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REVIEW

Antithrombotic and anticoagulation therapies in cardiogenic shock: a critical review of the published literature

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Abstract

Cardiogenic shock (CS) is a complex multifactorial clinical syndrome, developing as a continuum, and progressing from the initial insult (underlying cause) to the subsequent occurrence of organ failure and death. There is a large phenotypic variability in CS, as a result of the diverse aetiologies, pathogenetic mechanisms, haemodynamics, and stages of severity. Although early revascularization remains the most important intervention for CS in settings of acute myocardial infarction, the administration of timely and effective antithrombotic therapy is critical to improving outcomes in these patients. In addition, other clinical settings or non-acute myocardial infarction aetiologies, associated with high thrombotic risk, may require specific regimens of short-term or long-term antithrombotic therapy. In CS, altered tissue perfusion, inflammation, and multi-organ dysfunction induce unpredictable alterations to antithrombotic drugs' pharmacokinetics and pharmacodynamics. Other interventions used in the management of CS, such as mechanical circulatory support, renal replacement therapies, or targeted temperature management, influence both thrombotic and bleeding risks and may require specific antithrombotic strategies. In order to optimize safety and efficacy of these therapies in CS, antithrombotic management should be more adapted to CS clinical scenario or specific device, with individualized antithrombotic regimens in terms of type of treatment, dose, and duration. In addition, patients with CS require a close and appropriate monitoring of antithrombotic therapies to safely balance the increased risk of bleeding and thrombosis.

Keywords Cardiogenic shock; Antithrombotic therapy; Antiplatelet therapy; Anticoagulation therapy

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Introduction

Cardiogenic shock (CS) is a complex multifactorial clinical syndrome, developing as a continuum, and progressing from the initial insult (underlying cause) to the subsequent occurrence of organ failure and death.[1] Despite advanced management, including aetiological treatment, adjunctive pharmacotherapies, and circulatory or other organ function support, CS represents the most severe manifestation of acute heart failure with in-hospital mortality between 30% and 50%.[2] Because 50% of deaths secondary to CS occur in the first 24 h after admission,[3] hypoperfusion signs should be identified

early in the course of the disease and specific therapies must be given to the appropriately selected patients, in a timely manner, while avoiding iatrogenic harm.[4]

In CS, early identification of the underlying cause is crucial, and without identification and treatment of the underlying cause, the outcome is usually fatal.[1] Categorization according to the underlying aetiology, acute coronary syndrome (ACS)-related vs. non-ACS-related, aims to guide early management strategies towards the underlying cause. Although early revascularization remains the most important intervention for CS in settings of ACS, the administration of timely and effective antithrombotic therapy is critical to improving outcome. In addition, other clinical settings or non-ACS aetiologies, associated with high thrombotic risk, may require specific regimens of antithrombotic therapy.

The main goal of this manuscript is to describe pathophysiological factors relevant for thrombosis in CS and to review the available evidence focusing on adjunctive antithrombotic therapy and the technical aspects of percutaneous coronary interventions (PCIs) in patients with acute myocardial infarction (AMI) and CS. Other therapeutic interventions in CS, such as mechanical circulatory support (MCS) or renal replacement therapy (RRT), influence both thrombotic and bleeding risks and may require specific antithrombotic regimens, while others such as targeted temperature management (TTM) may interact with antithrombotic drug absorption and metabolism and predispose to a coagulopathic state. Antithrombotic therapies associated to several other non-ACS aetiologies or concomitant cardiac conditions that predispose to high thrombotic risk in CS are contemporarily reviewed in the manuscript.

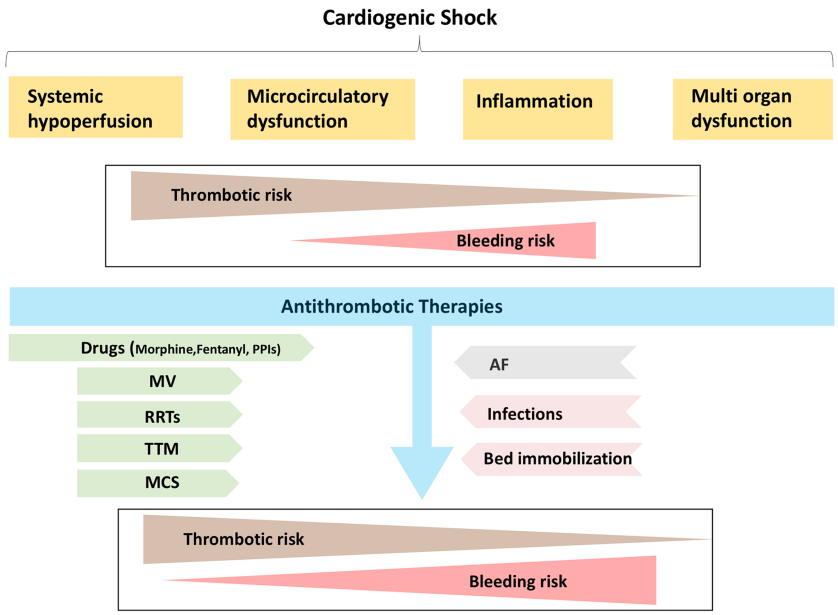
Pathophysiology

Although aetiologies vary widely, the pathophysiology of CS comprises several overlapping components to be considered: an initial cardiac insult that decreases cardiac output, central haemodynamic alterations, microcirculatory dysfunction, a systemic inflammatory response syndrome, and multi-organ failure[1] (*Figure 1*).

Microcirculatory dysfunction is the most important determinant of the development of multi-organ failure and predicts a poor outcome in patients with CS complicating AMI.[5,6] The pathophysiology of microcirculatory dysfunction in CS is multifactorial, but the main cause remains the alteration of vascular responsiveness to metabolic need.[7] Coronary microcirculatory dysfunction is associated with a high thrombus burden in AMI–CS, and the presence of thrombotic aggregates in coronary microcirculation is responsible for the no-reflow phenomenon, highlighting the beneficial roles of direct thrombin inhibitor (DTI) and glycoprotein IIb/IIIa inhibitor (GPI) therapies in these settings.[8–10]

Systemic inflammatory response syndrome may significantly affect the response to aspirin by alternative pathways of platelet activation with hyperproduction of thromboxane A2 regardless of the arachidonic acid pathways.[11]

Figure 1 Pathophysiology of cardiogenic shock and the balance between thrombotic and bleeding risks considering various management interventions and in-hospital complications. AF, atrial fibrillation; MCS, mechanical circulatory support; MV, mechanical ventilation; PPIs, proton pump inhibitors; RRTs, renal replacement therapies; TTM, targeted temperature management.



