

# 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** <sup>1,2,\*</sup>, **Susanna Price**<sup>1,3</sup>, **Dirk Sibbing**<sup>4</sup>, **Andreas Baumbach** <sup>5</sup>, **Davide Capodanno**<sup>6</sup>, **Bruna Gigante**<sup>7,8</sup>, **Sigrun Halvorsen**<sup>9</sup>, **Kurt Huber**<sup>10,11</sup>, **Maddalena Lettino** <sup>12</sup>, **Sergio Leonardi**<sup>13</sup>, **Joao Morais**<sup>14,15</sup>, **Andrea Rubboli**<sup>16</sup>, **Jolanta M. Siller-Matula**<sup>17</sup>, **Robert F. Storey**<sup>18</sup>, **Pascal Vranckx**<sup>19</sup>, and **Bianca Rocca**<sup>20</sup>

<sup>1</sup>Department of Medicine, National Heart & Lung Institute, Imperial College, London, UK; <sup>2</sup>Postgraduate Medical School, University of Hertfordshire, Hatfield, UK; <sup>3</sup>Intensive Care Unit, Royal Brompton Hospital, London, UK; <sup>4</sup>Ludwig-Maximilians-Universität, München, Medizinische Klinik und Poliklinik I, Campus Großhadern, München, Germany; <sup>5</sup>Barts Heart Centre, William Harvey Research Institute, Bartshealth NHS Trust, Queen Mary University of London, West Smithfield, London, UK; <sup>6</sup>Division of Cardiology, A.O.U. "Policlinico-Vittorio Emanuele", University of Catania, Catania, Italy; <sup>7</sup>Unit of Cardiovascular Medicine, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; <sup>8</sup>Department of Clinical Science, Danderyds Hospital, Danderyd, Sweden; <sup>9</sup>Department of Cardiology, Oslo University Hospital Ullevål, University of Oslo, Oslo, Norway; <sup>10</sup>3rd Department of Medicine, Cardiology and Intensive Care Medicine, Wilhelminenhospital, Vienna, Austria; <sup>11</sup>Sigmund Freud University, Medical School, Vienna, Austria; <sup>12</sup>Cardio-Thoracic and Vascular Department, San Gerardo Hospital, ASST-Monza, Monza, Italy; <sup>13</sup>Coronary Care Unit, University of Pavia and Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; <sup>14</sup>Cardiology Division, Leiria Hospital Center, Pousos, Leiria, Portugal; <sup>15</sup>ciTechCare, Polytechnic of Leiria, Leiria, Portugal; <sup>16</sup>Division of Cardiology, Department of Cardiovascular Diseases – AUSL Romagna, Ospedale S. Maria delle Croci, Ravenna, Italy; <sup>17</sup>Department of Cardiology, Austria Medical University of Vienna, Vienna, Austria; <sup>18</sup>Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK; <sup>19</sup>Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Hasselt, Belgium; and <sup>20</sup>Department of Pharmacology, Catholic University School of Medicine, Rome, Italy

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Timely and effective antithrombotic therapy is critical to improving outcome, including survival, in patients with acute coronary syndrome (ACS). 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 a recurrent ischaemic event over the subsequent 30 days. 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 focuses on patients presenting with CS or immediately post-OHCA, of presumed ischaemic aetiology, and examines issues related to thrombosis and bleeding risk. Both the physical and pharmacological impacts of CS, namely impaired drug absorption, metabolism, altered distribution and/or excretion, associated multiorgan failure, co-morbidities and co-administered treatments such as opiates, targeted temperature

\* Corresponding author. Tel: +44 207 034 8841, Fax: +44 207 0348935, Email: [d.gorog@imperial.ac.uk](mailto:d.gorog@imperial.ac.uk)

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management, renal replacement therapy and circulatory or left ventricular assist devices, can have major impact on the effectiveness and safety of antithrombotic drugs. Careful attention to the choice of antithrombotic agent(s), route of administration, drug-drug interactions, 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. This paper provides expert opinion, based on best available evidence, and consensus statements on optimising antithrombotic therapy in these very high-risk patients, in whom minimising the risk of thrombosis and bleeding is critical to improving outcome.

## Keywords

Antithrombotic medication • Cardiogenic shock • Acute coronary syndrome • Cardiac arrest  
• Antiplatelet • Thrombosis

## Introduction

The administration of timely and effective antithrombotic therapy is critical to improving outcome, including survival, in patients with acute coronary syndrome (ACS).<sup>1</sup> 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.<sup>2,3</sup> 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 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), examines issues related to this topic and provides consensus statements, based on best available evidence and expert opinion, on optimizing treatment in these high-risk patients.

