial fibrillation). The study

selection and eligibility criteria, search strategy and information sources are detailed in

Supplementary Material Appendix 1. The results of the systematic review, together with

existing guidelines (as referenced), impact of disease state and organ dysfunction, as well as

pharmacokinetic and pharmacodynamic data were used to evaluate the evidence base for

antithrombotic therapy and inform the decision-making consensus statements.

3. Patient-related factors affecting pharmacological treatment

Complex pharmacokinetic (PK) variation in drug absorption, distribution, metabolism and

excretion occurs in critically-ill patients (Table 1) due to acute renal and/or hepatic

dysfunction, underlying illness, variable plasma protein concentration, drug-drug interactions

(DDIs), extracorporeal membrane oxygenation (ECMO), TTM and/or renal replacement

therapy (RRT) (Figure 1).[8–15] PK changes also depend on the drug characteristics (size,

lipophilicity, volume of distribution [Vd], protein binding) and may vary over time (hourly,

daily) within the same patient. PK data on antithrombotic drugs in critically-ill patients are

limited.

Shock can reduce the effectiveness of oral antithrombotic drugs due to delayed

administration, reduced gastrointestinal blood flow and motility, delayed gastric emptying

and/or diminished absorption.[16] Vasoactive drugs used to restore blood pressure do not *per se*

normalize splanchnic perfusion. Reduced peripheral perfusion may also impair the absorption

of subcutaneous drugs, such as low-molecular-weight heparins (LMWH), and therefore intravenous (i.v.) administration is preferable.[17]

CS may reduce hepatic blood flow, increase congestion and consequently impair hepatic function, decreasing biotransformation rate via the cytochrome P450 (CYP) enzymes.[18] VKAs are predominantly biotransformed by CYP3A4, 1A2, 2C9 and 2C19 and eliminated by the liver. Drugs used in CS, such as amiodarone, may generate DDIs interfering with these processes and necessitate frequent INR monitoring, if warfarin is used. Among the direct oral FXa inhibitors, CYP-dependent biotransformation is ~30% for apixaban and rivaroxaban and <10% for edoxaban.[19,20] Dabigatran metabolism is largely P-glycoprotein-dependent therefore dronedarone, amiodarone, verapamil and phenytoin generate clinically-relevant DDIs (Table 1).[19] DDIs specifically related to non-vitamin K antagonist OACs have been described elsewhere.[21] P2Y$_{12}$ inhibitors are contraindicated in patients with severe hepatic impairment.[22–24]

Since acute kidney injury (AKI) is common in CS,[13] medications with limited renal elimination are preferable. AKI can increase Vd, which affects maintenance rather than loading dosing, particularly for hydrophilic drugs. Moreover, fluid replacement and vasoactive drugs may generate temporarily augmented renal elimination (creatinine clearance >130ml/min/1.73m^2), enhancing excretion as well as reducing the half-life of renally-excreted drugs,[25] such as dabigatran and LMWHs. RRT can variably and unpredictably modify PK depending on RRT mode, dose, timing, filter material, surface area and flow rate.

Thus, frequent therapeutic drug monitoring with drug-specific assays is of particular clinical relevance in CS patients. VKA, LMWH and unfractionated heparin (UFH) can be monitored

with INR, anti-FXa activity and aPTT or activated clotting time (ACT) respectively, direct oral anti-Xa drugs may be monitored with specific anti-FXa assays and dabigatran with ecarin clotting time or diluted thrombin time.[21]

Consensus statements:

- *The risk of sub- or supra-therapeutic drug concentrations in CS indicates the relevance of and prompts the need for vigilance in anticoagulant drug monitoring*

4. Specific drug considerations

4.1 Aspirin

Aspirin is a first-line treatment in patients presenting with ACS, including those with OHCA or CS (Figure 2).[24] Aspirin should be administered as soon as possible, with a loading dose of 150–300 mg orally (non-enteric-coated formulation if available) or i.v. There are no randomized controlled trials (RCTs) assessing the effect of aspirin in CS, and data are extrapolated from early trials showing the benefit of aspirin in AMI.[26,27] Observational studies showed that patients with CS were less likely to receive aspirin than those without CS, which was associated with worse prognosis.[28–30] Among patients treated with primary percutaneous coronary intervention (pPCI) with CS or OHCA, the incidence of early stent thrombosis (ST) in those with residual treatment platelet reactivity assessed by impedance aggregometry while on standard aspirin dosing was 21.4% versus 1.8% in those without increased platelet reactivity.[31] There are sparse data on the optimal i.v. dose or the safety and efficacy of oral versus i.v. administration.[24] A

recent randomized study showed that a single dose of 250 or 500 mg i.v. aspirin compared to 300 mg orally achieved faster and more complete inhibition of thromboxane generation and platelet aggregation, without increasing bleeding.[32] The ESC guidelines recommend i.v. loading with 75-250 mg if oral ingestion is not possible.[24] Although evidence is limited and based on PK or pharmacodynamic (PD) studies only, i.v. aspirin may be preferable, at least early following resuscitation (Figure 2).[33]

- *Consensus statement: In patients with CS or OHCA, i.v. aspirin 75-250mg may be preferable to oral aspirin loading*

4.2 P2Y$_{12}$ inhibitors

Differences in pharmacology between the oral P2Y$_{12}$ receptor inhibitors as well as the only available parenteral P2Y$_{12}$ inhibitor (cangrelor) may be particularly relevant in critically-ill patients (Table 2, Figure 1). Reduced absorption is the main limitation of oral P2Y$_{12}$ receptor inhibitors in ACS, particularly in patients with CS or post-OHCA, receiving sedation or TTM, with vomiting, gastroparesis or unable to swallow.[34] As clopidogrel is associated with high variability in response, including inadequate inhibition of ADP-induced platelet activation, and relatively slow onset of action, especially in patients with CS or TTM (up to 24 hours),[35] and since mean levels of platelet inhibition are significantly lower in those treated with clopidogrel compared to prasugrel or ticagrelor,[15] prasugrel and ticagrelor should be used in these patients when there is no excessive bleeding risk (Figure 2). There are no RCTs comparing the choice of

P2Y$_{12}$ inhibitor in this population, with evidence derived from extrapolation of ACS trials and pharmacodynamic studies assessing the rapidity and extent of platelet inhibition. Amongst patients with OHCA treated with PCI and TTM, a small retrospective study found no difference in ST between patients receiving clopidogrel and those receiving newer oral P2Y$_{12}$ inhibitors,[36] whilst another small observational study of 144 patients showed that ST was more frequent with clopidogrel than ticagrelor (11.4% vs. 0%; p= 0.04) without impact on mortality.[37] In a randomised study in 70 comatose survivors of OHCA undergoing PCI, crushed ticagrelor achieved faster and higher platelet inhibition than clopidogrel, without impact on ST or survival.[38] A meta-analysis of 5 studies including 290 patients receiving TTM after PCI showed no difference between clopidogrel and newer oral P2Y$_{12}$ inhibitors with regard to ST or in-hospital mortality.[39] A retrospective study of 88 patients with CS showed that cangrelor-treated patients had greater improvement in TIMI flow than those receiving oral P2Y$_{12}$ inhibitors, with similar rates of ST, 30-day and 1-year mortality.[40] A report from the Swedish Coronary Angiography and Angioplasty Registry comparing 899 patients undergoing pPCI with cangrelor to matched patients not receiving cangrelor (n=4614), including 273 STEMI patients with cardiac arrest, showed that although cangrelor was more often used in very high-risk patients (left main PCI, thrombus aspiration, and cardiac arrest), 30-day ST rates were similar in the two groups.[41] Recently, the ISAR REACT 5 trial showed the superiority of prasugrel over ticagrelor in ACS with respect to 1-year adverse cardiovascular events, but only 1.6% of these subjects had CS.[42] Prasugrel and ticagrelor are also associated with delayed onset of action in ST-elevation myocardial infarction (STEMI) (up to 8 h).[43,44] The administration of crushed ticagrelor or prasugrel through a naso-gastric tube, or orodispersible ticagrelor,[20] may be the optimal route to deliver dual antiplatelet therapy.[45,46] Administration of opiates such as morphine and fentanyl,

which inhibit gastric emptying and delay intestinal absorption, can delay the onset of effect of all oral $P2Y_{12}$ inhibitors, which might increase the risk of ischaemic events.[47–49] This delay in absorption with a potential reduced bioavailability is unlikely to be overcome by increasing the loading dose of $P2Y_{12}$ inhibitor, and may require administration of parenteral antiplatelet therapy to cover the lag time before onset of action of oral $P2Y_{12}$ inhibitors. Cangrelor provides one potential option in the initial treatment phase with subsequent transitioning to oral $P2Y_{12}$ inhibitors.[50,51] In patients with cardiac arrest, cangrelor was shown to inhibit platelet aggregation more effectively than orally-administered $P2Y_{12}$ inhibitors without increasing bleeding.[50] Unlike ticagrelor, the active metabolites of prasugrel and clopidogrel bind to the ADP-binding site on the $P2Y_{12}$ receptor, just like cangrelor, creating potential PD interaction when cangrelor and thienopyridines (prasugrel and clopidogrel) are co-administered.[51] Although one small study showed that prasugrel loading at the start of a 2-hour cangrelor infusion achieved sufficient platelet inhibition,[52] due to this potential PD interaction, prasugrel and clopidogrel should be administered at the end of cangrelor infusion (Table 2).[34,51] Ticagrelor can be administered at any time during or at the end of cangrelor infusion and may be the oral $P2Y_{12}$ inhibitor of choice for transition, although not formally proven in this population. The optimal duration of cangrelor infusion in pPCI patients has not been established but a 2-hour infusion may not sufficiently cover the delayed absorption of oral $P2Y_{12}$ inhibitors in some opiate-treated patients since their onset of action may be delayed for more than 6 hours.