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Catecholamine burst, as a compensatory mechanism and systemic inflammatory response syndrome, may directly activate platelets that are non-sensitive to aspirin.[12]

Altered tissue perfusion and organ dysfunction, including acute hepatic and kidney injury, induce unpredictable pharmacokinetic and pharmacodynamic alterations of antithrombotic drugs, translating into uncertain clinical consequences. Shock states 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.[13,14]

Several additional therapies, such as sedatives, antiarrhythmics, high dose of diuretics, and excessive volume loading, could further interfere with route of administration, volume of distribution, metabolism, and excretion of antithrombotic therapies.[14] Other interventions, such as MCS or RRTs, influence both thrombotic and bleeding risks and may require specific antithrombotic regimens, while others such as TTM may interact with antithrombotic drug absorption and metabolism and predispose to a coagulopathic state. Also, precipitating factors, such as infections, may alter efficacy of antithrombotic drugs. Patients with CS are at high risk of developing infection, particularly respiratory infections, by several mechanisms including associated pulmonary congestion, aspiration pneumonia resulting from broncho-aspiration during cardiopulmonary resuscitation, ventilator-associated respiratory infection due to prolonged mechanical ventilation, respiratory infections secondary to hypothermia from TTM, and multiple invasive access vascular sites, especially in patients with MCS.[15–18] Infections produce vasodilation that further decrease organ perfusion and are associated with the prolonged mechanical ventilation that determines administration of drugs via nasogastric tubes, and commonly require antibiotic therapies that may interfere through drug-to-drug interactions with antithrombotic drugs. In addition, insertion of intravenous and arterial lines, higher use of femoral access, prolonged concomitant systemic anticoagulation with MCS, and acquired platelet dysfunction with TTM increase the bleeding risk.

Cardiogenic shock in settings of acute coronary syndrome

Cardiogenic shock is the leading cause of mortality in patients with ACS,[19] as contemporary mortality rates are still as high as 40–50%[20]; 7–10% of ACSs are complicated by CS.[21]

There are several specific key issues in the management of patients with ACS and CS, and these include type of revascularization, type of stent, vascular access, aspiration thrombectomy, and adjunctive antithrombotic pharmacotherapy (*Figure 2*).

No properly powered definitive randomized controlled trials have been conducted to evaluate different antithrombotic therapies or various PCI strategies (vascular access, thrombectomy, or choice of stent) to optimize the care of patients with CS in the settings of AMI.[22] Most of the evidence for any of these drugs and devices are derived from randomized trials conducted among patients undergoing revascularization for ACS without haemodynamic instability. Extrapolating the evidence generated from trials conducted in haemodynamically stable myocardial infarction populations to those presenting with ACS–CS is not optimal considering the distinctive haemodynamic characteristics of patients in CS, the multiple compensating physiological mechanisms, and the need for complex therapies.

Revascularization

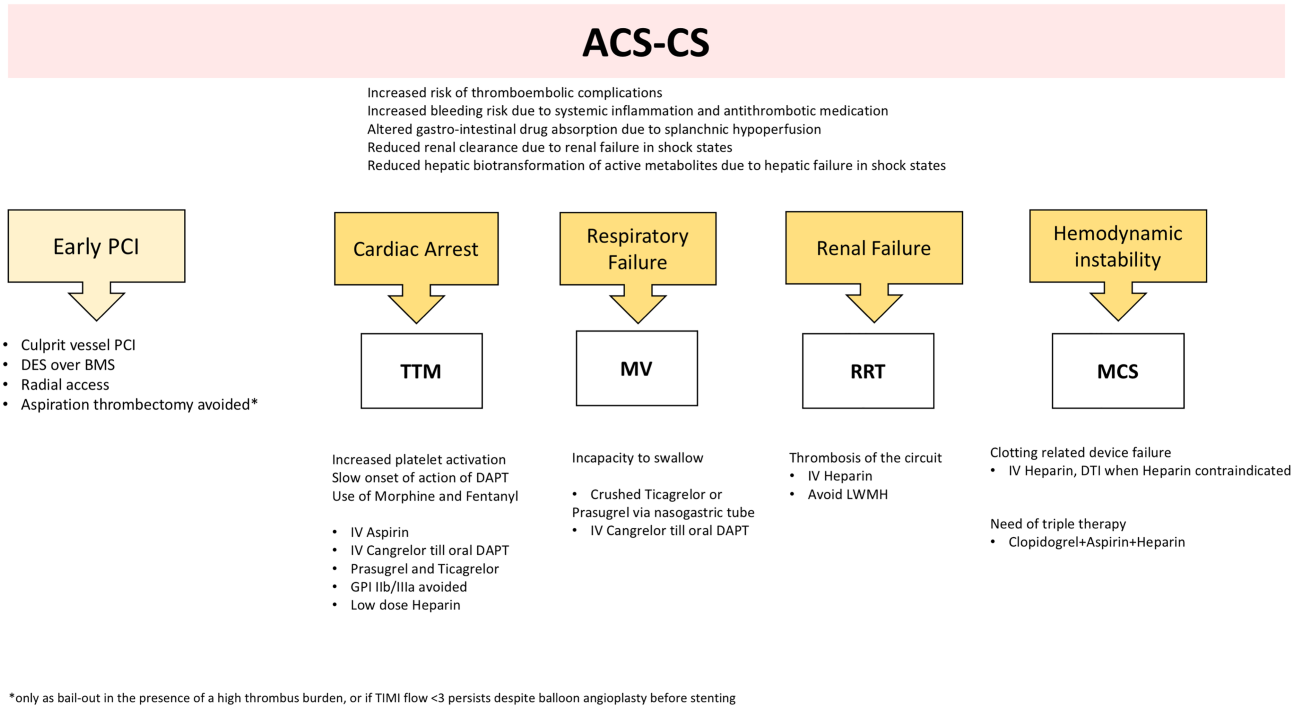
Early reperfusion is the most important intervention in patients with AMI complicated or not by CS. Fibrinolysis should be reserved for ST-elevation myocardial infarction (STEMI) patients with CS when primary PCI cannot be performed within 120 min from STEMI diagnosis.[2,23] Fibrinolysis may increase the risk of bleeding particularly in the context of subsequent MCS.

In the SHOCK trial,[24] early revascularization (PCI or coronary artery bypass graft) was associated with a significant reduction in mortality at 6 and 12 months and at long-term follow-up.[25,26] SHOCK trial showed a significant difference in mortality between patients with successful revascularization and those with failed revascularization (35% vs. 80%).[24] Coronary angioplasty with stent implantation was performed only in 34% of the patients, while the remaining patients underwent balloon PCI.[27] All implanted stents were bare metal stents (BMSs). Although contemporary guideline recommendations for PCI in the settings of AMI–CS[23] mentioned drug-eluting stents (DESs), there are no randomized clinical trial data to compare BMSs with DESs in patients with ACS–CS. A large Swiss registry compared BMSs vs. DESs in CS patients using a propensity-matched analysis and found lower long-term all-mortality in patients treated with DESs.[28]

For patients with AMI–CS and multi-vessel disease, CULPRIT-SHOCK study[29] showed that 'culprit-lesion-only strategy' compared with 'immediate multi-vessel PCI' resulted in a significant reduction in 30 day mortality or RRT (45.9% vs. 55.4%).[29] A 'culprit-lesion-only strategy' possibly followed by a staged revascularization during hospitalization represents the current recommended approach in patients with AMI–CS and multi-vessel disease.[1]