## 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 stent thrombosis (ST)-segment deviation on the ECG.<sup>4</sup> 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 min in the absence of hypovolaemia, with a cardiac index <1.8 L/min/m<sup>2</sup> without support or 2.0–2.2 L/min/m<sup>2</sup> with support, and in the presence of a raised pulmonary capillary wedge pressure (>15 mmHg).<sup>2,3,5</sup> Because haemodynamic measurements are rarely available in the emergency setting, CS is conventionally defined as persistent hypotension (systolic blood pressure <90 mmHg) in the absence of hypovolaemia, with clinical evidence of hypoperfusion (which can include cool/clammy extremities, oliguria, altered mental status) that is presumed to be due to cardiac dysfunction.<sup>6</sup> With regards to the recent Society for

Cardiovascular Angiography and Interventions (SCAI) definitions, we refer to stages C to E.<sup>5</sup>

## Systematic review

We performed a systematic review through search of PubMed/MEDLINE, Ovid/Embase, and Cochrane databases up to 1 September 2019 (Supplementary material online, Figure S1). 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, ACS, 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, ST-elevation myocardial infarction (STEMI), AMI, primary PCI (pPCI), targeted temperature management (TTM), therapeutic hypothermia, and atrial fibrillation (AF)]. The study selection and eligibility criteria, search strategy, and information sources are detailed in Supplementary material online, Appendix S1. The results of the systematic review, together with existing guidelines (as referenced), impact of disease state and organ dysfunction, as well as pharmacokinetic (PK) and pharmacodynamic (PD) data were used to evaluate the evidence base for antithrombotic therapy and inform the decision-making consensus statements.<sup>7</sup>

## Patient-related factors affecting pharmacological treatment

Complex 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).<sup>8–10,11,12,13–15</sup> PK changes also depend on the drug characteristics [size, lipophilicity, volume of distribution (Vd), protein binding] and may vary over time (hourly, daily) within

**Table 1** Pharmacokinetic mechanisms affecting antithrombotic drugs in critically ill patients

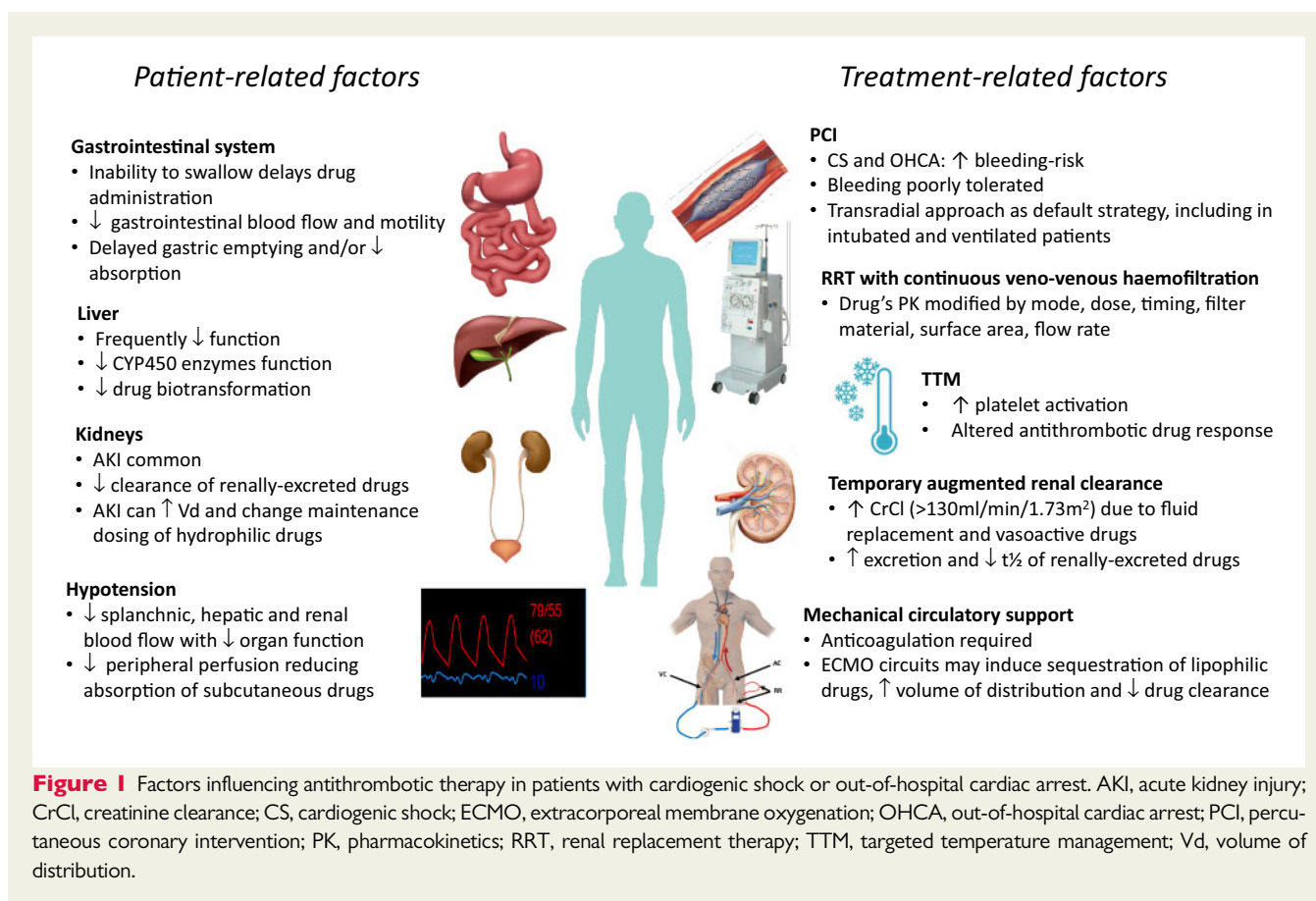
	References
Absorption	
<ul style="list-style-type: none"> <li>• Delayed GI absorption: <ul style="list-style-type: none"> <li>• Decreased gastric emptying rate</li> <li>• Prolonged gut transit time (e.g. ileus)</li> <li>• Altered gastric pH</li> <li>• Decreased blood flow to and from the gut</li> <li>• Intestinal wall oedema</li> </ul> </li> <li>• Impaired absorption: <ul style="list-style-type: none"> <li>• Accelerated gut transit time due to diarrhoea or prokinetics</li> <li>• Brush border loss due to ischaemia</li> </ul> </li> <li>• Slower i.m. or s.c. absorption due to impaired peripheral blood flow</li> </ul>	16
Distribution	
<ul style="list-style-type: none"> <li>• Volume of distribution commonly increased by increased total body water (e.g. capillary leak syndrome and fluid resuscitation) <ul style="list-style-type: none"> <li>• May result in under-dosing of hydrophilic drugs</li> <li>• Decreased albumin leading to increase in free/active drug increased acute-phase proteins</li> </ul> </li> </ul>	8–18
Metabolism	
<ul style="list-style-type: none"> <li>• Decreased hepatic metabolism and phase I enzyme function <ul style="list-style-type: none"> <li>• Decreased hepatic blood flow</li> <li>• Inflammation-induced effects</li> <li>• Hepatic injury</li> <li>• Hypothermia</li> <li>• DDI</li> </ul> </li> <li>• Increased metabolism in the liver <ul style="list-style-type: none"> <li>• DDI leading to enzyme induction</li> </ul> </li> <li>• Decreased spontaneous degradation <ul style="list-style-type: none"> <li>• Hypothermia</li> </ul> </li> <li>• Decreased tissue metabolism <ul style="list-style-type: none"> <li>• Decreased tissue blood flow</li> <li>• Hypothermia</li> </ul> </li> <li>• Decreased plasma metabolism <ul style="list-style-type: none"> <li>• Deficiency of serum enzymes responsible for drug removal in severe hepatic dysfunction</li> </ul> </li> </ul>	8,9,12,13,17
Excretion	
<ul style="list-style-type: none"> <li>• Decreased renal clearance <ul style="list-style-type: none"> <li>• Decreased renal blood flow</li> <li>• Decreased glomerular filtration rate</li> <li>• Poor tubular active transport</li> <li>• Acute renal injury (e.g. acute tubular necrosis)</li> <li>• Augmented renal clearance syndrome: increased renal clearance</li> </ul> </li> <li>• Decreased biliary clearance <ul style="list-style-type: none"> <li>• Biliary stasis</li> <li>• decreased gut transit leading to recirculation</li> </ul> </li> </ul>	9,10,25