Alternative potential parenteral strategies to cangrelor includes the administration of a glycoprotein IIb/IIIa inhibitor (GPI) bolus and infusion.[53,54] A particular concern is ventilated patients who may receive opioids such as fentanyl infusion, which theoretically could delay

absorption of oral $P2Y_{12}$ inhibitors much more than peri-PCI boluses of morphine, and this requires consideration in deciding the optimal parenteral strategy.

Consensus statements:

- *In patients with CS or TTM, prasugrel and ticagrelor should be used (as opposed to clopidogrel) when there is no excessive bleeding risk*

- *Clopidogrel should only be used in ACS patients with CS at high bleeding risk (such as those with prior intracranial bleeding, recent gastrointestinal bleeding or in those requiring OAC*

- *Administration of opiates, such as morphine and fentanyl, contributes to significant delay in the absorption of clopidogrel, prasugrel and ticagrelor, which might increase the risk of ischaemic events*

- *Parenteral antithrombotic therapy should be considered to cover the period before onset of action of oral $P2Y_{12}$ inhibitors. Cangrelor is preferred due to lower bleeding risk, unless there is no-reflow or bailout during PCI, when GPI can be considered*

4.3 Glycoprotein IIb/IIIa inhibitors

GPI, including abciximab, eptifibatide and tirofiban may reduce major adverse cardiac events, including death, AMI, and urgent revascularization, particularly in high-risk ACS patients undergoing PCI,[55,56] although most evidence was obtained before more potent $P2Y_{12}$ inhibitors were routinely used in ACS. [56,57] There are no adequately-powered RCTs assessing the efficacy

and safety of GPI in CS or OHCA settings, with evidence for use extrapolated from ACS studies in the general population. The PRAGUE-7 prospective, open-label, randomised study of 80 patients with AMI and CS showed no benefit of routine compared to selective abciximab-use on 30-day outcomes, in patients treated with clopidogrel and aspirin.[57] However, small registries of ~100 patients each with AMI complicated by CS, show that abciximab-treated patients had a higher rate of procedural TIMI 3 flow and lower 30-day mortality, than those not treated with abciximab.[58–60] However, a larger registry of unselected pPCI patients revealed no difference in clinical outcomes, including ST, between patients treated with abciximab or bivalirudin, although CS was less prevalent in the bivalirudin group.[61] In a registry of 6,489 patients with CS undergoing PCI, abciximab use was more frequent in patients who survived compared to those who died (47.3% vs. 52.1%, $p < 0.0002$) but was not a predictor of 30-day mortality.[2] GPI potentially may be most beneficial in ACS patients with CS or after OHCA.[55,56] Whereas GPI are conventionally administered by i.v. bolus followed by infusion,[56] similar efficacy has been reported for intracoronary or intralesional bolus-only administration.[62,63] Although existing guidelines state that GPI may only be considered in specific 'bail-out' situations including high intraprocedural thrombus burden, slow flow, or no-flow with abrupt vessel closure or in high-risk PCI in $P2Y_{12}$-inhibitor naïve patients,[64] in the setting of CS or OHCA, we consider that GPI may also be used as bridge to achieve sufficient platelet inhibition whilst awaiting onset of oral $P2Y_{12}$ inhibitor effect. GPI treatment appears particularly suitable for critically-ill patients for whom short duration of treatment is crucial. Because the effect is comparable between the various agents,[55,56] GPI may be used interchangeably, with consideration given to route of elimination and half-life of different agents (Table 2), although abciximab has recently been withdrawn in the Europe. Recently published data on a short duration of tirofiban in morphine-

treated STEMI patients show significant reduction in acute ST with acceptable bleeding penalty,[53] although larger prospective studies are warranted to explore the safety of this approach. Irrespective of the route of administration, or the concomitant P2Y$_{12}$ inhibitor used, GPI treatment is associated with increased bleeding risk.[55,56]

Consensus statements:

- *GPI administration in ACS patients with CS or OHCA undergoing PCI, may improve outcomes*
- *GPI may be used as bridge to achieve sufficient platelet inhibition whilst awaiting onset of oral P2Y$_{12}$ inhibitor treatment*
- *GPI use increases the risk of bleeding*

4.4 Heparins

Compared with UFH, LMWHs and fondaparinux have more predictable pharmacokinetics.[64] The use of LMWHs may be less ideal in the setting of CS, particularly in the aftermath of PCI, because of the high prevalence of AKI and acute liver injury in this population.[65,66] In addition, crossover of UFH and LMWHs is discouraged in the setting of PCI.[64] As such, in the absence of RCTs in this cohort, i.v. UFH might be preferable for CS patients either before, during or for continued anticoagulation after PCI, similarly to patients without CS (Figures 2 and 3).[64] There are no clinical studies assessing the effect of heparin or the choice of heparin on outcomes in CS. In the CULPRIT-SHOCK trial, where choice of anticoagulant agent was left to operator discretion, UFH and LMWHs were used in ~80% and 15% of patients,

respectively, whilst 5% received bivalirudin.[66] In current guidelines for myocardial revascularization, an i.v. bolus of 70-100 U/Kg UFH is recommended as the standard anticoagulant for PCI in both non-ST-segment elevation ACS and STEMI.[64] A reduced dose (50-70 U/Kg) may be preferable in case of co-administration with GPI.[64] Enoxaparin should be considered to support PCI as an alternative to UFH, particularly in patients pre-treated with subcutaneous enoxaparin.[67] During PCI, the dose of UFH should be adjusted according to ACT and, if necessary, reversed by protamine sulphate, in case of life-threatening bleeding. During TTM, UFH dose requirements are reduced and prolonged infusion interruption may be required to allow adequate drug clearance, mandating tight drug monitoring using ACT.[68,69]

Consensus statements:

- *UFH is the heparin of choice for CS patients either before or during PCI or for continued anticoagulation after PCI*
- *An i.v. bolus dose of 70-100 U/Kg UFH is preferred as the standard anticoagulant for PCI in the setting of both non-ST-segment elevation ACS and ST-segment elevation myocardial infarction*
- *Reduced dose UFH (50-70 U/Kg) should be considered in case of planned concomitant GPI use*
- *UFH dosing is reduced in TTM and prolonged infusion interruption may be required to allow adequate drug clearance, guided by ACT*

4.5 Direct intravenous thrombin inhibitors (DTI)

Intravenous DTIs inhibit both soluble thrombin and fibrin-bound thrombin.[70] Other key advantages include more predictable anticoagulant effect compared with UFH due to lack of binding to plasma proteins and the absence of possible heparin-induced thrombocytopenia (HIT).[71,72] Bivalirudin has been extensively evaluated across the spectrum of ACS and PCI.[73–84] Compared to UFH, use of bivalirudin, with or without GPI, may reduce bleeding complications.[85,86] There are no RCTs assessing bivalirudin in CS or OHCA, with evidence extrapolated from data in ACS or STEMI patients undergoing PCI. A small retrospective registry of patients with CS undergoing pPCI showed that patients treated with bivalirudin had significantly lower in-hospital mortality than patients treated with GPI.[87] Although there is little evidence specifically in CS and OHCA, bivalirudin may be considered, especially in patients at high bleeding risk, including CS.[87]

- *Consensus statement: Bivalirudin may be considered as an alternative to UFH*

4.6 Antithrombotic strategies in relation to radial vs. femoral PCI procedure

Because of the substantial reduction in major bleeding compared to the transfemoral approach, transradial access (TRA) should be the default vascular access whenever possible, including in patients undergoing PCI for CS or post-OHCA.[88] In meta-analyses of patients undergoing pPCI, including those with CS, TRA reduced major bleeding by > 50% and 30-day mortality by 35-50% compared with transfemoral access.[88,89] In another meta-analysis including 27,491 ACS patients, TRA reduced bleeding preferentially with UFH while bivalirudin reduced bleeding only with femoral access, suggesting limited benefit of the

combined use of bivalirudin and TRA.[90] The reduction of access-site-related major bleeding with TRA is particularly attractive in critically-ill patients who may be at high bleeding risk when intense peri-procedural antithrombotic therapy (such as GPI) is used.[86,91] However, TRA implementation in these patients is suboptimal,[91,92] probably as a consequence of a steeper learning curve, challenges with using large bore catheters, slightly longer procedural times, as well as perceived logistical challenges including wrist pronation in unconscious patients.