When considering vascular access site, several consensus documents favour transradial access (TRA) compared with transfemoral access (TFA) because reducing access-related major bleedings is very important in critically ill patients and the groin area often needs to be preserved for insertion

Figure 2 Antithrombotic medication in patients with cardiogenic shock in settings of acute coronary syndrome (ACS). Technical consideration regarding primary percutaneous coronary intervention (PCI) and specific recommendations for antithrombotic therapies when different strategies are used. BMS, bare metal stent; DAPT, double antiplatelet therapy; DES, drug-eluting stent; DTI, direct thrombin inhibitor; GPI, glycoprotein inhibitor; IV, intravenous; LWMH, low-weight-molecular heparin; MCS, mechanical circulatory support; MV, mechanical ventilation; TTM, targeted temperature management.



of MCS.[1,2,30,31] However, TRA may be challenging in hypotensive patients with CS due to the systemic vasoconstriction.[1] In the CULPRIT-SHOCK trial, TRA was used in only 18% of participants and interaction between vascular access site and endpoints was not reported.[29]

In the Matrix trial, including 8404 patients with ACS, TRA was associated with a lower risk of vascular complications, access site-related bleeding, need for transfusion, and a significant mortality benefit over TFA.[32] Other two trials, comparing TRA with TFA, RIVAL and RIFLE-STEACS confirmed the lower rate of access site-related bleedings in TRA group.[33,34]

In the two meta-analyses including patients with CS, TRA compared with the TFA reduced 30 day mortality by 45–50%, mainly by decreasing major bleeding.[35,36]

However the recent, Safety and Efficacy of Femoral Access Versus Radial for Primary Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction (SAFARI-STEMI) trial showed no significant differences in 30 day mortality rates between the two approaches.[37]

The reduction of access site-related major bleeding with TRA is particularly useful in critically ill patients who may be at high bleeding risk, when intense peri-procedural antithrombotic therapy is used, or in CS centres with high level of expertise.[14] In the current European guidelines for the management STEMI and non-STEMI patients, TRA has a Class IA indication.[23,38]

Routine use of aspiration thrombectomy may lead to an excess risk of strokes and is not routinely recommended in STEMI patients.[39] However, patients with CS may have higher thrombus burden and may benefit from thrombectomy before stent implantation in selected cases. Direct evidence is lacking in these settings, as patients with CS were poorly represented in the thrombectomy trials, and there is no other convincing available evidence to support a role for routine thrombectomy in the treatment of AMI–CS. This strategy can however be used as bailout in the presence of a high thrombus burden, or if TIMI flow <3 persists despite balloon angioplasty before stenting[22] (*Figure 2*).

Antithrombotic management

All patients with ACS and CS on admission should receive double antiplatelet therapy, according to the guidelines recommendations for STEMI and non-STEMI.[23,38] There are no specific trials for oral antiplatelet therapy in patients with

CS; the data available are derived from patients with ACS and haemodynamic stability (*Table 1*).

Aspirin is recommended in all patients who present with ACS, with and without CS (IA).[23] A loading dose of 150–300 mg orally should be used and administered as soon as possible. Observational studies suggest that patients with CS are less likely to receive aspirin and may have a worse prognosis.[40] In CS patients with cardiac arrest or those mechanically ventilated who cannot swallow orally administered aspirin, intravenous aspirin should be used, in a loading dose of 75–250 mg, as stated in the European Society of Cardiology (ESC) STEMI guidelines.[23] Particularly, in patients with CS and out-of-hospital cardiac arrest (OHCA), intravenous aspirin 75–250 mg may be preferable to oral aspirin loading.

P2Y12 inhibitors used in the settings of ACS are thienopyridines: clopidogrel, prasugrel, and cangrelor and non-thienopyridines: ticagrelor. There are no specific recommendations for the use of oral P2Y12 inhibitors in CS. There are some particularities to consider when a dual antiplatelet therapy (DAPT) strategy is suggested. Poor splanchnic perfusion, particularly gastric, is noted in the settings of CS, and these patients are predisposed to gastrointestinal (GI) bleedings.[1,7] The use of proton pump inhibitors (PPIs) reduces the risk of upper GI bleeding, but concomitant use of DAPT and PPIs may increase the rates of stent thrombosis and repeated revascularization.[41] PPIs decreases secretion of gastric acid and subsequently diminishes gastric absorption of aspirin.[42] Clopidogrel is a prodrug that needs hepatic metabolic transformation to generate its active metabolite, and this depends on the cytochrome P-450 (CYP) enzyme system, which is also responsible for the metabolism of PPIs. The competitive inhibition and adverse interactions of clopidogrel and PPIs have been confirmed by pharmacokinetics and platelet aggregation studies.[42–44] In a recent meta-analysis, the combined use of PPIs and DAPT decreased GI bleeding but increased the rates of major adverse cardiovascular events, stent thrombosis, and repeated revascularization.[41] Thus, in CS, the GI bleeding benefits should be weighed against the thrombotic risk when prescribing PPIs to patients taking aspirin and clopidogrel.

In patients with CS and global hypoperfusion, there may be impaired absorption and metabolism of prodrugs requiring bioactivation (i.e. clopidogrel and prasugrel), particularly in the setting of OHCA and TTM. This in turn may result in an increased risk of in-stent thrombosis.[22] Consequently, a relatively slow onset of action and lower mean levels of platelet inhibition in patients treated with P2Y12 inhibitors, particularly for treated with clopidogrel compared with prasugrel or ticagrelor, confer a 'window of early high thrombotic risk' in CS (*Figure 3*).

Prasugrel and ticagrelor are newer-generation oral P2Y12 inhibitors characterized by more potent platelet inhibitory effect.[23] Clopidogrel should only be used in patients with high bleeding risk or in those with pre-existent atrial fibrillation (AF).[14,23] There are some clinical scenarios and therapies that further decrease the absorption and metabolization of P2Y12 inhibitors in the context of CS.