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.<sup>16</sup> 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.<sup>17</sup>

Cardiogenic shock may reduce hepatic blood flow, increase congestion and consequently impair hepatic function, decreasing biotransformation rate via the cytochrome P450 (CYP) enzymes.<sup>18</sup> 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.<sup>19,20</sup> Dabigatran metabolism is largely P-glycoprotein-dependent, therefore, dronedarone, amiodarone, verapamil, and phenytoin generate clinically relevant DDIs (Table 1).<sup>19</sup> DDIs specifically related to non-VKA OACs have been described elsewhere.<sup>21</sup> P2Y<sub>12</sub> inhibitors are contraindicated in patients with severe hepatic impairment.<sup>22–24</sup>

Since acute kidney injury (AKI) is common in CS,<sup>10</sup> 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 > 130 mL/min/1.73 m<sup>2</sup>), enhancing excretion as well as reducing the half-life of renally excreted drugs,<sup>25</sup> such as dabigatran and LMWHs. Renal replacement therapy 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 activated partial thromboplastin time (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.<sup>21</sup>

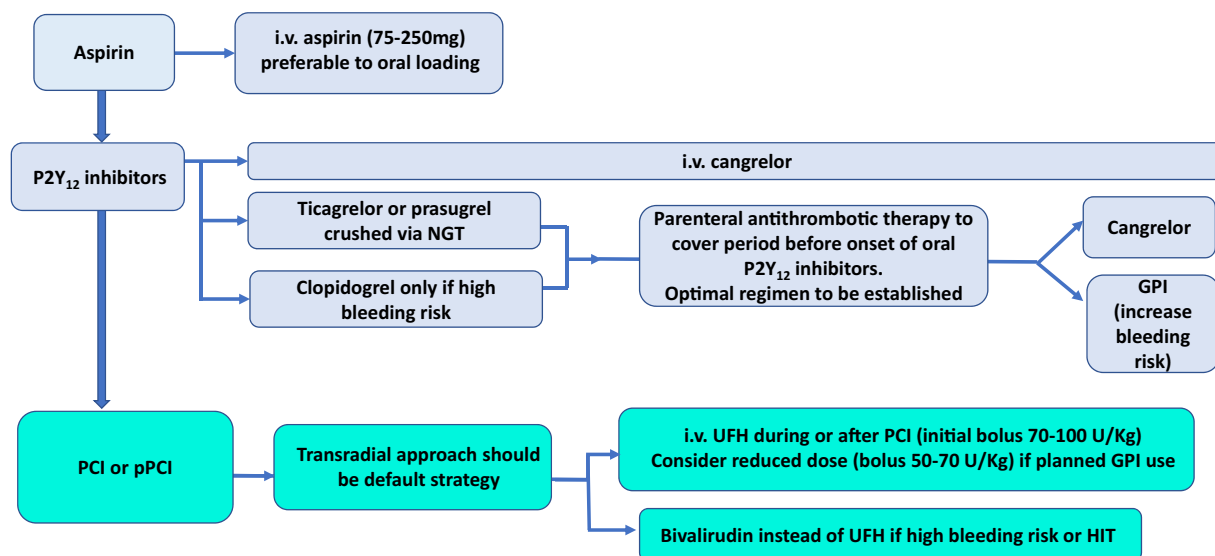
#### Consensus statement:

- **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**

## Specific drug considerations

### Aspirin

Aspirin is a first-line treatment in patients presenting with ACS, including those with OHCA or CS (Figure 2).<sup>24</sup> 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.<sup>26,27</sup> Observational studies showed that patients with CS were less likely to receive aspirin than those without CS, which was associated with worse prognosis.<sup>28–30</sup> Among patients treated with pPCI with CS or OHCA, the incidence of early ST in those with residual treatment platelet reactivity assessed by impedance aggregometry while on standard aspirin dosing was 21.4% vs. 1.8% in those without increased platelet reactivity.<sup>31</sup> There are sparse data on the optimal i.v. dose or the safety and efficacy of oral vs. i.v. administration.<sup>24</sup> 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



**Figure 2** Summary suggestions for initial antithrombotic therapy in patients with cardiogenic shock or out-of-hospital cardiac arrest. GPI, glycoprotein IIb/IIIa inhibitor; HIT, heparin-induced thrombocytopenia; NGT, nasogastric tube; PCI, percutaneous coronary intervention; pPCI, primary percutaneous coronary intervention; UFH, unfractionated heparin.

generation and platelet aggregation, without increasing bleeding.<sup>32</sup> The ESC guidelines recommend i.v. loading with 75–250 mg if oral ingestion is not possible.<sup>24</sup> Although evidence is limited and based on PK or PD studies only, i.v. aspirin may be preferable, at least early following resuscitation (Figure 2).<sup>33</sup>

#### Consensus statement:

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

### P2Y<sub>12</sub> inhibitors

Differences in pharmacology between the oral P2Y<sub>12</sub> receptor inhibitors as well as the only available parenteral P2Y<sub>12</sub> inhibitor (cangrelor) may be particularly relevant in critically ill patients (Table 2 and Figure 1). Reduced absorption is the main limitation of oral P2Y<sub>12</sub> receptor inhibitors in ACS, particularly in patients with CS or post-OHCA, receiving sedation or TTM, with vomiting, gastroparesis, or unable to swallow.<sup>34</sup> 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 h),<sup>35</sup> and since mean levels of platelet inhibition are significantly lower in those treated with clopidogrel compared to prasugrel or ticagrelor,<sup>12</sup> 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<sub>12</sub> inhibitor in this population, with evidence derived from extrapolation of ACS trials and PD studies assessing the rapidity and extent of platelet inhibition. Among 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<sub>12</sub> inhibitors,<sup>36</sup> while 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.<sup>37</sup> In a randomized 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.<sup>38</sup> A meta-analysis of five studies including 290 patients receiving TTM after PCI showed no difference between clopidogrel and newer oral P2Y<sub>12</sub> inhibitors with regard to ST or in-hospital mortality.<sup>39</sup> A retrospective study of 88 patients with CS showed that cangrelor-treated patients had greater improvement in thrombolysis in myocardial infarction (TIMI) flow than those receiving oral P2Y<sub>12</sub> inhibitors, with similar rates of ST, 30-day and 1-year mortality.<sup>40</sup> 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.<sup>41</sup> 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.<sup>42</sup> Prasugrel and ticagrelor are also associated with delayed onset of action in STEMI (up to 8 h).<sup>43,44</sup> The administration of crushed ticagrelor or prasugrel through a nasogastric tube, or orodispersible ticagrelor,<sup>20</sup> may be the optimal route to deliver dual antiplatelet therapy.<sup>45,46</sup> 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<sub>12</sub> inhibitors, which might increase the risk of ischaemic events.<sup>47–49</sup> This delay in absorption with a potential reduced bioavailability is unlikely to be overcome