Consensus statements:

- *Transradial approach should be the default strategy in ACS patients undergoing PCI with CS or OHCA, including in intubated and ventilated patients*
- *A transradial approach effectively minimizes bleeding in this context*

5. Early post-PCI antithrombotic management in the intensive care unit

5.1 Targeted temperature management (TTM)

TTM, defined as body temperature between 32°C and 34°C, provides neurologic protection for survivors of OHCA who remain unconscious after return of spontaneous circulation.[93] During TTM, UFH requirement is drastically reduced, and guideline-recommended UFH dosing protocols should therefore not be used.[68,69] The UFH dose should be reduced by roughly 50% and frequent aPTT monitoring both during cooling and rewarming should be performed (Figure 3).[69]

TTM has been associated with increased platelet activation in some studies[94] and reduced platelet reactivity in others.[95,96] In resuscitated patients, TTM may cause mild platelet dysfunction although this has not been associated with an increased risk of bleeding in the absence of acidosis.[97] Reduced platelet inhibition on aspirin has been observed after hypothermia and may be partly related to increased platelet turnover.[98] Small studies in resuscitated patients show increased platelet reactivity to arachidonic acid and collagen three days after a loading dose of 150-300 mg i.v. aspirin[99] and a daily dose of 100 mg i.v. compared to 100 mg orally was associated with greater platelet inhibition.[98] In the setting of TTM,[21] i.v. aspirin administration is preferred.[50] In the setting of TTM, lower plasma concentration of active clopidogrel metabolites and attenuated $P2Y_{12}$-dependent platelet inhibition are reported, compared to patients without TTM.[100] In a meta-analysis of 5 randomized and non-randomized studies comprising of 290 patients receiving TTM, administration of ticagrelor and prasugrel was not associated with a lower incidence of ST or in-hospital mortality compared to clopidogrel.[39] Analysis of >49,000 patients with cardiac arrest undergoing PCI did not show an increased incidence of ST in patients treated with TTM compared to no TTM (3.9 vs 4.7%, p=0.61), irrespective of antiplatelet treatment type.[14] In 25 resuscitated ACS patients treated with TTM, cangrelor achieved greater platelet inhibition than oral $P2Y_{12}$ inhibitors, without an increase in bleeding.[50] Routine use of GPI with TTM should be avoided because of the higher incidence of bleeding without significant improvement in outcome,[101] possibly attributable to TTM-mediated effects on platelet function that can be direct and indirect, through augmentation of GPI effects.[102]

Consensus statements:

In resuscitated patients treated with PCI and TTM

- *Intravenous aspirin may be preferable for the first 2-3 days post-PCI before switching to oral therapy*
- *Crushed/orodispersible ticagrelor or crushed prasugrel administered through a naso-gastric tube or i.v. cangrelor are preferred for the first 2-3 days post-PCI before switching to oral antiplatelet therapy*
- *UFH, if required, should be titrated downward and strictly monitored to maintain aPTT within therapeutic range*
- *Routine GPI use during TTM should be avoided to reduce bleeding complications*

5.2 Haemofiltration

Continuous venovenous haemofiltration (CVVH) is commonly used as RRT in critically ill patients (Figure 3). The impact of RRT on effectiveness of antithrombotic therapy is highly variable, largely unpredictable since PK data are often lacking, and may depend on RRT mode, dose, timing, filter material, surface area and flow rate.[103,104] Anticoagulation, required to guarantee patency and functioning of the circuit,[105] can be achieved with low-dose UFH, LMWH, mesilates or prostaglandins, as well as regional citrate anticoagulation (RCA). Systemic UFH or RCA are the main strategies used, with UFH used most commonly, due to ease-of-use and ability to monitor, although side effects include major or minor bleeding in up to 50% of cases[106] and HIT. Contraindications to RCA include acute liver failure (transaminases >1000 units/L) and lactate >8 mmol/L. Studies comparing systemic UFH and

RCA show no difference in mortality, but RCA appears superior to UFH in prolongation of circuit life and reduction in bleeding.[106–110]

Consensus statements:

- *RCA (if available) and systemic UFH (with aPTT monitoring) are the preferred anticoagulant strategies in patients undergoing CVVH*
- *In patients with acute liver failure and lactic acidosis, RCA is contraindicated*

6. Antithrombotic treatment in critically-ill patients on circulatory or left ventricular assist devices

Patients with CS and/or OHCA may require mechanical circulatory support. Acutely, support provided includes left and/or right-sided cardiac support with/without an oxygenator (e.g. ECMO)[111] or isolated left-sided support, including the Impella device.[7] To avoid clotting of the circuit and reduce the risk of embolization, anticoagulation is required for left-sided support as long as mechanical support is in place (Figure 3). Anticoagulation is usually achieved with i.v. UFH in the acute setting.[112] There are few data pertaining to other anticoagulants[113] and DTI should be considered only when UFH is contraindicated (e.g. allergy to UFH or HIT). The degree of anticoagulation depends on the device and the clinical setting, with ACT usually between 180 and 300 s.[114] Effectiveness of anticoagulation can be monitored through different tests that include aPTT, ACT, anti-FXa levels and thromboelastography.[115–117] With ECMO, anticoagulation is monitored by aPTT and heparin

concentration measured by anti-FXa assay.[116,117] The choice of test depends on the unit and the expertise available. Emerging data, mainly from paediatric observational studies indicate heparin concentration measured by anti-FXa assay is emerging as superior to aPTT and ACT for monitoring of UFH anticoagulation in the setting of ECMO,[118–122] and studies are urgently needed to define the optimal monitoring strategy in adults. In patients with concomitant sepsis, anticoagulation should be interpreted synthesising all available laboratory investigations and in discussion with a haematologist, in particular where excessive bleeding or thrombosis, or simultaneous bleeding and/or thrombosis, occur.

Both bleeding and ischaemic complications occur frequently, often simultaneously, in patients requiring acute mechanical circulatory support.[123] A meta-analysis of 1,866 CS patients reported incidences of lower limb ischaemia in >15%, stroke in >5% and major or significant bleeding in >40% of patients.[124] Over-anticoagulation[125] as well as low platelet count, often seen in CS, can exacerbate bleeding on ECMO.[126,127] Patients frequently develop acquired von Willebrand factor defect within 24 hours of ECMO implantation, which significantly increases bleeding risk.[128]

The impact of extracorporeal life support on the effectiveness and safety of antithrombotic drugs is unclear. Patients with ACS and urgent PCI should receive dual antiplatelet therapy, comprising of aspirin and a $P2Y_{12}$ receptor inhibitor (usually clopidogrel considering that such patients will be anticoagulated, resulting in administration of triple antithrombotic therapy where potent agents like prasugrel or ticagrelor are contraindicated). Since absorbtion of antiplatelet drugs is inconsistent in CS, when DAPT treatment is essential (such as recent

stent implantation in the left main stem or other high risk territory) this needs careful discussion with the haematologist and interventional cardiologist. Cangrelor could be considered in this setting due to its rapid offset of effect if bleeding were to occur. ECMO circuits may induce sequestration of lipophilic drugs (high partition coefficient), increase volume of distribution and reduce drug clearance, but data are limited to antimicrobials and sedatives, such as propofol and fentanyl.[129]

In CS complicating AMI, intra-aortic balloon-pump (IABP) implantation is no longer routinely recommended.[130] However, ECMO may be used in combination with IABP or Impella in order to offload the left ventricle.[131] Here, the level of anticoagulation should be determined by the type of mechanical circulatory support and underlying clinical condition.

Consensus statements:

- *Bleeding and ischaemic complications are both very common in patients on circulatory assist devices – often occurring simultaneously*
- *Anticoagulation may be required depending upon the type of device*
- *Expert input and close liaison with haematologist and interventional cardiologist is required and laboratory results interpreted in the clinical context*
- *UFH should be used in the acute setting*
- *Bivalirudin should be considered only when UFH is contraindicated*
- *ECMO circuits may induce sequestration of lypophilic drugs, increase volume of distribution and reduce drug clearance*

7. Patients with existing or new-onset atrial fibrillation

Atrial fibrillation (AF) occurs in approximately 20% of patients with ACS complicated by CS,[132] in comparison to only about 9% of patients with uncomplicated ACS.[133] The occurrence of AF in CS during the acute hospital stay does not appear to impact on all-cause mortality at 30 days and 1 year.[132] However, patients with CS and ACS showing AF already on admission have a higher mortality compared to those with new onset AF during hospitalization.[132,133]

Patients already taking an OAC pre-admission and who undergo emergency PCI should be treated with additional intraprocedural low-dose parenteral anticoagulation (e.g. enoxaparin 0.5 mg/kg i.v. or UFH 60 IU/kg i.v.), irrespective of the time of the last administration of OAC.[134,135]

There have been no randomized trials to assess optimal antithrombotic strategy in patients with AF and ACS with CS or OHCA, nor specifically comparing dual with triple antithrombotic therapy. Prevention of stroke and systemic embolism is an important consideration in this cohort.[133] By definition, almost all patients with ACS and CS will have a CHA_2DS_2VASC score of ≥2 (1 point each for congestive heart failure/left ventricular systolic dysfunction and vascular disease [in this case, coronary disease]). Given that patients with CS are at high ischaemic risk, including ST, these patients should receive anticoagulation in conjunction with dual antiplatelet therapy for the first month, unless there are unacceptable bleeding risks.[24,133–136]

Peri-PCI and in patients with AF who are haemodynamically unstable or on the ICU, anticoagulation is best managed with UFH because of the increased risk of bleeding from multi-organ dysfunction, urgent invasive procedures, the effects of TTM and artificial circuits such as RRT or circulatory/LV assist devices. Patients with AF on OAC should receive standard aspirin loading as described earlier for patients without OAC, and clopidogrel (600 mg loading dose) is the P2Y$_{12}$ inhibitor of choice.[24,134,135]

Consensus statements:

- *Triple antithrombotic therapy comprising of aspirin, clopidogrel and anticoagulation is recommended as the initial treatment for the first month in patients with AF and without unacceptable bleeding risk*

- *Anticoagulated patients with ACS and CS undergoing pPCI should receive additional low-dose parenteral anticoagulation regardless of the timing of the last dose of OAC*

- *Peri-PCI and in patients who are haemodynamically unstable on the ICU, anticoagulation is best managed with UFH*

- *OAC -treated patients with AF who present with ACS and CS should receive aspirin loading (as for patients without AF)*

- *Clopidogrel is the P2Y$_{12}$ inhibitor of choice (600 mg loading dose)*

8. Conclusions

Patients with CS or OHCA of presumed ischaemic cause constitute a very high-risk group, in whom minimising the risk of thrombosis is critical to improving outcome.