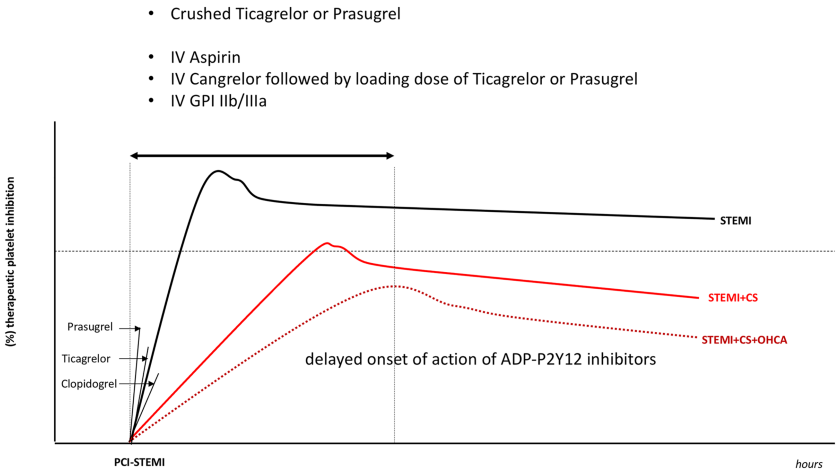
In a well-designed study, morphine was associated with delayed onset of action of the new P2Y12 inhibitors prasugrel and ticagrelor.[45] The morphine–antiplatelet agent interaction is likely a non-drug-specific phenomena probably related to the inhibition of the normal muscular activity of the stomach and the intestines, which may lead to vomit or delayed gastric emptying, which in turn delays absorption and decreases

Table 1 Antiplatelet administration: route, mechanism of action, advantages, and disadvantages

Drug	Route	Mechanism	Advantages	Disadvantages
Aspirin	Oral/crushed/IV	Irreversible inhibition of platelet function	No alternative, no hepatic bioactivation, renal clearance	Aspirin resistance, diminished effectiveness in SIRS
Clopidogrel	Oral/crushed	Thienopyridine, P2Y12 inhibitor, irreversible inhibition of platelet function, mean IPA 40–60%, 2–6 h after loading dose. Peak activity 4–8 h	Better safety profile in high bleeding risk, liver failure, severe renal failure	Prodrug, hepatic biotransformation, delayed gastric absorption, 5 days offset
Prasugrel	Oral/crushed	Thienopyridine, P2Y12 inhibitor, irreversible inhibition of platelet function. Peak activity 2 h after loading dose, IPA 85% at 6 h	Better, faster platelet inhibition than clopidogrel	Prodrug, hepatic biotransformation, 7 days offset
Ticagrelor	Oral/crushed	Non-thienopyridine P2Y12 inhibitor, reversible inhibition of platelet active drug, IPA 76% at 6 h	Does not require metabolic activation. Onset 30 min, peak 2 h; 72–120 h offset time	Contraindicated in liver failure
Cangrelor	IV	Non-thienopyridine P2Y12 reversible inhibition	Rapid onset 2–5 min, unaffected by severe hepatic or renal impairment	Short offset time (<60 min)
GPI IIb/IIIa	IV	Short-term GP IIb and IIIa receptor inhibition	Rapid onset/offset of action	Increase incidence of bleeding complications Very long offset time (5–7 h)

GP, glycoprotein; GPI, glycoprotein IIb/IIIa inhibitor; IPA, inhibition of ADP-induced platelet aggregation; IV, intravenous; SIRS, systemic inflammatory response syndrome.

Figure 3 Possible options to overcome delayed onset of action of antiplatelet therapies. CS, cardiogenic shock; GPI, glycoprotein inhibitor; IV, intravenous; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary interventions; STEMI, ST-elevation myocardial infarction.



peak plasma levels of orally administered drugs.[45–48] Morphine has a half-life of ≈2 h, and >8 h is needed to spontaneously reverse the effects of morphine. In a recent meta-analysis, morphine was associated with a delay in the onset of P2Y12 inhibitors that persists approximately 8 h, resulting in a greater prothrombotic milieu and more myocardial damage in patients with ACS.[48]

Fentanyl is a potent synthetic opioid used to alleviate severe and chronic pain and used as an adjunct to general or local anaesthesia.[49] A recent trial showed that fentanyl treatment in patients with ACS increased platelet reactivity compared with placebo.[50] Fentanyl administration impaired ticagrelor absorption and delayed platelet inhibition, resulting in excess of myocardial damage suggesting a possible class effect of opioids on antiplatelet drugs.

An alternative to oral $P2Y_{12}$ inhibitors is the intravenous administration of cangrelor, another P2Y12 inhibitor. Cangrelor intravenous infusion provides rapid onset of action (reaches its maximum concentration in 2 min), and interrupting the infusion results in a restoration of normal platelet function within 60 min.[51] Cangrelor bioavailability does not depend on hepatic and GI perfusion, and no dose modification is required depending on renal function,[51] supporting its role in CS settings (*Figure 3*). Cangrelor has excellent bioavailability, fast-acting properties, and a safe profile in renal impairment; it reduces ischaemic events and stent thrombosis compared with oral clopidogrel.[52] In a retrospective analysis of the IABP-SHOCK II trial, cangrelor had similar bleeding risk but better TIMI flow compared with orally administered antiplatelets.[53]

According to the 2017 STEMI guidelines recommendations, cangrelor may be considered in STEMI patients who have not received an oral P2Y12 receptor antagonist before PCI and GPIs were not administered and in whom the use of oral DAPT therapy is not possible, and the same level of recommendation may be applied to patients with CS.[23]

In CS, organ dysfunction, TTM in patients with OHCA, administration of fentanyl or morphine, gastroparesis, impaired emptying of the stomach, vomiting, or inability to swallow are associated with delay in the onset of effect of all antiplatelet medications.[14,54] The use of a high loading dose regimen of ticagrelor and prasugrel has been largely ineffective in accelerating platelet inhibition, while crushing tablets via nasogastric tube offers an early antiplatelet activity with a gain of only 1 h compared with the classic oral loading,[54–56] supporting utilization of intravenous cangrelor. In addition, the possibility of administering cangrelor in catheterization laboratories may lead to avoiding surgical delays for patients with mechanical complications of STEMI.[54,56,57] Cangrelor may provide a more favourable index of safety compared with GPIs, and in CHAMPION trials, cangrelor reduced peri-procedural thrombotic events similar as the combination of clopidogrel and GPI but with less bleeding events.[58] Cangrelor and ticagrelor can be administered together in high ischaemic risk patients, without significant drug-to-drug interaction and achieving greater and faster platelet inhibition, as shown in the CANTIC study.[59]

Transition from cangrelor to oral P2Y12 inhibitors requires the loading doses of clopidogrel (600 mg) and prasugrel (60 mg) to be administered at the end of the cangrelor infusion.[56,60] Administration of clopidogrel during cangrelor infusion can lead to inadequate P2Y12 inhibition, because clopidogrel's active metabolite is rapidly degraded if it is not bound to the receptor.[61] Ticagrelor can be administered during or after the cangrelor infusion.[60]

A recent randomized trial showed similar efficacy of loading dose of ticagrelor and prasugrel given at the start of the second hour of cangrelor infusion.[62]

Parenteral antithrombotic therapy with cangrelor should be considered to cover the period of delayed onset of oral P2Y12 inhibitors, and because of the lower bleeding risk, cangrelor is preferred over GPIs,[59] especially in patients with AMI–CS.

Glycoprotein IIb/IIIa inhibitors are very potent antiplatelet agents. Current guideline indications of GPIs (abciximab, eptifibatide, and tirofiban) are for bailout in situations such as high intraprocedural thrombus, abrupt vessel closure, slow flow, or no reflow (IIa/C).[63] The role of GPIs may also be to bridge platelet inhibition in patients naive to P2Y12 inhibitors and in patients who were just recently administered an oral P2Y12 inhibitor that has not had enough time to reach its full antiplatelet effect or when delayed absorption of P2Y12 inhibitors is presumed.