**Table 2** Antithrombotic therapy strategies in critically ill patients

	Pharmacokinetics	Pharmacodynamics	Specific considerations in critically ill patients
Aspirin	Crushing and/or dissolving tablets via NGT may fasten absorption and increase bioavailability	Maximal (>96%) platelet TXA <sub>2</sub> inhibition 4 h after standard oral dosing Variable absorption may cause incomplete suppression of platelet TXA <sub>2</sub> biosynthesis in CS	Acutely, i.v. administration is preferable TTM may reduce effectiveness of oral aspirin No CYP450-mediated metabolism
Oral P2Y <sub>12</sub> inhibitors	Clopidogrel Thienopyridine prodrug, requires hepatic biotransformation to active metabolite Crushing tablets via NGT provides faster and greater bioavailability	Mean IPA (40–60%) achieved 2–6 h after 600 mg clopidogrel During critical illness, cytochrome-dependent conversion of clopidogrel to its active metabolite may be substantially reduced, resulting in insufficient P2Y <sub>12</sub> -dependent platelet inhibition in majority of patients Offset 5–10 days	Interaction with: <i>CYP3A4, CYP3A5 or CYP2C19 inhibitors:</i> Including calcium channel blockers (diltiazem, verapamil, amlodipine), omeprazole, esomeprazole, erythromycin, clarithromycin <i>Opioids:</i> Morphine, fentanyl <i>Interaction with:</i> <i>Opioids:</i> Morphine, fentanyl-based on GI motility (not CYP-450 mediated)
	Prasugrel Thienopyridine prodrug, requires hepatic conversion to active metabolite Crushing tablets via NGT provides faster and greater bioavailability	In STEMI, mean IPA of 85% at 6 h compared with 90% at 24 h IPA highly variable in critically ill patients, but less compared to clopidogrel Offset 7–10 days	<i>Interaction with:</i> <i>Strong CYP3A4 inducers or inhibitors:</i> Contraindications include clarythromycin, high-dose simvastatin and lovastatin (>40 mg). <i>Opioids:</i> Morphine, fentanyl-based on GI motility Contraindicated in liver failure
	Ticagrelor Does not require metabolic activation Ticagrelor has a CYP3A4-generated metabolite (AR-C124910XX) that has similar potency and contributes ~30% of the antiplatelet activity Crushed or orodispersible ticagrelor can be given via NGT to increase speed of onset of effect	In STEMI, mean IPA of 76% at 6 h compared with 84% at 24 h IPA during TTM significantly reduced, but less compared to clopidogrel Offset 3–5 days	
	Intravenous P2Y <sub>12</sub> inhibitor (cangrelor)	P2Y <sub>12</sub> antagonist with a reversible action Onset of action 2–5 min 70% of baseline platelet aggregation recovered within 1 h of stopping infusion	No CYP-450-associated drug interactions. No interaction with opiates based on administration via i.v. route
Glycoprotein IIb/IIIa inhibitors	Tirofiban and eptifibatide Low-molecular-weight molecules for i.v. administration Plasma half-life 1.6–2.5 h Dose adjustment required in renal insufficiency	Tirofiban and eptifibatide competitively inhibit GP IIb/IIIa receptor Rapid restoration of normal haemostatic function Abciximab binds non-competitively with high affinity to the GP IIb/IIIa receptor	Avoid during TTM due to higher incidence of bleeding without significant improvement in outcome
	Abciximab Monoclonal antibody for i.v. administration Half-life 8–12 h Restoration of normal haemostatic function after 72 h	Slow restoration of normal haemostatic function	
UFH	Half-life is dose-related	Anticoagulant response to UFH varies especially among acute patients	In TTM, UFH dose should be reduced by at least 45% and

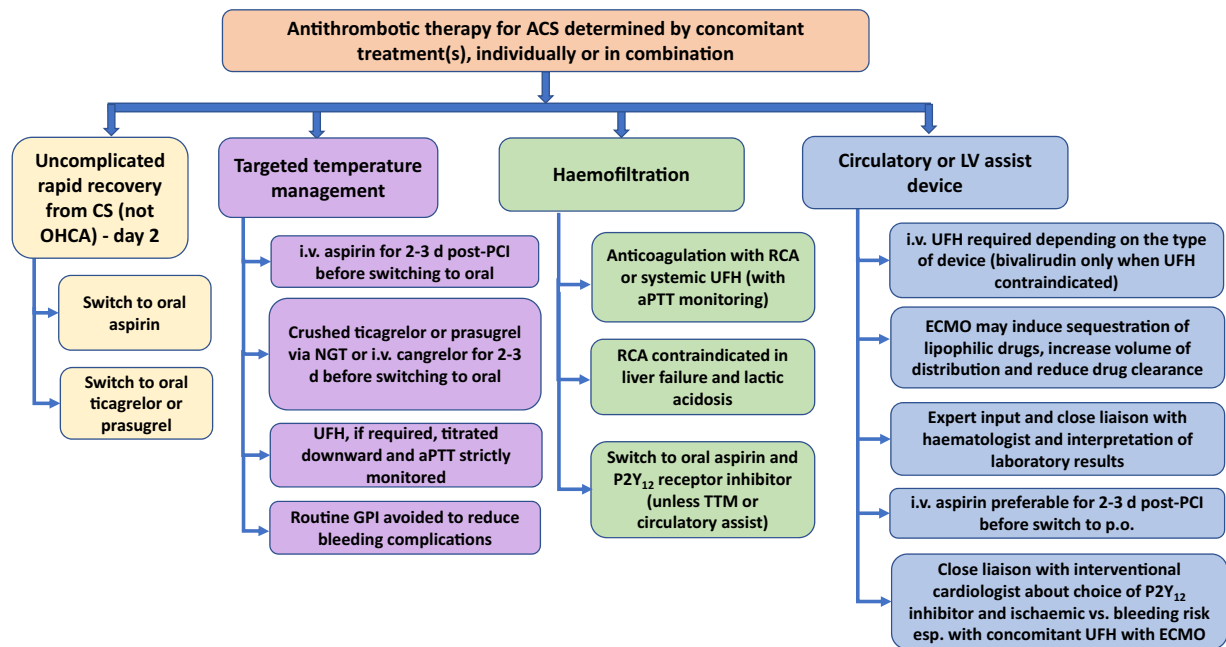
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**Table 2** Continued

