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Thromboprophylaxis with argatroban in critically ill patients with sepsis: a review

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During sepsis, an initial prothrombotic shift takes place, in which coagulatory acute-phase proteins are increased, while anticoagulatory factors and platelet count decrease. Further on, the fibrinolytic system becomes impaired, which contributes to disease severity. At a later stage in sepsis, coagulation factors may become depleted, and sepsis patients may shift into a hypo-coagulable state with an increased bleeding risk. During the pro-coagulatory shift, critically ill patients have an increased thrombosis risk that ranges from developing micro-thromboses that impair organ function to life-threatening thromboembolic events. Here, thrombin plays a key role in coagulation as well as in inflammation. For thromboprophylaxis, low molecular weight heparins (LMWH) and unfractionated heparins (UFHs) are recommended. Nevertheless, there are conditions such as heparin resistance or heparin-induced thrombocytopenia (HIT), wherein heparin becomes ineffective or even puts the patient at an increased prothrombotic risk. In these cases, argatroban, a direct thrombin inhibitor (DTI), might be a potential alternative anticoagulatory strategy. Yet, caution is advised with regard to dosing of argatroban especially in sepsis. Therefore, the starting dose of argatroban is recommended to be low and should be titrated to the targeted anticoagulation level and be closely monitored in the further course of treatment. The authors of this review recommend using DTIs such as argatroban as an alternative anticoagulant in critically ill

patients suffering from sepsis or COVID-19 with suspected or confirmed HIT, HIT-like conditions, impaired fibrinolysis, in patients on extracorporeal circuits and patients with heparin resistance, when closely monitored. *Blood Coagulation and Fibrinolysis* 33:239–256 Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

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Sepsis

The number of patients hospitalized for sepsis has been increasing worldwide for decades [1–4]. Sepsis is the most common cause of death in hospitalized patients. In Germany, the incidence of sepsis increased by 5.7% from 2007 to 2013 [5]. Although the overall mortality rate among patients with sepsis is declining [1–5], an increase in severe sepsis with organ failure can be observed [2,6,7]. Since 2016, organ failure has been a mandatory component of the new sepsis definition [8].

Sepsis is characterized by a dysregulated host response to pathogen-associated molecular patterns (PAMPs) and host-derived damage-associated molecular patterns (DAMPs) triggering the proinflammatory response [9]. This leads to severe organ dysfunction, whereby inflammation and coagulation interact in a complex way [10], leading to an exaggeration of both systems. When immune response

and coagulation become exaggerated during sepsis, tissue and organ damage can occur [8].

After the initial shift to a pro-coagulatory state characterized by tissue factor (TF)-mediated endothelial dysfunction, activation of the coagulation system and fibrin deposition in the microcirculation [11], later stages of the disease-related interplay between coagulation and immune response to inflammation may lead to consumption of platelets and coagulation factors associated with coagulopathy and a strong tendency to overt bleeding [12]. Sepsis is the most common clinical picture associated with coagulopathy in critical care medicine and sepsis involving the coagulation system is associated with a worse prognosis for the patient [13,14].

Recently, high mortality and its relationship with thromboembolic diseases in COVID-19 have been reported [15–17]. Despite the limited knowledge of this disease,

the characteristics of COVID-19-associated coagulopathy are distinct from those seen in DIC [18]. Whereas DIC in bacterial sepsis is characterized by a more thrombotic phenotype in the earlier and a hypocoagulability with decreased clot firmness in viscoelastic tests and low antithrombin activity in the later course of the disease [19,20], COVID-19-associated coagulopathy is characterized by hypercoagulability as indicated by increased clot firmness in viscoelastic tests and normal antithrombin activity [21–23]. Both conditions are characterized by impaired fibrinolysis or even fibrinolytic shutdown in severe cases [21,24,25].