Data on the use of GPIs in ACS–CS are still limited; most of the trials included a low proportion of CS patients and were conducted in the era before routine use of novel oral P2Y12 receptor antagonists, ticagrelor and prasugrel.[64,65] In a recent meta-analysis, including 8585 STEMI patients predominantly treated with clopidogrel, routine use of GPIs significantly reduced the mortality 30 day and 6 month mortality and recurrent ischaemic events, but at the cost of an increased bleeding risk.[66] In a subgroup analysis of the ATLANTIC trial, which enrolled a contemporary STEMI population treated with ticagrelor, the use of adjunctive GPIs was associated with an increased risk of PLATO major bleeding and no further improvement in ischaemic outcomes at 30 days.[67]

In the PRAGUE-7 trial, the routine upfront use of abciximab did not improve outcomes in STEMI patients with CS.[68]

In the most recent meta-analysis, including six observational studies and PRAGUE-7 trial, GPI therapy as an adjunct to standard treatment in STEMI patients with CS was associated with a higher probability of achieving TIMI-3 flow and improved 30 day and 1 year survival without an increased bleeding risk.[69] However, in a sensitivity analysis by timeline of inclusion, the advantage conferred by GPI in short-term mortality disappeared after exclusion of older studies before year 2000. The potent antiplatelet activity of GPI, the intravenous use, and their rapid onset of action may denote an important advantage in CS settings, but finding a balance that minimizes both thrombotic and bleeding risks remains fundamental.[70] Particularly in CS patients, strategies to minimize bleeding should be applied and include shorter GPI infusions, dose adjustments of heparin (reduced dose of bolus and infusion), more frequent use of the TRA approach, and use of smaller sheaths.[71] Further randomized controlled trials to assess the benefit of GPIs in CS patients and in the context of novel oral P2Y12 receptor antagonists are urgently required.

Anticoagulants used in CS setting are unfractionated heparin (UFH), low-molecular-weight heparin (LMWHs), DTIs, and fondaparinux. UFH is the preferred option in CS, especially in PCI setting.[23,38] UFH should be used for PCI procedure in a loading dose of 70–100 IU/kg, which can be lowered to 50–70 IU/kg when using GPIs.[56] UFH contraindications are an allergy to heparin and heparin-induced thrombocytopenia (HIT). In case of severe bleeding, heparin can be reversed by protamine sulfate.

The activated partial thromboplastin time (aPTT) is used to monitor the anticoagulant effect of UFH, which is adjusted to achieve a predefined 'therapeutic range'. aPTT monitoring requires internal laboratory standardization, as numerous variables impact the result, including elevated levels of fibrinogen that result from acute phase reactions.[72,73] The standard therapeutic range, defined as 1.5–2.5 greater than the upper limit of normal, is mainly derived from older studies,[74] and a more recent study including a heterogeneous population suggested that this range could potentially lead to inappropriate UFH dosing.[75] An analysis of the OASIS study population found lower limit of the therapeutic range of 60 s to be associated with the lowest risk for recurrent ischaemic events.[76] Recent data support transitioning to anti-factor Xa heparin level monitoring, allowing to achieve the therapeutic anticoagulation range more rapidly, maintains the target values for a longer time, requires fewer adjustments in dosage and repeated tests, and yields more consistent result and is less prone to reagent variability.[77–80] The standard therapeutic range used is 0.3–0.7 U/mL.[79,81,82]

Nonetheless, there is uncertainty about the therapeutic intervals for both assays, and the results may be discordant.[82] Although either strategy is accepted, anti-Xa level monitoring could benefit patients with heparin resistance, a prolonged baseline aPTT, or altered heparin responsiveness.[81] For special populations with concomitant increased thrombotic and bleeding risks, as is the case of CS patients, both assays should be used for UFH monitoring.[82]

The activated clotting time (ACT) is typically performed bedside and can yield results rapidly. ACT is insensitive to heparin at lower concentrations, including concentrations in the therapeutic range (i.e. 0.3–0.7 U/mL), but prolongation of the ACT in response to heparin is fairly linear at heparin concentrations >1 U/mL.[84] Thus, the use of the ACT for monitoring low to moderate doses of heparin in critically ill patients cannot be recommended. In particular, the ACT is useful in areas where high concentrations of heparin are used, such as PCI or extracorporeal membrane oxygenation (ECMO).[14] Haemodilution and hypothermia can prolong the ACT.[83]

To note, patients with ACS–CS are already on double antiplatelet therapy, and the physician must balance the ischaemic vs. haemorrhagic risk. Therapeutic anticoagulation is not recommended after PCI, except for other indications such as the presence of mechanical valves, left ventricular (LV) thrombus, atrial fibrillation, or MCS.[23] All patients in CS without other indications for therapeutic anticoagulation should receive prophylactic doses because of prolonged bed immobilization.

Following the increase in the use of heparin for anticoagulation in CS patients, the incidence of bleeding and non-bleeding complications such as HIT also increases. Management of bleeding should be tailored to every patient with reverse of anticoagulation, transfusion (when the indication exists), and re-evaluation of anticoagulation strategy. HIT appears secondary to the administration of heparin (unfractionated or low molecular weight), and only type 2 HIT is clinically significant, as it manifests with low platelet count and thrombosis.[84] A sudden drop of 50% in platelet count 5–10 days after initiation of heparin with or without thrombosis should warrant HIT diagnosis workup.[84]

After establishing a diagnosis of HIT, all heparin products should be discontinued and replaced with other non-heparin anticoagulants. DTIs, such as argatroban (hepatic clearance) and bivalirudin (partial renal excretion), may be used for parenteral anticoagulation, but DTIs have not been studied in patients with CS. Bivalirudin is an alternative to UFH in PCI settings. Among its potential advantages are that it does not bind to plasma proteins, so it has a more predictable effect, and it does not cause HIT and may reduce bleeding complication. Fondaparinux, which is a synthetic pentasaccharide LMWH, is used for management of HIT.[85]

Therapeutic interventions in cardiogenic shock requiring specific antithrombotic regimens

Targeted temperature management and out-of-hospital cardiac arrest

Comatose survivors of OHCA pose a unique challenge, mostly because they are mechanically ventilated and thus unable to take drugs orally.[1] This can often lead to significant delays in the administration of many drugs until a gastric tube is inserted.[1,14] In addition, several other factors may play a role in the efficacy of antiplatelet drugs, including reduced intestinal drug absorption due to gastroparesis and hypoperfusion, therapeutic hypothermia, and increased platelet reactivity in response to systemic inflammation following resuscitation.[86,87]