	Pharmacokinetics	Pharmacodynamics	Specific considerations in critically ill patients
LMWH	Increases from 30 min after i.v. bolus of 25 IU/kg to 60 min with bolus of 100 IU/kg	Frequent monitoring and dose adjustment based on aPTT or ACT results required	frequent aPTT or ACT monitoring performed
	Pharmacokinetic advantages over UFH due to less variability	Produce more predictable anticoagulant response than UFH, however, in critically ill patients with AKI anti-FXa activity can be measured	Poor peripheral perfusion during shock may impair s.c. absorption
	Bioavailability of LMWH after s.c. injection is >90%, Half-life is dose dependent and varies between different LMWHs Renally eliminated, therefore can accumulate in renal impairment		
Direct intravenous thrombin inhibitors (bivalirudin)	Rapid onset of action Partly degraded and partly excreted by kidney (20%) Half-life 25 min after i.v. injection Half-life prolonged in patients with renal impairment	Reversible thrombin inhibitor No need to titrate dose No need for routine ACT monitoring A good option to manage patients with heparin-induced thrombocytopenia	No CYP450-mediated metabolism Clinically relevant DDI not reported
NOACs	Dabigatran Very low bioavailability <10% High rate of renal excretion ≥85% Contraindicated if CrCl <30 mL/min Dose reduction if CrCl 30–50 mL/min Half-life 11–17 h, affected by renal function	Prodrug AM inhibits free and bound FIIa No need for routine monitoring In urgent situations ECT and dTT can be used if needed	Strong P-gp-dependent biotransformation Clinically relevant P-gp-mediated DDI, including: Concomitant dronedarone contraindicated Dose reduction recommended if co-administered with verapamil, amiodarone, quinidine, clarithromycin Phenytoin and carbamazepine should be avoided
	Apixaban Bioavailability 50% Mixed excretion: kidney (≈30%), faecal (≈70%) Half-life 8–15 h Dose reduction if serum creatinine ≥1.5 mg/dL (133 micromol/L) associated with age ≥80 years or body weight ≤60 kg	Blocks free and fibrin-bound FXa No need for routine monitoring, in urgent situations anti-FXa activity can be used if needed	Clinically relevant DDI only in the presence of strong inducer or inhibitor of both 3A4 and P-gp including phenytoin, carbamazepine, phenobarbital (not recommended)
	Edoxaban Bioavailability ≈60% Rate of kidney excretion ≈40%, faecal excretion ≈60% Half-life of 8–10 h	Blocks free and fibrin-bound FXa No need for routine monitoring In urgent situations anti-FXa activity can be used if needed	P-gp-based DDI: reduce dose if concomitant dronedarone is needed
	Rivaroxaban High bioavailability (>80%) Rate of kidney excretion ≈35%, faecal excretion ≈65% Half-life of 10 h	Blocks free and fibrin-bound FXa No need for routine monitoring In urgent situations anti-FXa activity can be used if needed	DDIs only with strong inducers or inhibitors of the 3A4

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

ACT, activated clotting time; AKI, acute kidney injury; aPTT, activated partial thromboplastin time; CS, cardiogenic shock; CrCl, creatinine clearance; DDI, drug–drug interaction; GI, gastrointestinal; IPA, inhibition of ADP-induced platelet aggregation; i.v., intravenous; LMWH, low-molecular-weight heparin; NGT, nasogastric tube; NOACs, non-vitamin K antagonist oral anticoagulants; s.c., subcutaneous; TTM, targeted temperature management; TXA<sub>2</sub>, thromboxane A<sub>2</sub>; UFH, unfractionated heparin.



**Figure 3** Summary of suggestions for subsequent antithrombotic therapy in patients with cardiogenic shock or out-of-hospital cardiac arrest. 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; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; pPCI, primary percutaneous coronary intervention; UFH, unfractionated heparin.

by increasing the loading dose of P2Y<sub>12</sub> inhibitor, and may require administration of parenteral antiplatelet therapy to cover the lag time before onset of action of oral P2Y<sub>12</sub> inhibitors. Cangrelor provides one potential option in the initial treatment phase with subsequent transitioning to oral P2Y<sub>12</sub> inhibitors.<sup>50,51</sup> In patients with cardiac arrest, cangrelor was shown to inhibit platelet aggregation more effectively than orally administered P2Y<sub>12</sub> inhibitors without increasing bleeding.<sup>50</sup> Unlike ticagrelor, the active metabolites of prasugrel and clopidogrel bind to the ADP-binding site on the P2Y<sub>12</sub> receptor, just like cangrelor, creating potential PD interaction when cangrelor and thienopyridines (prasugrel and clopidogrel) are co-administered.<sup>51</sup> Although one small study showed that prasugrel loading at the start of a 2 h cangrelor infusion achieved sufficient platelet inhibition,<sup>52</sup> due to this potential PD interaction, prasugrel and clopidogrel should be administered at the end of cangrelor infusion (Table 2).<sup>34,51</sup> Ticagrelor can be administered at any time during or at the end of cangrelor infusion and may be the oral P2Y<sub>12</sub> 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 h infusion may not sufficiently cover the delayed absorption of oral P2Y<sub>12</sub> inhibitors in some opiate-treated patients since their onset of action may be delayed for >6 h.