Coagulation in sepsis

The pro-coagulant shift in sepsis initially comprises high levels of fibrinogen and FVIII as acute reactant [26,27] and complement-mediated endothelial damage characterized by elevated von Willebrand factor concentrations with ultra-large multimers [11,28,29] due to decreased ADAMTS13 levels [30,31]. High levels of ultra-large VWF multimers in combination with low ADAMTS13 activity are associated with disease severity and with parameters of inflammation and disseminated intravascular coagulation [32–34].

Both coagulation pathways, the TF pathway as well as the contact pathway, play an important role in the pathogenesis of sepsis. Activated FXII activates FXI and *vice versa*. The FXII pathway is activated via platelets, immune cells or their microparticles [35]. Although total FXI levels appear to be decreased in sepsis, the reduced form of FXI, modified by cleavage of disulphide bonds, is increased in patients with sepsis and correlates with disease severity and platelet count as a marker of sepsis-induced DIC [36].

TF also plays a crucial role in the pro-coagulatory shift during sepsis and contributes to disease severity, as this factor is not only presented on cells of subendothelial tissue, but also on activated platelets, endothelial cells and immune cells [37]. Notably, TF expression on circulating cells (monocytes) and microparticles can be measured by NATEM CT and is associated with increased mortality [37–39]. Therefore, gene polymorphisms regarding TF expression, for example of the NF-kappa B promoter gene, play an important role in sepsis [39].

Concurrent with these coagulation deficiencies, levels of coagulation inhibitors such as antithrombin [26,40] and protein C [41,42] may be decreased, which is explained by consumption due to increased activation of the coagulation system. Furthermore, serum thrombomodulin, a biomarker of endothelial dysfunction, is increased during sepsis [42,43]. These factors are all associated with sepsis severity, organ failure and outcome [40–43].

The mechanism of procoagulant response in sepsis is complex and often accompanied by a decrease in the platelet

count [26,27] that is attributed to the formation of fibrin-platelet-thrombi, platelet-neutrophil aggregates, neutrophil extracellular traps (NETs) in the microvasculature and a dysregulated balance of platelet formation in the bone marrow and an increased consumption by the infectious condition [44]. The extent of thrombocytopenia is associated with increased mortality [26,27,45], especially when thrombocytopenia is persistent [46,47]. In addition, the proportion of immature platelets increases in sepsis [48].

Reports about platelet function in sepsis are conflicting. On the one hand, increased platelet activation may initially occur during sepsis [49–52], whereas vWF-dependent platelet adhesion seems to be impaired [51]. Also, platelet surfaces and their granule content provide a substrate for plasmatic coagulation activation via, for example, polyphosphates that activate the contact pathway [53]. In addition, the platelet-derived extracellular vesicles (PEVs) or microparticles (PMPs) provide such a pro-coagulatory surface [35] and enhance the procoagulant response in sepsis.

On the other hand, flow cytometry shows a change in platelet receptor patterns, whole blood impedance aggregometry demonstrates early platelet dysfunction in sepsis [54–57]. Furthermore, bacterial toxins seem to result in desialylation of platelet glycoproteins and accelerated platelet clearance by hepatic Ashwell-Morel receptors, which play an important role in bacterial sepsis [58,59]. Here, the P2Y₁₂ receptor inhibitor ticagrelor and the antiinfluenza sialidase inhibitor oseltamivir have shown some therapeutic benefits [60,61].

Platelets are also involved in immune response and therefore interact with various immune cells [62]. For example, platelets bind to neutrophils and initiate the formation of NETs, a host defense mechanism [63]. Furthermore, they bind to monocytes and form aggregates, which increases the inflammatory response [64].