Both the physical and pharmacological impacts of CS, namely impaired drug absorption, metabolism, altered distribution and/or excretion, and associated multiorgan failure, and co-administered treatments such as opiates, TTM, RRT and ECMO, can have major impact on the effectiveness and safety of antithrombotic drugs.

Careful attention to the choice of antithrombotic agent(s), route of administration, minimisation of DDIs, therapeutic drug monitoring and factors that affect drug efficacy and safety, may reduce the risk of sub- or supra-therapeutic dosing and associated adverse events.

Clinical outcome data assessing efficacy of antithrombotic drugs patients with CS or OHCA, as well as studies on PK/PD, are urgently needed, especially regarding the interaction between opiates and oral P2Y$_{12}$ receptor inhibitors and the optimal anticoagulant regimen in patients on circulatory assist devices.

Figure Legends

Figure 1. Factors influencing antithrombotic therapy in patients with cardiogenic shock or out-of-hospital cardiac arrest

Abbreviations: AKI = acute kidney injury, CrCl = creatinine clearance, CS = cardiogenic shock, ECMO = extracorporeal membrane oxygenation, OHCA = out-of-hospital cardiac arrest, PCI = percutaneous coronary intervention, PK = pharmacokinetics, RRT = renal replacement therapy, TTM = targeted temperature management, Vd = volume of distribution.

Figure 2. Summary suggestions for initial antithrombotic therapy in patients with cardiogenic shock or out-of-hospital cardiac arrest

Abbreviations: GPI = glycoprotein IIb/IIIa inhibitor, HIT = heparin induced thrombocytopenia, NGT = nasogastric tube, PCI = percutaneous coronary intervention, pPCI = primary percutaneous coronary intervention, UFH = unfractionated heparin.

Figure 3. Summary of suggestions for subsequent antithrombotic therapy in patients with cardiogenic shock or out-of-hospital cardiac arrest

Abbreviations: ACS = acute coronary syndrome, aPTT = activated partial thromboplastin time, CS = cardiogenic shock, ECMO = extracorporeal membrane oxygenation, GPI = glycoprotein IIb/IIIa inhibitor, i.v.= intravenous, NGT = nasogastric tube, OHA = out-of-hospital cardiac arrest, PCI = percutaneous coronary intervention, pPCI = primary percutaneous coronary intervention, UFH = unfractionated heparin.

Supplementary Figures

Supplementary Figure 1. Consort diagram showing literature search and systematic review

Tables

Table 1. Pharmacokinetic mechanisms affecting antithrombotic drugs in critically-ill patients

Table 2. Antithrombotic therapy strategies in critically-ill patients

Characteristics of antithrombotic medications with specific relevant points pertaining to patients with cardiogenic shock or post-out of hospital arrest.

1. Van de Werf F. Decade in review - acute coronary syndromes: Successes and future objectives in acute coronary syndrome. *Nature Reviews Cardiology* 2014;**11**:624–625.

2. Kunadian V, Qiu W, Ludman P, Redwood S, Curzen N, Stables R, Gunn J, Gershlick A. Outcomes in patients with cardiogenic shock following percutaneous coronary intervention in the contemporary era: an analysis from the BCIS database (British Cardiovascular Intervention Society). *JACC Cardiovasc Interv* 2014;**7**:1374–1385.

3. Hochman J, Sleeper L, Webb J, Sanborn T, White H, Talley J, Buller C, Jacobs A, Slater J, Col J, McKinlay S, LeJemtel T. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *The New England Journal of Medicine* 1999;**341**:625–634.

4. The Oxford 2011 Levels of Evidence. *OCEBM Levels of Evidence Working Group Oxford Centre for Evidence-Based Medicine* 2011.

5. Radsel P, Knafelj R, Kocjancic S, Noc M. Angiographic characteristics of coronary disease and postresuscitation electrocardiograms in patients with aborted cardiac arrest outside a hospital. *The American Journal of Cardiology* 2011;**108**:634–638.

6. Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, Henry TD, Hollenberg SM, Kapur NK, O'Neill W, Ornato JP, Stelling K, Thiele H, Diepen S van, Naidu S. SCAI clinical expert consensus statement on the classification of cardiogenic shock: This document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. *Catheterization and Cardiovascular Interventions* 2019; 1-9.

7. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland J, Coats A, Falk V, González-Juanatey JR, Harjola V-PP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano G, Ruilope LM, Ruschitzka F, Rutten FH, Meer P van der, Group E. 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. *European Heart Journal* 2016;**37**:2129–2200.

8. Papadopoulos J, Smithburger PL. Common drug interactions leading to adverse drug events in the intensive care unit: management and pharmacokinetic considerations. *Critical Care Medicine* 2010;**38**:S126-35.

9. Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient--concepts appraised by the example of antimicrobial agents. *Advanced Drug Delivery reviews* 2014;**77**:3–11.

10. Stavchansky S, Tung I. Effects of hypothermia on drug absorption. *Pharmaceutical Research*

1987;**4**:248–250.

11. Ha MA, Sieg AC. Evaluation of Altered Drug Pharmacokinetics in Critically Ill Adults Receiving Extracorporeal Membrane Oxygenation. *Pharmacotherapy* 2017;**37**:221–235.

12. Ibrahim K, Christoph M, Schmeinck S, Schmieder K, Steiding K, Schoener L, Pfluecke C, Quick S, Mues C, Jellinghaus S, Wunderlich C, Strasser R, Kolschmann S. High rates of prasugrel and ticagrelor non-responder in patients treated with therapeutic hypothermia after cardiac arrest. *Resuscitation* 2014;**85**:649–656.

13. Smith BS, Yogaratnam D, Levasseur-Franklin KE, Forni A, Fong J. Introduction to drug pharmacokinetics in the critically ill patient. *Chest* 2012;**141**:1327–1336.

14. Shah N, Chaudhary R, Mehta K, Agarwal V, Garg J, Freudenberger R, Jacobs L, Cox D, Kern KB, Patel N. Therapeutic Hypothermia and Stent Thrombosis: A Nationwide Analysis. *JACC Cardiovascular Interventions* 2016;**9**:1801–1811.

15. Bednar F, Kroupa J, Ondrakova M, Osmancik P, Kopa M, Motovska Z. Antiplatelet efficacy of P2Y12 inhibitors (prasugrel, ticagrelor, clopidogrel) in patients treated with mild therapeutic hypothermia after cardiac arrest due to acute myocardial infarction. *Journal of Thrombosis and Thrombolysis* 2016;**41**:549–555.

16. Chapman MJ, Nguyen NQ, Fraser RJ. Gastrointestinal motility and prokinetics in the critically ill. *Current Opinion in Critical Care* 2007;**13**:187–194.

17. Erstad BL. Designing drug regimens for special intensive care unit populations. *World Journal of Critical Care Medicine* 2015;**4**:139.

18. Deitchman AN, Derendorf H. Measuring drug distribution in the critically ill patient. *Advanced Drug Delivery Reviews* 2014;**77**:22–26.

19. Hellwig T, Gulseth M. Pharmacokinetic and pharmacodynamic drug interactions with new oral anticoagulants: what do they mean for patients with atrial fibrillation? *The Annals of Pharmacotherapy* 2013;**47**:1478–1487.

20. Qamar A, Vaduganathan M, Greenberger NJ, Giugliano RP. Oral Anticoagulation in Patients With Liver Disease. *Journal of the American College of Cardiology* 2018;**71**:2162–2175.

21. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm A, Heidbüchel H, Group E. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *European heart journal* 2018;**39**:1330–1393.

22. European Medicines Agency. Clopidogrel - Summary of Product Characteristics.

23. European Medicines Agency. Brilique - Summary of Product Characteristics.

24. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio A, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *European Heart Journal* 2018;**39**:119–177.

25. Mahmoud SH, Shen C. Augmented Renal Clearance in Critical Illness: An Important Consideration in Drug Dosing. *Pharmaceutics* 2017;**9**.

26. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988;**2**:349–360.

27. Antithrombotic Trialists' Collaboration: Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;**373**:1849–1860.

28. Krumholz H, Radford M, Ellerbeck E, Hennen J, Meehan T, Petrillo M, Wang Y, Kresowik T, Jencks S. Aspirin in the treatment of acute myocardial infarction in elderly Medicare beneficiaries. Patterns of use and outcomes. *Circulation* 1995;**92**:2841–2847.

29. Dziewierz A, Siudak Z, Rakowski T, Dubiel JS, Dudek D. Predictors and in-hospital outcomes of cardiogenic shock on admission in patients with acute coronary syndromes admitted to hospitals without on-site invasive facilities. *Acute Cardiac Care* 2010;**12**:3–9.

30. Frilling B, Schiele R, Gitt A, Zahn R, Schneider S, Glunz H, Gieseler U, Baumgärtel B, Asbeck F, Senges J, et al. Characterization and clinical course of patients not receiving aspirin for acute myocardial infarction: results from the MITRA and MIR studies. *American HeartJjournal* 2001;**141**:200–205.

31. Tilemann L, Mohr SK, Preusch M, Chorianopoulos E, Giannitsis E, Katus HA, Müller OJ. Platelet function monitoring for stent thrombosis in critically III patients with an acute Coronary syndrome. *Journal of Interventional Cardiology* 2018;**31**:277–283.

32. Zeymer U, Hohlfeld T, Dahl J, Erbel R, Münzel T, Zahn R, Roitenberg A, Breitenstein S, Pap ÁF, Trenk D. Prospective, randomised trial of the time dependent antiplatelet effects of 500 mg and 250 mg acetylsalicylic acid i. v. and 300 mg p. o. in ACS (ACUTE). *Thrombosis and Haemostasis* 2017;**117**:625–635.

33. Noc M, Fajadet J, Lassen JF, Kala P, MacCarthy P, Olivecrona GK, Windecker S, Spaulding C, et al. Invasive coronary treatment strategies for out-of-hospital cardiac arrest: a consensus

statement from the European association for percutaneous cardiovascular interventions (EAPCI)/stent for life (SFL) groups. *EuroIntervention* 2014;**10**:31–37.

34. Tantry U, Chaudhary R, Kubica J, Bliden K, Gurbel PA. Cangrelor for the treatment of patients with Arterial Thrombosis. *Expert Opinion on Pharmacotherapy* 2018;**19**:1389–1398.

35. Schoergenhofer C, Hobl E-LL, Schellongowski P, Heinz G, Speidl WS, Siller-Matula J, Schmid M, Sunder-Plaßmann R, Stimpfl T, Hackl M, Jilma B. Clopidogrel in Critically Ill Patients. *Clinical Pharmacology and Therapeutics* 2018;**103**:217–223.

36. Gouffran G, Rosencher J, Bougouin W, Jakamy R, Joffre J, Lamhaut L, Dumas F, Cariou A, Varenne O. Stent thrombosis after primary percutaneous coronary intervention in comatose survivors of out-of-hospital cardiac arrest: Are the new P2Y12 inhibitors really more effective than clopidogrel? *Resuscitation* 2016;**98**:73–78.

37. Jiménez-Brítez G, Freixa X, Flores-Umanzor E, Antonio R, Caixal G, Garcia J, Hernandez-Enriquez M, Andrea R, Regueiro A, Masotti M, Brugaletta S, Martin V, Sabaté M. Out-of-hospital cardiac arrest and stent thrombosis: Ticagrelor versus clopidogrel in patients with primary percutaneous coronary intervention under mild therapeutic hypothermia. *Resuscitation* 2017;**114**:141–145.

38. Steblovnik K, Blinc A, Mijovski MB, Fister M, Mikuz U, Noc M. Ticagrelor Versus Clopidogrel in Comatose Survivors of Out-of-Hospital Cardiac Arrest Undergoing Percutaneous Coronary Intervention and Hypothermia: A Randomized Study. *Circulation* 2016;**134**:2128–2130.

39. Elbadawi A, Elgendy IY, Mohamed AH, Barssoum K, Alotaki E, Ogunbayo GO, Ziada KM. Clopidogrel Versus Newer P2Y12 Antagonists for Percutaneous Coronary Intervention in Patients with Out-of-Hospital Cardiac Arrest Managed with Therapeutic Hypothermia: A Meta-Analysis. *Cardiology and Therapy* 2018;**7**:185–189.

40. Droppa M, Vaduganathan M, Venkateswaran RV, Singh A, umita P, Roberts RJ, Qamar A, Hack L, Rath D, Gawaz M, Fuernau G, Waha-Thiele S de, Desch S, Schneider S, Ouarrak T, Jaffer FA, Zeymer U, Thiele H, Bhatt DL, Geisler T. Cangrelor in cardiogenic shock and after cardiopulmonary resuscitation: A global, multicenter, matched pair analysis with oral P2Y12 inhibition from the IABP-SHOCK II trial. *Resuscitation* 2019;**137**:205–212.

41. Grimfjärd P, Lagerqvist B, Erlinge D, Varenhorst C, James S. Clinical use of cangrelor: nationwide experience from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *European Heart Journal - Cardiovascular Pharmacotherapy* 2019;

42. Schüpke S, Neumann F-JJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, Richardt G, Liebetrau C, Witzenbichler B, Antoniucci D, Akin I, Bott-Flügel L, Fischer M, Landmesser U, Katus HA, Sibbing D, Seyfarth M, Janisch M, Boncompagni D, Hilz R, Rottbauer W, Okrojek R, Möllmann H, Hochholzer W, Migliorini A, Cassese S, Mollo P, Xhepa E, Kufner S, Strehle A, et al. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. *The New England*

Journal of Medicine 2019; Sept 1.

43. Parodi G, Valenti R, Bellandi B, Migliorini A, Marcucci R, Comito V, Carrabba N, Santini A, Gensini GF, Abbate R, Antoniucci D. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. *Journal of the American College of Cardiology* 2013;**61**:1601–1606.

44. Alexopoulos D, Xanthopoulou I, Gkizas V, Kassimis G, Theodoropoulos KC, Makris G, Koutsogiannis N, Damelou A, Tsigkas G, Davlouros P, Hahalis G. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. *Circulation Cardiovascular Interventions* 2012;**5**:797–804.

45. Rollini F, Franchi F, Hu J, Kureti M, Aggarwal N, Durairaj A, Park Y, Seawell M, Cox-Alomar P, Zenni MM, Guzman LA, Suryadevara S, Antoun P, Bass TA, Angiolillo DJ. Crushed Prasugrel Tablets in Patients With STEMI Undergoing Primary Percutaneous Coronary Intervention: The CRUSH Study. *Journal of the American College of Cardiology* 2016;**67**:1994–2004.

46. Parodi G, Xanthopoulou I, Bellandi B, Gkizas V, Valenti R, Karanikas S, Migliorini A, Angelidis C, Abbate R, Patsilinakos S, Baldereschi GJ, Marcucci R, Gensini GF, Antoniucci D, Alexopoulos D. Ticagrelor crushed tablets administration in STEMI patients: the MOJITO study. *Journal of the American College of Cardiology* 2015;**65**:511–512.

47. Montalescot G, Hof AW van, Lapostolle F, Silvain J, Lassen JF, Bolognese L, Cantor WJ, Cequier A, Chettibi M, Goodman SG, Hammett CJ, Huber K, Janzon M, Merkely B, Storey RF, Zeymer U, Stibbe O, Ecollan P, Heutz WM, Swahn E, Collet J-PP, Willems FF, Baradat C, Licour M, Tsatsaris A, Vicaut E, Hamm CW, Investigators A. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *The New England Journal of Medicine* 2014;**371**:1016–1027.

48. Meine TJ, Roe MT, Chen AY, Patel MR, Washam JB, Ohman E, Peacock W, Pollack CV, Gibler W, Peterson ED, Investigators C. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *American Heart Journal* 2005;**149**:1043–1049.

49. Farag M, Spinthakis N, Srinivasan M, Sullivan K, Wellsted D, Gorog DA. Morphine Analgesia Pre-PPCI Is Associated with Prothrombotic State, Reduced Spontaneous Reperfusion and Greater Infarct Size. *Thrombosis and Haemostasis* 2018;**118**:601–612.

50. Prüller F, Bis L, Milke OL, Fruhwald F, Pätzold S, Altmanninger-Sock S, Siller-Matula J, Lewinski F von, Ablasser K, Sacherer M, Lewinski D von. Cangrelor Induces More Potent Platelet Inhibition without Increasing Bleeding in Resuscitated Patients. *Journal of Clinical Medicine* 2018;**7**.

51. Angiolillo DJ, Rollini F, Storey RF, Bhatt DL, James S, Schneider DJ, Sibbing D, So DY,

Trenk D, Alexopoulos D, Gurbel PA, Hochholzer W, Luca L, Bonello L, Aradi D, Cuisset T, Tantry US, Wang TY, Valgimigli M, Waksman R, Mehran R, Montalescot G, Franchi F, Price MJ. International Expert Consensus on Switching Platelet P2Y12 Receptor-Inhibiting Therapies. *Circulation* 2017;**136**:1955–1975.