Alternative potential parenteral strategies to cangrelor include the administration of a glycoprotein IIb/IIIa inhibitor (GPI) bolus and infusion.<sup>53,54</sup> A particular concern is ventilated patients who may receive opioids such as fentanyl infusion, which theoretically could delay absorption of oral P2Y<sub>12</sub> 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<sub>12</sub> inhibitors. Cangrelor is preferred due to lower bleeding risk, unless there is no-reflow or bailout during PCI, when GPI can be considered.

### Glycoprotein IIb/IIIa inhibitors

Glycoprotein IIb/IIIa inhibitor, 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,<sup>55,56</sup> although most evidence was obtained before more potent P2Y<sub>12</sub> inhibitors were routinely used in ACS.<sup>56,57</sup> 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, randomized 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.<sup>57</sup> 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.<sup>58–60</sup> 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.<sup>61</sup> In a registry of 6489 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.<sup>2</sup> Glycoprotein IIb/IIIa inhibitor potentially may be most beneficial in ACS patients with CS or after OHCA.<sup>55,56</sup> Whereas GPI are conventionally administered by i.v. bolus followed by infusion,<sup>56</sup> similar efficacy has been reported for intracoronary or intralesional bolus-only administration.<sup>62,63</sup> Although existing guidelines state that GPI may only be considered in specific 'bailout' situations including high intraprocedural thrombus burden, slow flow, or no-flow with abrupt vessel closure or in high-risk PCI in P2Y<sub>12</sub>-inhibitor naïve patients,<sup>64</sup> in the setting of CS or OHCA, we consider that GPI may also be used as bridge to achieve sufficient platelet inhibition while awaiting onset of oral P2Y<sub>12</sub> inhibitor effect. Glycoprotein IIb/IIIa inhibitor 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,<sup>55,56</sup> 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,<sup>53</sup> although larger prospective studies are warranted to explore the safety of this approach. Irrespective of the route of administration, or the concomitant P2Y<sub>12</sub> inhibitor used, GPI treatment is associated with increased bleeding risk.<sup>55,56</sup>

#### Consensus statements:

- **Glycoprotein IIb/IIIa inhibitor administration in ACS patients with CS or OHCA undergoing PCI, may improve outcomes.**
- **Glycoprotein IIb/IIIa inhibitor may be used as bridge to achieve sufficient platelet inhibition while awaiting onset of oral P2Y<sub>12</sub> inhibitor treatment.**
- **Glycoprotein IIb/IIIa inhibitor use increases the risk of bleeding.**

## Heparins

Compared with UFH, LMWHs and fondaparinux have more predictable PKs.<sup>64</sup> 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.<sup>65,66</sup> In addition, crossover of UFH and LMWHs is discouraged in the setting of PCI.<sup>64</sup> 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).<sup>64</sup> 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, while 5% received bivalirudin.<sup>66</sup> 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 (NSTEMI) ACS and STEMI.<sup>64</sup> A reduced dose (50–70 U/kg) may be preferable in case of co-administration with GPI.<sup>64</sup> Enoxaparin should be considered to support PCI as an alternative to UFH, particularly in patients pre-treated with subcutaneous enoxaparin.<sup>67</sup> 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.<sup>68,69</sup>

#### Consensus statements:

- **Unfractionated heparin 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 NSTEMI ACS and ST-segment elevation myocardial infarction.**
- **Reduced dose UFH (50–70 U/kg) should be considered in case of planned concomitant GPI use.**
- **Unfractionated heparin dosing is reduced in TTM and prolonged infusion interruption may be required to allow adequate drug clearance, guided by ACT.**

## Direct intravenous thrombin inhibitors

Intravenous direct thrombin inhibitors (DTIs) inhibit both soluble thrombin and fibrin-bound thrombin.<sup>70</sup> 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).<sup>71,72</sup> Bivalirudin has been extensively evaluated across the spectrum of ACS and PCI.<sup>73–84</sup> Compared to UFH, use of bivalirudin, with or without GPI, may reduce bleeding complications.<sup>85,86</sup> 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.<sup>87</sup> Although there is little evidence specifically in CS and OHCA, bivalirudin may be considered, especially in patients at high bleeding risk, including CS.<sup>87</sup>

#### Consensus statement:

- **Bivalirudin may be considered as an alternative to UFH.**

## Antithrombotic strategies in relation to radial vs. femoral percutaneous coronary intervention 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.<sup>88</sup> 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.<sup>88,89</sup> 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.<sup>90</sup> 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.<sup>86,91</sup> However, TRA implementation in these patients is sub-optimal,<sup>91,92</sup> 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.**

## Early post-percutaneous coronary intervention antithrombotic management in the intensive care unit

### Targeted temperature management

Targeted temperature management, 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.<sup>93</sup> During TTM, UFH requirement is drastically reduced, and guideline-recommended UFH dosing protocols should therefore not be used.<sup>68,69</sup> The UFH dose should be reduced by roughly 50% and frequent aPTT monitoring both during cooling and rewarming should be performed (Figure 3).<sup>69</sup>