Thrombin, on the contrary, also plays a crucial role in the initiation of endothelial dysfunction, which is a characteristic disease during sepsis and especially septic shock [65]. During septic shock, large amounts of thrombin are generated via various mechanisms. Although longer lag times in thrombin generation have been observed during sepsis, the thrombin is formed with higher-velocity indices during thrombin generation [66]. In sepsis the high thrombin levels lead to direct disruption of the endothelial barrier mainly via PAR-1, thus unravelling the basal membrane, a subcellular structure that is highly pro-coagulant [67], and resulting in the formation of microvessel thrombi that impair microcirculation and oxygen supply to the tissue. The latter enhances a vicious circle by induction of hypoxia, which stimulates hypoxia-inducible factor (HIF)-1, which in turn enhances PAR-1 [68] expression and also endothelial disruption via the formation of VEGF [69].

Another shift to pro-coagulation is the 'fibrinolytic shut-down'. It becomes important once thromboses have formed. Although tissue-derived plasminogen activators (t-PA) are elevated during sepsis, fibrinolysis inhibitors, plasminogen activator inhibitor 1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI) increase as well [25,70]. The increase in PAI-1 levels consequently affects fibrinolysis more than does t-PA [70], and the higher the PAI-1 levels are during sepsis, the worse the outcome is, as seen in a study where PAI-1 levels were significantly higher in deceased patients [71]. In short, impaired fibrinolysis and fibrinolytic shut-down are not only associated with sepsis severity and mortality [70], but can also be used to discriminate between sepsis and SIRS in critically ill patients [72,73]. Furthermore, impaired fibrinolysis and fibrinolytic shut-down are also associated with increased markers of cellular damage and morbidity [74].

From an evolutionary point of view, this pro-coagulatory shift must have an advantage. This can be seen from the fact that septic patients who have shifted into a hypo-coagulable state present increased mortality [75]. One can speculate that the advantage produced by the pro-coagulatory state is most likely due to the coagulation system being a part of host defense and inflammation.

Recent studies have revealed that each of the coagulation factors plays a role in host defense and inflammation. For instance, FXII and plasma prekallikrein reciprocally activate each other and result in the release of bradykinin. There are also hints that both FXII and FXIIa upregulate neutrophil functions, contribute to macrophage polarization and induce T-cell differentiation [76]. Moreover, complement factors are more correlated to coagulation factors than to inflammation [77]. The extent of complement activation is related to DIC, sepsis severity and outcome during sepsis [78].

Not only do the individual coagulation factors function as part of the immune system, but activation of the coagulation system also leads to fibrin formation and thus also functions as part of the immune system. High fibrinogen levels during sepsis are associated with increased survival [26,27,79].

The reason why fibrinogen has a positive effect on survival during sepsis could be that it helps the immune system limit bacterial growth and enhance bacterial clearance [80]. The fibrin net captures and immobilizes invasive bacteria [81], thus restricting local spreading [81,82]. Once fibrinolysis sets in, plasminogen releases fibrinogen-derived so-called AMPs (antimicrobial peptides), thus creating an antimicrobial environment in the clot. Such a peptide is the BB15–42 fragment and an unambiguous antimicrobial effect of this protein was already proven by *Staphylococcus aureus*, group A streptococci (GAS) and group B streptococci (GBS) [83]. In addition, this peptide binds to the vascular endothelial cadherin (VE cadherin) of the endothelial cells and

thereby reinforcing the tight junctions, which has a positive effect on organ failure and survival of sepsis [84,85]. The importance of fibrinogen, fibrinolysis, and the consequently released peptides during sepsis and their beneficial impact on infection, multiple-organ dysfunction and reduced mortality have already been proven in several clinical studies [86–88]. Thrombosis as host defense during infection and inflammation is also called 'immuno-thrombosis' [89].

Although a pro-coagulatory state in sepsis is associated with better outcome regarding survival and organ function [90], when coagulation becomes exaggerated, it contributes significantly to organ dysfunction and higher mortality from sepsis [91]. Furthermore, thrombin itself has proinflammatory properties [92], which are attenuated when direct thrombin inhibitors (DTIs) are used [93,94]. In this context, thrombin plays a significant role, as it is the direct driver of fibrin formation as well as inflammation and is therefore a critical factor for the development of thrombosis and inflammation.