Reducing a patient's temperature by 1°C decelerates cellular metabolism by 6–7%; therefore, artificial induction of 'therapeutic hypothermia' could provide metabolic protection.[88] However, hypothermia has several deleterious systemic consequences, including coagulopathy, electrolyte imbalance, haemodynamic changes, and altered drug pharmacokinetics.[89] These mechanisms place OHCA patients at a particularly high risk of acute and subacute stent thrombosis, ranging from 1.4% up to 31%.[90–92] Also, as a result of possible injuries due to chest compression, intubation, and trauma during the OHCA, these patients are at an increased risk of bleeding.[93,94]

Approximately 45% of comatose OHCA survivors had an insufficient response to aspirin.[95] The intravenous route is justified not only for initial but also for subsequent aspirin administration because the absorption of enterally administered aspirin remains affected by hypothermia.[87] The antiplatelet effects of all oral P2Y12 inhibitors, including ticagrelor, are known to be reduced by therapeutic hypothermia, leading to a higher rate of stent thrombosis.[96] P2Y12 inhibitors, even if given via a nasogastric tube, have delayed onset of antiplatelet activity, particularly in the case of clopidogrel.[92] Even for ticagrelor, there is still a 3–4 h delay until target platelet inhibition is reached.[97]

Peri-procedural treatment with intravenous cangrelor can bridge the 3 h gap in platelet inhibition following administration of the novel oral P2Y12 inhibitors via nasogastric tube in comatose survivors of OHCA.[87]

Glycoprotein IIb/IIIa inhibitors inhibit the platelet response to all agonists and are therefore more potent antiplatelet agents than cangrelor but at the cost of the increasing bleeding risk and thrombocytopenia that become clinical relevant in this fragile population with uncertain neurological status and possible injuries and trauma.[98] Also, the metabolism of cangrelor is independent from renal or hepatic function, commonly altered during CS and OHCA, that represents an important advantage compared with GPIs.[98,99]UFH is generally used, but CS patients on TTM who receive intravenous heparin experience reduced heparin metabolism because heparin's clearance is saturable and reduced at low temperature resulting in supratherapeutic aPTTs and requiring lowering heparin doses and specific monitoring protocols.[100]

Glycoprotein IIb/IIIa inhibitors may be used as a bailout strategy, but in a recent observational study including patients with OHCA treated with therapeutic hypothermia, the use of GPIs was associated with increased bleeding risk with no benefit with regard to thrombotic events.[101]

Mechanical circulatory support devices

Bleeding and ischaemic complications may occur simultaneously in patients with CS treated with MCS, and finding the optimal antithrombotic regimen is challenging. Bleedings occur because of heparin and antiplatetet therapy (both required in the prevention of pump and acute stent thrombosis) and due to device-related and disease-related coagulopathy. Different devices may require different intensity of anticoagulation. Patients on veno-venous ECMO require prophylactic heparin therapy. Full therapeutic heparin anticoagulation levels are recommended in intra-aortic

balloon pump, Impella, and venoarterial ECMO, to prevent clotting-related device failure. Anticoagulation in MCS is mostly based on pathophysiological considerations and experience, rather than on evidence, because prospective trials comparing UFH with other anticoagulants are lacking. From this perspective, UFH has a clinically acceptable risk–benefit ratio in patients with CS on MCS. Heparin is a short-acting anticoagulant targeting both the intrinsic and extrinsic systems, has a short half-life and is readily reversible by protamine, has a predictable effect in critically ill patients with widely accepted monitoring, and is not contraindicated in renal failure.[102]

One major disadvantage of UFH therapy in patients on ECMO is HIT. Although up to 70% of patients on cardiopulmonary bypass develop anti-PF4 heparin antibodies, only 0.3–4% had proven HIT.[103] A potential solution in HIT in patients with MCSs, especially when heparin is contraindicated, is DTIs, but these molecules have renal and hepatic clearance affected by shock states and challenging monitoring.[104]

Unfractionated heparin monitoring can be very challenging, and the UFH dose–response effect is unpredictable because of the indirect effect on the coagulation cascade via antithrombin (AT).[102,104] Indeed, acquired AT deficiency is common in intensive care unit patients due to decreased production, increased losses, or consumption by the MCS. aPTT may not provide an accurate measure of UFH anticoagulant effect due to of various confounding factors, which are more marked in critically patients (low fibrinogen, liver failure, and inflammation). Values of aPTT 1.5–2.5 times the control value or ACT 180–300s indicate efficient anticoagulation, but prospective trials assessing optimal UFH levels are lacking.[105] Anti-FXa level monitoring may be superior to ACT or aPTT monitoring,[106] as it is not significantly affected by these confounding factors and has been proposed as a first-choice assay for monitoring UFH during MCS.[107]

Another test used to monitor UFH anticoagulation is thromboelastography, which includes platelet effects and fibrinolysis, but there are no clinically implemented protocols.[108]

Patients with ACS–CS on MCS require triple antithrombotic therapy, and in this instance, ticagrelor and prasugrel should be avoided, clopidogrel remaining the preferred option. When clinical setting of CS is cardiac arrest, intravenous cangrelor should be used to support the delayed onset of action of clopidogrel.

Left ventricular assist devices

Although most patients with CS require anticoagulation and/or antiplatelet therapy because of a history of atrial fibrillation, thrombosis, or ischaemic heart disease, normalization of coagulation before left ventricular assist device (LVAD) implantation is crucial to avoid the post-operative bleeding, transfusions, and volume overload with subsequent right ventricular (RV) failure and surgical re-exploration.[109]

Recommendations for preoperative antiplatelet management are to continue aspirin until the day of surgery and discontinue ticagrelor, clopidogrel, or prasugrel 3, 5, or 7 days before surgery, respectively.[110] Vitamin K antagonist (VKAs) are regularly stopped 3–5 days before surgery to obtain an international normalized ratio (INR) <1.5.[109] In patients having urgent or emergency surgery, the effect of VKA can be completely reversed by administering prothrombin complex concentrate.[109–110] Depending on the indication for anticoagulation, bridging with UFH and LWMH can be used to limit the time off anticoagulation prior to surgery. LMWH should be discontinued 12 h prior to surgery and UFH 6 h prior to surgery.[111] Preoperative temporary MCS, in particular VA-ECMO, requires continuation of antithrombotic regimen with intravenous UFH.[109]

In the early post-operative phase, the International Society for Heart and Lung Transplantation guidelines recommend initiating intravenous UFH within 48 h after LVAD implantation. The target aPTT is 40–60 s.[112] From the third post-operative day, upward titration of UFH is recommended to achieve an aPTT in the regular therapeutic range of 60–80 s. This should be continued after initiation of VKA therapy, till international normalized ratio (INR) levels are within target range.