Targeted temperature management has been associated with increased platelet activation in some studies<sup>94</sup> and reduced platelet reactivity in others.<sup>95,96</sup> 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.<sup>97</sup> Reduced platelet inhibition on aspirin has been observed after hypothermia and may be partly related to increased platelet turnover.<sup>98</sup> Small studies in resuscitated patients show increased platelet reactivity to arachidonic acid and collagen 3 days after a loading dose of 150–300 mg i.v. aspirin<sup>99</sup> and a daily dose of 100 mg i.v. compared to 100 mg orally was associated with greater platelet inhibition.<sup>98</sup> In the setting of TTM,<sup>21</sup> i.v. aspirin administration is preferred.<sup>50</sup> In the setting of TTM, lower plasma concentration of active clopidogrel metabolites and attenuated P2Y<sub>12</sub>-dependent platelet inhibition are reported, compared to patients without TTM.<sup>100</sup> In a meta-analysis of five 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.<sup>39</sup> 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.<sup>15</sup> In 25 resuscitated ACS patients treated with TTM, cangrelor achieved greater platelet inhibition than oral P2Y<sub>12</sub> inhibitors, without an increase in bleeding.<sup>50</sup> Routine use of GPI with TTM should be avoided because of the higher incidence of bleeding without significant improvement in outcome,<sup>101</sup> possibly attributable to TTM-mediated effects on platelet function that can be direct and indirect, through augmentation of GPI effects.<sup>102</sup>

#### 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 nasogastric tube or i.v. cangrelor are preferred for the first 2–3 days post-PCI before switching to oral antiplatelet therapy.**
- **Unfractionated heparin, 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.**

### 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.<sup>103,104</sup> Anticoagulation, required to guarantee patency and functioning of the circuit,<sup>105</sup> can be achieved with low-dose UFH, LMWH, mesitates 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<sup>106</sup> 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.<sup>106–110</sup>

#### Consensus statements:

- **Regional citrate anticoagulation (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.**

## 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)<sup>111</sup> or isolated left-sided support, including the Impella device.<sup>6</sup> 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.<sup>112</sup> There are few data pertaining to other anticoagulants<sup>113</sup> 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.<sup>114</sup> Effectiveness of anticoagulation can be monitored through different tests that include aPTT, ACT, anti-FXa levels, and thromboelastography.<sup>115–117</sup> With ECMO, anticoagulation is monitored by aPTT and heparin concentration measured by anti-FXa assay.<sup>116,117</sup> 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,<sup>118–122</sup> and studies are urgently needed to define the optimal monitoring strategy in adults. In patients with concomitant sepsis, anticoagulation should be interpreted synthesizing 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.<sup>123</sup> A meta-analysis of 1866 CS patients reported incidences of lower limb ischaemia in >15%, stroke in >5%, and major or significant bleeding in >40% of patients.<sup>124</sup> Over-anticoagulation<sup>125</sup> as well as low platelet count, often seen in CS, can exacerbate bleeding on ECMO.<sup>126,127</sup> Patients frequently develop acquired von Willebrand factor defect within 24 h of ECMO implantation, which significantly increases bleeding risk.<sup>128</sup>

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<sub>12</sub> 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 absorption 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 Vd and reduce drug clearance, but data are limited to antimicrobials and sedatives, such as propofol and fentanyl.<sup>129</sup>

In CS complicating AMI, intra-aortic balloon pump (IABP) implantation is no longer routinely recommended.<sup>130</sup> However, ECMO may be used in combination with IABP or Impella in order to offload the left ventricle.<sup>131</sup> 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.**

- **Unfractionated heparin should be used in the acute setting.**
- **Bivalirudin should be considered only when UFH is contraindicated.**
- **Extracorporeal membrane oxygenation circuits may induce sequestration of lipophilic drugs, increase Vd and reduce drug clearance.**

## Patients with existing or new-onset atrial fibrillation

Atrial fibrillation occurs in ~20% of patients with ACS complicated by CS,<sup>132</sup> in comparison to only ~9% of patients with uncomplicated ACS.<sup>133</sup> 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.<sup>132</sup> However, patients with CS and ACS showing AF already on admission have a higher mortality compared to those with new-onset AF during hospitalization.<sup>132,133</sup>

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.<sup>134,135</sup>

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.<sup>133</sup> By definition, almost all patients with ACS and CS will have a CHA<sub>2</sub>DS<sub>2</sub>-VASc 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 1st month, unless there are unacceptable bleeding risks.<sup>24,133–136</sup>

Peri-PCI and in patients with AF who are haemodynamically unstable or on the intensive care unit (ICU), anticoagulation is best managed with UFH because of the increased risk of bleeding from multiorgan 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<sub>12</sub> inhibitor of choice.<sup>24,134,135</sup>

#### Consensus statements:

- **Triple antithrombotic therapy comprising of aspirin, clopidogrel, and anticoagulation is recommended as the initial treatment for the 1st 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.**
- **Oral anticoagulant-treated patients with AF who present with ACS and CS should receive aspirin loading (as for patients without AF).**

- Clopidogrel is the P2Y<sub>12</sub> inhibitor of choice (600 mg loading dose).

## Conclusions

Patients with CS or OHCA of presumed ischaemic cause constitute a very high-risk group, in whom minimizing 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, minimization 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<sub>12</sub> receptor inhibitors and the optimal anticoagulant regimen in patients on circulatory assist devices.

## Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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