Summary

During sepsis, an initial pro-coagulatory shift takes place, in which both coagulation pathways, the TF as well as the contact pathway, are involved. Acute phase proteins such as fibrinogen, FVIII and vWF are increased. At the same time, anticoagulatory factor deficiencies occur, while biomarkers of endothelial dysfunction are elevated. Another mechanism of the pro-coagulatory shift of the coagulation system is the fibrinolytic shut-down that contributes to disease severity.

At a later stage in sepsis, coagulation factors are depleted as a result of synthesis impairment or consumption or both, and sepsis patients shift into a hypo-coagulable state, which can be associated with an even worse outcome.

The reason for the initial pro-coagulatory shift in sepsis patients could be that platelets and coagulation factors dependent thrombosis play a crucial role in the patient's immune response; both act as direct host defense and limit pathogen dissemination or modulate inflammation via, for example, binding to immune cells. At any stage, when coagulation becomes exaggerated, it is associated with adverse outcome during sepsis. In this context, thrombin plays a significant role since it is the direct driver of fibrin formation and is therefore a critical factor for the development of thrombosis.

Thrombosis risk in critically ill patients

Due to systemic inflammation and the pro-coagulatory shift as host responses, critically ill patients are at an increased risk for developing thrombosis. These thromboses comprise a whole clinical spectrum ranging from micro-thrombosis that impair organ function to directly life-threatening events such as pulmonary embolism or

disseminated intravascular coagulation with early broad microvessel thrombosis and later, after broad consumption of coagulation factors, a severe bleeding state with life-threatening bleeding complications.

The incidence of deep vein thrombosis (DVT) is about 10–30% in critically ill patients who receive no thrombosis prophylaxis [7]. The rate of DVT is even higher in posttraumatic patients, namely up to 60% in the first 2 weeks after trauma. When an acute spinal cord injury is involved, the incidence of DVT increases up to 80% [95].

The administration of thrombosis prophylaxis reduces the incidence of thrombotic events in critically ill patients. The administration of heparin halved the risk of thrombotic events in medical-surgical critically ill [96] as well as trauma patients [95]. This might also influence mortality rates. The mortality rate in patients with thromboprophylaxis decreased significantly compared with that in patients not receiving prophylaxis, with the exception of patients with ischemic stroke [97].

Despite appropriate thrombosis prophylaxis, the rate of thrombotic events in critically ill patients remains high. Patients receiving thromboprophylaxis with heparins after acute ischemic stroke showed smaller rates of DVT and pulmonary embolism, but thrombotic events could not be completely prevented [98]. The overall incidence of DVT in medical and postsurgical critically ill patients despite receiving thrombosis prophylaxis is still between 7.5 and 12% [99–101]. In severely injured trauma patients, namely the patient population with the highest risk for thrombosis, the incidence of DVT is still about 15–22% [102–104] and the rate of pulmonary embolism in these patients is between 3 and 6% [103,105]. In critically ill patients with sepsis, the incidence of thrombotic events is also very high, ranging from 10.8 to 16.9% [26,106]. Clinically, the administration of unfractionated heparin, as for example in ECMO patients, is also challenging, as it is difficult to achieve the aPTT target range because the effect of heparin is dependent on many factors such as antithrombin, plasma protein concentration and so on. Therefore, a substance that is clinically easier to handle is of great interest in septic patients with unfractionated heparin therapy.

Summary

Due to systemic inflammation and the pro-coagulatory shift, critically ill patients have an increased thrombosis risk that ranges from developing micro-thromboses that impair organ function to life-threatening thromboembolic events. Depending on the underlying disease, the rate can be up to 80% in patients, when not anticoagulated. Even in anticoagulated patients, the incidence of thrombosis remains relatively high, especially in trauma patients and patients with systemic inflammation or sepsis.