One small observational study, including 78 LVAD patients, assessed the feasibility of LMWH as transition to warfarin.[113] The outcomes of this study were favourable with rapid and constant biological activity monitored by determination of anti-factor Xa levels and low risks of adverse events. However, UFH may still be preferred in the immediate post-operative phase given its easier reversibility by protamine and better feasibility in renal failure. During UFH or LMWH administration, physicians should screen for the occurrence of HIT, which most frequently occurs 5–10 days after initiation of heparin therapy. Once confirmed or strongly suspected, immediate implementation of an alternative non-heparin anticoagulation regimen such as argatroban or bilivarudin is indicated.[114]

In the early post-operative phase, due to the fragile balance between bleeding and thrombosis, LVAD patients may experience potentially adverse events leading to death or hampering the future cardiac transplantation. Major bleedings, including surgical bleeding, and neurological events (ischaemic and haemorrhagic stroke) are among the most common disabling and life-threatening events after LVAD implantation. Because there are no randomized clinical trials to guide antithrombotic recommendations for neurological and bleeding events in LVAD patients, management decisions (fibrinolysis for ischaemic stroke and temporary

interruption or even reversal of anticoagulation for haemorrhagic stroke and major bleeding) should be taken in Heart Team.[115]

Renal replacement therapy

During RRT, effective anticoagulation of the extracorporeal circuit is mandatory to prevent clotting of the circuit or filter and to maintain filter performance. Clotting of the blood within the circuit reduces solute clearance and may cause blood loss. In addition, a short filter lifetime increases workload and overall treatment cost.[14,102] The most common mode of anticoagulation is systemic administration of UFH. Although being implemented in clinical practice, systemic heparin anticoagulation in RRT exhibits some major and minor adverse effects including bleeding events, HIT-II, pro-inflammatory effects, and ineffective anticoagulation due to heparin resistance.

During RRT, UFH can be infused through a separate line or directly into the extracorporeal circuit, and in most cases, a direct infusion into the arterial limb of the RRT circuit is chosen.[116] The rationale is that the highest heparin concentration is present at the prefilter site and thus at the location where the coagulation system is activated predominantly.[117] The heparin effect can be controlled through aPTT measurements or as point-of-care test through the ACT. The target range is prescribed under consideration of the patient's bleeding risk and may vary widely.

In contrast to UFH, LMWHs are primarily cleared via renal excretion, and without appropriate monitoring, LMWHs can accumulate and increase the risk of bleeding.[118] Furthermore, LMWH dose adjustments to reduce the risk for bleeding in CS patients on dialysis are difficult to provide, and finally due to the variability in reported anti-Xa activity and lack of proven benefits with measuring and adjusting the dose of LMWH in this setting, caution should be considered.[119]

Antithrombotic therapies in settings of cardiogenic shock in non-acute coronary syndrome conditions

Regardless of the aetiology, patients with CS have high risk of deep venous thrombosis and pulmonary embolism (PE), and similarly to patients hospitalized for heart failure, thromboembolism prophylaxis (e.g. with LMWH) is recommended (Class IA) in patients not already anticoagulated and with no contraindication to anticoagulation. Further on, to safely balance the increased risk of thrombosis and bleeding, antithrombotic management should be adjusted to CS clinical scenario or specific device, with individualized antithrombotic regimens in terms of type of treatment, dose, and duration.[120]

Takotsubo syndrome

Cardiogenic shock primarily due to acute LV dysfunction occurs in 4–20% of patients with takotsubo syndrome, having a high mortality rate (17–30%).[116,121]

Expert consensus documents agree on the withdrawal of P2Y12 inhibitors once type 1 AMI has been excluded.[122] Also, aspirin had no impact on the incidence of major adverse cardiac and cerebrovascular events at 30 day and 5 year follow-up, as suggested in a retrospective analysis of a large database of takotsubo patients.[123]

Thrombus formation in the akinetic ventricular apex has been observed in 2–8% of takotsubo syndrome patients.[124] Efficient anticoagulation is recommended if intraventricular thrombus is detected until its resolution and LV function recovery, as well as in other concomitant indications for anticoagulation.[122] As catecholamines are contraindicated, MCS may have a more forward indication, and therefore, efficient anticoagulation will also be necessary in many other patients with takotsubo syndrome associated with CS.[1,2,122]

Left ventricular noncompaction

Left ventricular noncompaction is a rare cause of CS,[125] only a minority of patients evolving with CS, particularly those having a mid-basal involvement and reduced left ventricular ejection fraction (LVEF).[126] The extensive trabeculation of the LV cavity with deep intertrabecular recesses creates the premises for local thrombosis and the potential for thrombo-embolic complications.[127] Data from small case series and cohort studies described initially a higher thrombo-embolic risk (up to 24%) in patients with left ventricular noncompaction (LVNC), considering the need for therapeutical anticoagulation,[128,129] but such a high risk was not confirmed in the studies with longer follow-up periods (up to 7 years) in the absence of atrial fibrillation, severe systolic dysfunction (EF $<$ 40%), a history of embolic events, or LV cavity thrombosis.[130,131] LVNC by itself was not associated with the increase in thrombo-embolic event rates; therefore, an indication for anticoagulation is not reasonable unless other pathologies who meet standard criteria for anticoagulation according to current guidelines are present.[130,131]

Even in setting of CS, current data justify only prophylactic anticoagulation in LVNC.[130,131]

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is an idiopathic dilated cardiomyopathy that occurs in the last month of pregnancy or within 5 months post-partum in previously healthy women.[132,133] PPCM is associated to poor prognosis, the combined rate of death, or need for transplant ranging from 10% to 30%.[134,135]

Patients with significantly depressed LV function (LVEF $<$ 35%) may benefit from anticoagulation therapy to prevent thrombo-embolism as the procoagulant activity during the perinatal phase is very high[132] and thrombo-embolism is one of the most common complications in PPCM.[136]

Unfractionated heparin does not cross the placenta, and the ESC guidelines recommend heparin in all patients with acute PPCM and LVEF $\leq$ 35% and at least prophylactic heparin in those who have received bromocriptine, as thrombo-embolic events have been reported during the use of this drug.[137] The American Heart Association/American College of Cardiology guidelines have a lower LVEF threshold and suggest anticoagulation with LMWH or UFH only if the LVEF is $<$30% during late pregnancy or up to 6–8 weeks post-partum and in patients treated with bromocriptine. Patients in CS on MCS need anticoagulation with intravenous UFH.[138,139]

No published data are available to guide the decision of therapeutic vs. prophylactic anticoagulation in PPCM. Therapeutic anticoagulation with LMWH or UFH is recommended for patients with PPCM and atrial fibrillation or mechanical valves. UFH may be used around the time of delivery if the maintenance of anticoagulation is critical and when the ability to reverse anticoagulation urgently using protamine is advantageous.[140]

Prosthetic valve thrombosis

Patients with mechanical valve thrombosis are a high-risk subgroup for whom fibrinolytic therapy may be urgently and/or emergent indicated to specifically address the underlying pathophysiology and restore haemodynamic stability.[141–143]

The 2020 American College of Cardiology/American Heart Association guideline for the management of patients with valvular heart disease now recommends urgent initial treatment with either slow-infusion low-dose fibrinolytic therapy or emergency surgery for obstructive prosthetic valve thrombosis as first-line treatment strategies with Class IB indication.[144] A high surgical risk, first-time episode of prosthetic valve thrombosis, a smaller clot ($<$8 mm), and no atrial thrombosis favours fibrinolysis when compared with surgery.[144]