52. Hochholzer W, Kleiner P, Younas I, Valina CM, Löffelhardt N, Amann M, Bömicke T, Ferenc M, Hauschke D, Trenk D, Neumann F-J, Stratz C. Randomized Comparison of Oral P2Y12-Receptor Inhibitor Loading Strategies for Transitioning From Cangrelor: The ExcelsiorLOAD2 Trial. *JACC Cardiovasc Interventions* 2017;**10**:121–129.

53. Zwart B, Yazdani M, Ow KW, Richardson JD, Iqbal J, Gunn JP, Storey RF. Use of glycoprotein IIb/IIIa antagonists to prevent stent thrombosis in morphine-treated patients with ST-elevation myocardial infarction. *Platelets* 2019;1–5.

54. Siller-Matula J, Specht S, Kubica J, Alexopoulos D, Caterina R, Hobl E-LL, Jilma B, Christ G, Lang IM. Abciximab as a bridging strategy to overcome morphine-prasugrel interaction in STEMI patients. *British Journal of Clinical Pharmacology* 2016;**82**:1343–1350.

55. Safley D, Venkitachalam L, Kennedy KF, Cohen DJ. Impact of Glycoprotein IIb/IIIa Inhibition in Contemporary Percutaneous Coronary Intervention for Acute Coronary Syndromes: Insights From the National Cardiovascular Data Registry. *JACC Cardiovascular Interventions* 2015;**8**:1574–1582.

56. Rubboli A, Patti G. What is the Role for Glycoprotein IIb/IIIa Inhibitor Use in the Catheterization Laboratory in the Current Era? *Current Vascular Pharmacology* 2018;**16**:451–458.

57. Tousek P, Rokyta R, Tesarova J, Pudil R, Belohlavek J, Stasek J, Rohac F, Widimsky P. Routine upfront abciximab versus standard periprocedural therapy in patients undergoing primary percutaneous coronary intervention for cardiogenic shock: The PRAGUE-7 Study. An open randomized multicentre study. *Acute Cardiac Care* 2011;**13**:116–122.

58. Giri S, Mitchel J, Azar RR, Kiernan FJ, Fram DB, McKay RG, Mennett R, Clive J, Hirst JA. Results of primary percutaneous transluminal coronary angioplasty plus abciximab with or without stenting for acute myocardial infarction complicated by cardiogenic shock. *The American Journal of Cardiology* 2002;**89**:126–131.

59. Chan AW, Chew DP, Bhatt DL, Moliterno DJ, Topol EJ, Ellis SG. Long-term mortality benefit with the combination of stents and abciximab for cardiogenic shock complicating acute myocardial infarction. *The American Journal of Cardiology* 2002;**89**:132–136.

60. Antoniucci D, Valenti R, Migliorini A, Moschi G, Trapani M, Dovellini EV, Bolognese L, ntoro G. Abciximab therapy improves survival in patients with acute myocardial infarction complicated by early cardiogenic shock undergoing coronary artery stent implantation. *The American Journal of Cardiology* 2002;**90**:353–357.

61. Showkathali R, Davies JR, Parker M, Taggu W, Tang KH, Clesham GJ, Gamma RA, Sayer JW, Aggarwal RK, Kelly PA. Comparison of bivalirudin with heparin versus abciximab with heparin for primary percutaneous coronary intervention in 'Real World' practice. *Cardiovascular Revascularization Medicine* 2013;**14**:289–293.

62. Sun B, Liu Z, Yin H, Wang T, Chen T, Yang S, Jiang Z. Intralesional versus intracoronary administration of glycoprotein IIb/IIIa inhibitors during percutaneous coronary intervention in patients with acute coronary syndromes: A meta-analysis of randomized controlled trials. *Medicine* 2017;**96**:e8223.

63. Elbadawi A, Elgendy IY, Megaly M, Ha LD, Mahmoud K, Alotaki E, Ogunbayo GO, Baig B, Abuzaid A, Saad M, Depta JP. Meta-Analysis of Randomized Trials of Intracoronary Versus Intravenous Glycoprotein IIb/IIIa Inhibitors in Patients With ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. *The American Journal of Cardiology* 2017;**120**:1055–1061.

64. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic P, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO, ESC. 2018 ESC/EACTS Guidelines on myocardial revascularization. *European Heart Journal* 2019;**40**:87–165.

65. Diepen S van, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, Kilic A, Menon V, Ohman E, Sweitzer NK, Thiele H, Washam JB, Cohen MG, Lifeline A on on and on of and and. Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association. *Circulation* 2017;**136**:e232–e268.

66. Thiele H, Akin I, Sandri M, Fuernau G, Waha S de, Meyer-Saraei R, Nordbeck P, Geisler T, Landmesser U, Skurk C, Fach A, Lapp H, Piek JJ, Noc M, Goslar T, Felix SB, Maier LS, Stepinska J, Oldroyd K, Serpytis P, Montalescot G, Barthelemy O, Huber K, Windecker S, Savonitto S, Torremante P, Vrints C, Schneider S, Desch S, Zeymer U, et al. PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock. *The New England Journal of Medicine* 2017;**377**:2419–2432.

67. Silvain J, Beygui F, Barthélémy O, Pollack C, Bmj CM. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. *BMJ* 2012;344:e553.

68. Wahby KA, Jhajhria S, Dalal BD, Soubani AO. Heparin dosing in critically ill patients undergoing therapeutic hypothermia following cardiac arrest. *Resuscitation* 2014;**85**:533–537.

69. Fevold RT, Leung YT, Garofoli AC, White RD, Barsness GW, Dierkhising RA, Ou NN. Heparin dose adjustment required to maintain goal-activated partial thromboplastin time during therapeutic hypothermia. *Journal of Critical Care* 2015;**30**:574–578.

70. Weitz J, Leslie B, Hudoba M. Thrombin binds to soluble fibrin degradation products where it

is protected from inhibition by heparin-antithrombin but susceptible to inactivation by antithrombin-independent inhibitors. *Circulation* 1998;**97**:544–552.

71. Alban S. Pharmacological strategies for inhibition of thrombin activity. *Current Pharmaceutical Design* 2008;**14**:1152–1175.

72. Xiao Z, Théroux P. Platelet activation with unfractionated heparin at therapeutic concentrations and comparisons with a low-molecular-weight heparin and with a direct thrombin inhibitor. *Circulation* 1998;**97**:251–256.

73. Erlinge D, Omerovic E, Fröbert O, Linder R, Danielewicz M, Hamid M, Swahn E, Henareh L, Wagner H, Hårdhammar P, Sjögren I, Stewart J, Grimfjärd P, Jensen J, Aasa M, Robertsson L, Lindroos P, Haupt J, Wikström H, Ulvenstam A, Bhiladvala P, Lindvall B, Lundin A, Tödt T, Ioanes D, Råmunddal T, Kellerth T, Zagozdzon L, Götberg M, Andersson J, et al. Bivalirudin versus Heparin Monotherapy in Myocardial Infarction. *The New England Journal of Medicine* 2017;**377**:1132–1142.

74. Han Y, Guo J, Zheng Y, Zang H, Su X, Wang Y, Chen S, Jiang T, Yang P, Chen J, Jiang D, Jing Q, Liang Z, Liu H, Zhao X, Li J, Li Y, Xu B, Stone GW, Investigators B. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. *JAMA* 2015;**313**:1336–1346.

75. Kastrati A, Neumann FJ, Mehilli J, Byrne RA, Iijima R, Büttner HJ, Khattab AA, Schulz S, Blankenship JC, Pache J, Minners J, Seyfarth M, Graf I, Skelding KA, Dirschinger J, Richardt G, Berger PB, Schömig A, Investigators I-R. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *The New England Journal of Medicine* 2008;**359**:688–696.

76. Kastrati A, Neumann F-JJ, Schulz S, Massberg S, Byrne RA, Ferenc M, Laugwitz K-LL, Pache J, Ott I, Hausleiter J, Seyfarth M, Gick M, Antoniucci D, Schömig A, Berger PB, Mehilli J, Investigators I-R. Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. *The New England Journal of Medicine* 2011;**365**:1980–1989.

77. Lincoff A, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman J, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Kereiakes DJ, Rutsch W, Wilcox RG, Feyter PJ de, Vahanian A, Topol EJ, Investigators R-2. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003;**289**:853–863.

78. Mehran R, Lansky AJ, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Wong S, Nikolsky E, Gambone L, Vandertie L, Parise H, Dangas GD, Stone GW, Investigators H-A. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. *Lancet* 2009;**374**:1149–1159.

79. Shahzad A, Kemp I, Mars C, Wilson K, Roome C, Cooper R, Andron M, Appleby C, Fisher

M, Khand A, Kunadian B, Mills JD, Morris JL, Morrison WL, Munir S, Palmer ND, Perry RA, Ramsdale DR, Velavan P, Stables RH, investigators H-P trial. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet* 2014;**384**:1849–1858.