In the recent 2021 ESC/EACTS guidelines for the management of valvular heart disease, fibrinolysis should be considered when surgery is not available or is very high risk, or for thrombosis of right-sided prostheses (Class IIa/B).[145] Two fibrinolytic regimens are recommended, recombinant tissue plasminogen activator 10 mg bolus + 90 mg in 90 min with UFH or streptokinase 1 500 000 U in 60 min without UFH.[145]

Atrial fibrillation

The incidence of new-onset AF in critically ill patients ranged between 6% and 20%.[146] A higher incidence, 30–40%, is observed after mitral valve and coronary artery bypass graft surgery.[147,148] Overall, AF is associated with cardioembolic events, longer hospital stays, and increased mortality.[149,150]

Non-acute coronary syndrome cardiogenic shock and atrial fibrillation

While evidence for therapeutic anticoagulation in severe heart failure without atrial fibrillation is inconclusive,[151] this should be considered in all patients with AF for stroke prevention (CHA_2DS_2-VASc score $\geq$1 male and 2 female). The additional risk of thrombo-embolic complications is even higher in critically ill patients due to ongoing inflammation, the procoagulant state, and the complete immobilization.[152]

The cardioembolic risk and the individual bleeding risk can be established using CHA_2DS_2-VASc and HAS-BLED scores, although they were not validated in the setting of critical illness.

Acute coronary syndrome–cardiogenic shock and atrial fibrillation

The issue of antithrombotic therapy in ACS–CS and AF is challenging, and special considerations are needed to determine the optimal antithrombotic treatment, to reduce the risks of ischaemic events without increasing the risk of bleedings.

In ACS–CS, antithrombotic therapy does not differ from that in any ACS patient, but precaution is needed, as triple therapy increases two-fold to three-fold the risk of bleeding complications compared with anticoagulation alone.[23]

Neither prasugrel nor ticagrelor should be used in patients as part of triple antithrombotic therapy with aspirin and oral anticoagulation, due to the excess risk of bleeding.[23,28] Switching patients from triple to dual therapy (i.e. preferentially DOAC + P2Y12 inhibitor) should be performed after 1 month, as the thrombotic risk is highest during the first 30 days, whereas the bleeding risk is equally distributed over time. Shorter duration of antithrombotic therapy should be

considered when the haemorrhagic risk is elevated.[14,23,28] As the risk for haemorrhagic events in case of triple antithrombotic therapy is high, the dose intensity of parental anticoagulation with UFH should be carefully monitored with a target aPTT in the lower range of the recommended target.[152]

Cardiogenic shock in settings of acute pulmonary embolism

In patients with high-risk PE, parenteral anticoagulation with UFH, LMWH, or fondaparinux must be started immediately, but UFH remains the first option for patients with CS and in those with severe renal impairment (creatinine clearance $<$30 mL/min) or severe obesity.[153–155]In patients with PE and CS, systemic thrombolytic therapy compared with UFH is associated with a more rapid reduction of pulmonary artery pressure, pulmonary vascular resistance, right ventricle (RV dilation), and a significant reduction of overall mortality.[153,154] Accelerated intravenous administration of recombinant tissue-type plasminogen activator 100 mg over 2 h is preferable to prolong infusions of streptokinase and urokinase.[155] UFH may be administered during continuous infusion of recombinant tissue-type plasminogen activator but should be discontinued during infusion of streptokinase or urokinase.

Anticoagulation with UFH, LMWH, or fondaparinux should be continued in parallel with the VKA for $>$5 days and until INR value has been 2–3 for two consecutive days.[155]

When thrombolysis is contraindicated or has failed, percutaneous catheter-directed treatment or surgical embolectomy should be considered for patients with high-risk PE, including those with CS.[155] In patients with refractory CS, VA-ECMO may be considered in combination with surgical embolectomy or catheter-directed treatment but is associated with a high incidence of complications, and the results depend on the centre experience. The increased risk of bleeding related to the vascular access should be considered, particularly in patients previously undergoing systemic thrombolysis.[156]

Cardiogenic shock in settings of COVID-19 infection

COVID-19 infection is associated with a prothrombotic state, which can manifest as microvascular, venous, or arterial thrombosis, exacerbating organ injury. CS in settings of COVID-19 infection includes a broad spectrum of diseases manifesting with single or biventricular failure.[157,158] Severe LV dysfunction leading to shock has been reported in COVID-19 due to myocarditis, STEMI, or worsening of underlying cardiovascular disease. CS due to RV failure may develop because of PE or acute pulmonary hypertension due to hypoxia and/or high airway pressures.[159,160] CS secondary to AMI with large thrombotic loads can occur in the context of an infection with high inflammatory and prothrombotic potential, and powerful parenteral antiplatelet agents such as GPIs or cangrelor can be considered. There have been reports of interactions (related to CYP3A4) between some of the antiviral drugs, particularly lopinavir/ritonavir and darunavir/cobicistat, and clopidogrel and ticagrelor.[161] These interactions decrease the formation of the active metabolite of clopidogrel decreasing its antiplatelet efficacy, whereas they increase the concentrations of ticagrelor and increasing its antiplatelet efficacy. For this reason, the use of prasugrel has been proposed in patients treated with antiviral drugs.[162] Cangrelor may be of particular interest because there are no pharmacological interactions with antiviral COVID-19 drugs.

Typical changes in coagulation parameters among patients with COVID-19 include increased D-dimer and fibrinogen levels, aPTT prolongation, and decrease of AT levels.[163,164] This hypercoagulable state, particularly when associated to immobilization, prolonged ventilation and the direct viral-induced endothelial injury and increase the risk of thrombo-embolic complications.[163,164] Although there is no standardized management of severe and critical COVID-19 cases, routine anticoagulation with at a least prophylactic dose is recommended.[164,165] The decision between a prophylactic or therapeutic dose should be individualized depending on the thrombotic vs. haemorrhagic risk, until results from the currently enrolling anticoagulation trials (IMPACT and IMPROVE) in severe COVID patients are available and a more informed recommendation can be made.[166,167] Physiological reasoning suggests a possible resistance to UFH due to the decreased AT level.[163,164] Therefore, LMWH could be preferred for most patients, while UFH should be reserved for patients with severely decreased glomerular filtration rate.[164]

Conclusions

Cardiogenic shock patients require close management of antithrombotic therapies to safely balance the increased risk of bleeding and thrombosis. However, most of the evidence base for any of these drugs is derived from randomized trials conducted among patients undergoing revascularization for ACS without haemodynamic instability. Further research, including new antithrombotic therapies or more adapted antithrombotic regimen to CS clinical scenario or specific device, is required in order to optimize safety and efficacy of these therapies in patients with CS.

Conflict of interest

RIR, TBG, MA, ELA, MA, APA, OG, YL, AL, OM, MM,JP, SPC have nothing to disclose.

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