80. Steg PG, Hof A van, Hamm CW, Clemmensen P, Lapostolle F, Coste P, Berg J, Grunsven P, Eggink GJ, Nibbe L, Zeymer U, Orto M, Nef H, Steinmetz J, Soulat L, Huber K, Deliargyris EN, Bernstein D, Schuette D, Prats J, Clayton T, Pocock S, Hamon M, Goldstein P, Investigators E. Bivalirudin started during emergency transport for primary PCI. *The New England Journal of Medicine* 2013;**369**:2207–2217.

81. Stone GW, Ware JH, Bertrand ME, Lincoff A, Moses JW, Ohman E, White HD, Feit F, Colombo A, McLaurin BT, Cox DA, Manoukian SV, Fahy M, Clayton TC, Mehran R, Pocock SJ, Investigators A. Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: one-year results from the ACUITY trial. *JAMA* 2007;**298**:2497–2506.

82. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong S, Kirtane AJ, Parise H, Mehran R, Investigators H-A. Bivalirudin during primary PCI in acute myocardial infarction. *The New England Journal of Medicine* 2008;**358**:2218–2230.

83. Valgimigli M, Frigoli E, Leonardi S, Rothenbühler M, Gagnor A, Calabrò P, Garducci S, Rubartelli P, Briguori C, Andò G, Repetto A, Limbruno U, Garbo R, Sganzerla P, Russo F, Lupi A, Cortese B, Ausiello A, Ierna S, Esposito G, Presbitero P, Santarelli A, Sardella G, Varbella F, Tresoldi S, Cesare N de, Rigattieri S, Zingarelli A, Tosi P, Hof A van, et al. Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes. *The New England Journal of Medicine* 2015;**373**:997–1009.

84. Valgimigli M, Frigoli E, Leonardi S, Vranckx P, Rothenbühler M, Tebaldi M, Varbella F, Calabrò P, Garducci S, Rubartelli P, Briguori C, Andó G, Ferrario M, Limbruno U, Garbo R, Sganzerla P, Russo F, Nazzaro M, Lupi A, Cortese B, Ausiello A, Ierna S, Esposito G, Ferrante G, Santarelli A, Sardella G, Cesare N de, Tosi P, Hof A van, Omerovic E, et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. *Lancet* 2018;**392**:835–848.

85. Navarese E, Schulze V, Andreotti F, Kowalewski M, Kołodziejczak M, Kandzari DE, Rassaf T, Gorny B, Brockmeyer M, Meyer C. Comprehensive meta-analysis of safety and efficacy of bivalirudin versus heparin with or without routine glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndrome. *JACC: Cardiovascular Interventions* 2015;**8**:201–213.

86. Leonardi S, Frigoli E, Rothenbühler M, Navarese E, Calabró P, Bellotti P, Briguori C, Ferlini M, Cortese B, Lupi A, Lerna S, Zavallonito-Parenti D, Esposito G, Tresoldi S, Zingarelli A, Rigattieri S, Palmieri C, Liso A, Abate F, Zimarino M, Comeglio M, Gabrielli G, Chieffo A, Brugaletta S, Mauro C, Mieghem NM, Heg D, Jüni P, Windecker S, Valgimigli M, et al.

Bivalirudin or unfractionated heparin in patients with acute coronary syndromes managed invasively with and without ST elevation (MATRIX): randomised controlled trial. *BMJ* 2016;**354**:i4935.

87. Bonello L, Labriolle A, Roy P, Steinberg DH, Slottow TL, Xue Z, Smith K, Torguson R, Suddath WO, Satler LF, Kent KM, Pichard AD, Waksman R. Bivalirudin with provisional glycoprotein IIb/IIIa inhibitors in patients undergoing primary angioplasty in the setting of cardiogenic shock. *The American Journal of Cardiology* 2008;**102**:287–291.

88. Gandhi S, Kakar R, Overgaard CB. Comparison of radial to femoral PCI in acute myocardial infarction and cardiogenic shock: a systematic review. *Journal of Thrombosis and Thrombolysis* 2015;**40**:108–117.

89. Luca G, Schaffer A, Wirianta J, Suryapranata H. Comprehensive meta-analysis of radial vs femoral approach in primary angioplasty for STEMI. *Int J Cardiol* 2013;**168**:2070–2081.

90. Mina GS, Gobrial GF, Modi K, Dominic P. Combined Use of Bivalirudin and Radial Access in Acute Coronary Syndromes Is Not Superior to the Use of Either One Separately: Meta-Analysis of Randomized Controlled Trials. *JACC Cardiovascular Interventions* 2016;**9**:1523–1531.

91. Mamas MA, Anderson SG, Ratib K, Routledge H, Neyses L, Fraser DG, Buchan I, Belder MA de, Ludman P, Nolan J, Society B, Research N for. Arterial access site utilization in cardiogenic shock in the United Kingdom: is radial access feasible? *American Heart Journal* 2014;**167**:900-8.e1.

92. Valle JA, Kaltenbach LA, Bradley SM, Yeh RW, Rao SV, Gurm HS, Armstrong EJ, Messenger JC, Waldo SW. Variation in the Adoption of Transradial Access for ST-Segment Elevation Myocardial Infarction: Insights From the NCDR CathPCI Registry. *JACC Cardiovascular Interventions* 2017;**10**:2242–2254.

93. Neumar RW, Shuster M, Callaway CW, Gent LM, Atkins DL, Bhanji F, Brooks SC, Caen AR de, Donnino MW, Ferrer JM, Kleinman ME, Kronick SL, Lavonas EJ, Link MS, Mancini ME, Morrison LJ, O'Connor RE, Samson RA, hexnayder S, ngletary E, Sinz EH, Travers AH, Wyckoff MH, Hazinski MF. Part 1: Executive Summary: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2015;**132**:S315-67.

94. Xavier RG, White AE, Fox SC, Wilcox RG, Heptinstall S. Enhanced platelet aggregation and activation under conditions of hypothermia. *Thrombosis and Haemostasis* 2007;**98**:1266–1275.

95. Jeppesen AN, Hvas A-MM, Grejs AM, Duez C, Ilkjær S, Kirkegaard H. Platelet aggregation during targeted temperature management after out-of-hospital cardiac arrest: A randomised clinical trial. *Platelets* 2018;**29**:504–511.

96. Steblovnik K, Blinc A, Bozic-Mijovski M, Kranjec I, Melkic E, Noc M. Platelet reactivity in

comatose survivors of cardiac arrest undergoing percutaneous coronary intervention and hypothermia. *EuroIntervention* 2015;**10**:1418–1424.

97. Wolberg AS, Meng ZH, Monroe DM, Hoffman M. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. *The Journal of Trauma* 2004;**56**:1221–1228.

98. Llitjos J-FF, Sideris G, Voicu S, Sollier C, Deye N, Megarbane B, Drouet L, Henry P, Dillinger J-GG. Impaired biological response to aspirin in therapeutic hypothermia comatose patients resuscitated from out-of-hospital cardiac arrest. *Resuscitation* 2016;**105**:16–21.

99. Prüller F, Milke OL, Bis L, Fruhwald F, Scherr D, Eller P, Pätzold S, Altmanninger-Sock S, Rainer P, Siller-Matula J, Lewinski D von. Impaired aspirin-mediated platelet function inhibition in resuscitated patients with acute myocardial infarction treated with therapeutic hypothermia: a prospective, observational, non-randomized single-centre study. *Annals of Intensive Care* 2018;**8**:28.

100. Kaufmann J, Wellnhofer E, Stockmann H, Graf K, Fleck E, Schroeder T, Stawowy P, Storm C. Clopidogrel pharmacokinetics and pharmacodynamics in out-of-hospital cardiac arrest patients with acute coronary syndrome undergoing target temperature management. *Resuscitation* 2016;**102**:63–69.

101. Jiménez-Brítez G, Freixa X, Flores E, Penela D, Hernandez-Enríquez M, Antonio R, Caixal G, Garcia J, Roqué M, Martín V, Brugaletta S, Masotti M, Sabaté M. Safety of glycoprotein IIb/IIIa inhibitors in patients under therapeutic hypothermia admitted for an acute coronary syndrome. *Resuscitation* 2016;**106**:108–112.

102. Frelinger AL, Furman MI, Barnard MR, Krueger LA, Dae MW, Michelson AD. Combined effects of mild hypothermia and glycoprotein IIb/IIIa antagonists on platelet-platelet and leukocyte-platelet aggregation. *The American journal of cardiology* 2003;**92**:1099–1101.

103. Roberts DM, Sevastos J, Carland JE, Stocker SL, Lea-Henry TN. Clinical Pharmacokinetics in Kidney Disease: Application to Rational Design of Dosing Regimens. *Clinical Journal of the American Society of Nephrology* 2018;**13**:1254–1263.

104. Awdishu L, Bouchard J. How to optimize drug delivery in renal replacement therapy. *Seminars in Dialysis* 2011;**24**:176–182.

105. Uchino S, Kellum J, Bellomo R, Jama DG. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* 2005;294:813-8.

106. Wu M, Hsu Y, Bai C, Lin YF, Wu CH, Tam KW. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy: a meta-analysis of randomized controlled trials. *Am J Kidney Dis* 2012;59:810-8.

107. Schilder L, Nurmohamed S, Bosch FH, Purmer IM, Boer SS den, Kleppe CG, Vervloet

MG, Beishuizen A, Girbes AR, Wee PM, Groeneveld A, group C study. Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multi-center randomized clinical trial. *Critical Care* 2014;**18**:472.

108. Liu C, Mao Z, Kang H, Hu J, Zhou F. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: a meta-analysis with trial sequential analysis of randomized controlled trials. *Critical Care* 2016;**20**:144.

109. Huguet M, Rodas L, Blasco M, Quintana LF, Mercadal J, Ortiz-Pérez JT, Rovira I, Poch E. Clinical impact of regional citrate anticoagulation in continuous renal replacement therapy in critically ill patients. *The International Journal of Artificial Organs* 2017;**40**:676–682.

110. Borg R, Ugboma D, Walker D-MM, Partridge R. Evaluating the safety and efficacy of regional citrate compared to systemic heparin as anticoagulation for continuous renal replacement therapy in critically ill patients: A service evaluation following a change in practice. *Journal of the Intensive Care Society* 2017;**18**:184–192.

111. Stub D, Bernard S, Pellegrino V, Smith K, Walker T, Sheldrake J, Hockings L, Shaw J, Duffy SJ, Burrell A, Cameron P, Smit DV e, Kaye DM. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER trial). *Resuscitation* 2015;**86**:88–94.

112. Rossi M, Serraino GF, Jiritano F, Renzulli A. What is the optimal anticoagulation in patients with a left ventricular assist device? *Interactive Cardiovascular and Thoracic Surgery* 2012;**15**:733–740.

113. Wong JJ, Lam JCM, Mok YH, Lee JH. Anticoagulation in extracorporeal membrane oxygenation. *J Emergency Crit Care Med* 2018;**2**.

114. Rihal CS, Naidu SS, Givertz MM, Szeto WY, Burke JA, Kapur NK, Kern M, Garratt KN, Goldstein JA, Dimas V, Tu T. 2015 SCAI/ACC/HFSA/STS Clinical Expert Consensus Statement on the Use of Percutaneous Mechanical Circulatory Support Devices in Cardiovascular Care: Endorsed by the American Heart Assocation, the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencion; Affirmation of Value by the Canadian Association of Interventional Cardiology-Association Canadienne de Cardiologie d'intervention. *J Am Coll Cardiol* 2015;**65**:e7–e26.

115. Lequier et al. L. ELSO Anticoagulation Guideline 2014.

116. Winkler AM. Managing the Precarious Hemostatic Balance during Extracorporeal Life Support: Implications for Coagulation Laboratories. *Seminars in Thrombosis and Hemostasis* 2017;**43**:291–299.

117. Koster A, Ljajikj E, Faraoni D. Traditional and non-traditional anticoagulation management during extracorporeal membrane oxygenation. *Annals of Cardiothoracic Surgery* 2019;**8**:129–136.

118. Padhya D, Prutsky G, Nemergut M, Schears G, Flick R, Farah W, Wang Z, Prokop L, Murad M, Alsawas M. Routine laboratory measures of heparin anticoagulation for children on extracorporeal membrane oxygenation: Systematic review and meta-analysis. *Thrombosis Research* 2019;**179**:132–139.

119. Liveris A, Bello RA, Friedmann P, Duffy MA, Manwani D, Killinger JS, Rodriquez D, Weinstein S. Anti-factor Xa assay is a superior correlate of heparin dose than activated partial thromboplastin time or activated clotting time in pediatric extracorporeal membrane oxygenation. *Pediatric Critical Care Medicine* 2014;**15**:e72-9.

120. Delmas C, Jacquemin A, Vardon-Bounes F, Georges B, Guerrero F, Hernandez N, Marcheix B, Seguin T, Minville V, Conil J-MM, Silva S. Anticoagulation Monitoring Under ECMO Support: A Comparative Study Between the Activated Coagulation Time and the Anti-Xa Activity Assay. *Journal of Intensive Care Medicine* 2018;885066618776937.

121. Northrop MS, Sidonio RF, Phillips SE, Smith AH, Daphne HC, Pietsch JB, Bridges BC. The use of an extracorporeal membrane oxygenation anticoagulation laboratory protocol is associated with decreased blood product use, decreased hemorrhagic complications, and increased circuit life. *Pediatric Critical Care Medicine* 2015;**16**:66–74.

122. Niebler RA, Parker H, Hoffman GM. Impact of Anticoagulation and Circuit Technology on Complications During Extracorporeal Membrane Oxygenation. *American Society for Artificial Internal Organs* 2019;**65**:270–276.

123. Pavasini R, Cirillo C, Campo G, Menezes M, Biscaglia S, Tonet E, Ferrari R, Patel BV, Price S. Extracorporeal Circulatory Support in Acute Coronary Syndromes: A Systematic Review and Meta-Analysis. *Critical Care Medicine* 2017;**45**:e1173–e1183.

124. Cheng R, Hachamovitch R, Kittleson M, Patel J, Arabia F, Moriguchi J, Esmailian F, Azarbal B. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. *The Annals of Thoracic Surgery* 2014;**97**:610–616.

125. Jolivot P-AA, Pichereau C, Hindlet P, Hejblum G, Bigé N, Maury E, Guidet B, Fernandez C. An observational study of adult admissions to a medical ICU due to adverse drug events. *Annals of Intensive Care* 2016;**6**:9.

126. Guennec L, Cholet C, Huang F, Schmidt M, Bréchot N, Hékimian G, Besset S, Lebreton G, Nieszkowska A, Leprince P, Combes A, Luyt C-EE. Ischemic and hemorrhagic brain injury during venoarterial-extracorporeal membrane oxygenation. *Annals of Intensive Care* 2018;**8**:129.

127. Abrams D, Baldwin MR, Champion M, Agerstrand C, Eisenberger A, Bacchetta M, Brodie D. Thrombocytopenia and extracorporeal membrane oxygenation in adults with acute respiratory failure: a cohort study. *Intensive Care Medicine* 2016;**42**:844–852.

128. Kalbhenn J, Schmidt R, Nakamura L, Schelling J, Rosenfelder S, Zieger B. Early diagnosis of acquired von Willebrand Syndrome (AVWS) is elementary for clinical practice in patients treated with ECMO therapy. *Journal of Atherosclerosis and Thrombosis* 2015;**22**:265–271.

129. Cheng V, Abdul-Aziz M-HH, Roberts JA, Shekar K. Optimising drug dosing in patients receiving extracorporeal membrane oxygenation. *Journal of Thoracic Disease* 2018;**10**:S629–S641.

130. Thiele H, Zeymer U, Neumann F-JJ, Ferenc M, Olbrich H-GG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Böhm M, Ebelt H, Schneider S, Schuler G, Werdan K, Investigators I-SI. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *The New England Journal of Medicine* 2012;**367**:1287–1296.

131. Ouweneel DM, Schotborgh JV, Limpens J, Sjauw KD, Engström A, Lagrand WK, Cherpanath TG, Driessen AH, Mol BA de, Henriques JP. Extracorporeal life support during cardiac arrest and cardiogenic shock: a systematic review and meta-analysis. *Intensive Care Medicine* 2016;**42**:1922–1934.

132. Feistritzer H-JJ, Desch S, Zeymer U, Fuernau G, Waha-Thiele S de, Dudek D, Huber K, Stepinska J, Schneider S, Ouarrak T, Thiele H. Prognostic Impact of Atrial Fibrillation in Acute Myocardial Infarction and Cardiogenic Shock. *Circulation Cardiovascular Interventions* 2019;**12**:e007661.

133. Kalarus Z, Svendsen JH, Capodanno D, Dan G-AA, Maria E, Gorenek B, Jędrzejczyk-Patej E, Mazurek M, Podolecki T, Sticherling C, Tfelt-Hansen J, Traykov V, Lip GY, Fauchier L, Boriani G, Mansourati J, Blomström-Lundqvist C, Mairesse GH, Rubboli A, Deneke T, Dagres N, Steen T, Ahrens I, Kunadian V, Berti S. Cardiac arrhythmias in the emergency settings of acute coronary syndrome and revascularization: an European Heart Rhythm Association (EHRA) consensus document, endorsed by the European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Acute Cardiovascular Care Association (ACCA). *Europace* 2019;**21**:1603–1604.

134. Roffi M, Patrono C, Collet J-PP, 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. 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). *European Heart Journal* 2016;**37**:267–315.

135. Lip G, Collet J-PP, Haude M, Byrne R, Chung EH, Fauchier L, Halvorsen S, Lau D, Lopez-Cabanillas N, Lettino M, Marin F, Obel I, Rubboli A, Storey RF, Valgimigli M, Huber K, ESC. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm

Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). *Europace* 2019;**21**:192–193.

136. Boriani G, Fauchier L, Aguinaga L, Beattie JM, Lundqvist C, Cohen A, Dan G-AA, Genovesi S, Israel C, Joung B, Kalarus Z, Lampert R, Malavasi VL, Mansourati J, Mont L, Potpara T, Thornton A, Lip GY, ESC. European Heart Rhythm Association (EHRA) consensus document on management of arrhythmias and cardiac electronic devices in the critically ill and post-surgery patient, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), Cardiac Arrhythmia Society of Southern Africa (CASSA), and Latin American Heart Rhythm Society (LAHRS). *Europace* 2019;**21**:7–8.