Thrombin and protease-activated receptors

Thrombin activates several cell types such as platelets, immune cells, vascular smooth muscle cells or endothelial cells via the protease-activated receptors (PARs) with the exception of PAR2, although transactivation of PAR2 by cleaved PAR1 can happen in endothelial cells, especially when PAR-1 signalling is inhibited [107]. In humans, certain types of PARs depend on the cell type. For instance, in platelets, only PAR1 and PAR4 are expressed [108–110].

When thrombin activates PARs, the concentration of thrombin determines which type of receptor will be activated. PAR1 exclusively signals low thrombin concentrations, while PAR4 becomes the dominant player when high levels of thrombin are present [111,112].

PARs play a crucial role in coagulation, inflammation, embryogenesis, wound healing and cancer growth [113]. Apart from thrombin, these receptors have many different endogenous as well as exogenous ligands that induce different signalling pathways, especially regarding inflammation and activation and aggregation of platelets [114].

PAR1 has a critical role in maintaining the platelet activation induced by ADP [115]. Furthermore, binding and signalling via PAR1 requires the participation of GPIIb α and ADP to amplify the PAR1 responses, while PAR4 is activated independently of GPIIb α and ADP [111]. Binding to GPIIb α and PAR4 leads to the formation of thrombin-induced reactive oxygen species (ROS) [116]. ROS are known to be necessary for intra-platelet signalling and subsequently for further platelet activation. A further pro-coagulatory role of thrombin binding to platelets via PAR1 is the release of heparanase. Heparanase itself forms a procoagulant active complex with TF and thus enhances coagulation via the TF pathway. The same happens when thrombin binds to the PARs of granulocytes, for example, neutrophils [117].

Due to the net pro-coagulatory role of PAR signalling, the blocking of the thrombin receptors has become of clinical interest in reducing atherothrombotic events. One approach is the blocking of PAR1 or PAR4. A PAR4 blocker is under development [118] and vorapaxar, a PAR1 inhibitor, already has market authorization for the prevention of recurrent ischemic events in patients with prior myocardial infarction or peripheral artery disease [119]. The PAR1 inhibitor is not only effective, but also associated with an increased risk of bleeding [120–123], which therefore may limit its use in critically ill patients and especially patients suffering from sepsis.

Inhibition of these thrombin receptors is not only interesting with regard to prevention of thromboembolic events, but also because PARs play a role in cancer genesis as a result of their role in angiogenesis. Stimulation of PAR1 and PAR4 in platelets mediates angiogenesis via

the secretion of vascular endothelial growth factor (VEGF) [124]. Furthermore, PAR-1 activation on endothelial progenitor cells promotes cell proliferation and contributes to neo-angiogenesis [125].

As thrombin binds to PAR and promotes angiogenesis, it makes a crucial contribution to regulating wound healing or tumour spread. Thrombin binding to PAR1 in glioma cells participates in malignancy and glioblastoma neo-angiogenesis [126], resulting in glioma growth [127].

The PARs also play an important role in inflammatory processes. PAR4 is responsible for platelet and CD4⁺ T-cell recruitment induced by hepatic reperfusion injury [128]. Also, immune cells such as peripheral blood mononuclear cells (PBMCs) are activated by thrombin via the PAR1. Upon thrombin stimulation, the PBMCs release pro-inflammatory cytokines such as IL-1 β and IL-6 and also their cell proliferation is increased [129]. When binding to PARs, thrombin is involved in the regulation of monocyte differentiation for scar tissue formation after injury [130].

Especially the binding of thrombin to endothelial cells is a crucial step during disease. Thrombin is believed to participate in the regulation of blood pressure by binding to PAR1 and thus influences vasoconstriction as shown in microvessels [131] in pulmonary arterial hypertension [132].

Thrombin also regulates endothelial permeability and is therefore responsible for the development of oedema. An animal study showed that PAR1 activation increased vascular permeability mainly via mast cell degranulation, which led to oedema formation [133]. Thrombin binding to PAR1 of endothelial cells in an in-vitro and an animal study led to an enhancement of chemotaxis for the leukocytes and so increased leukocyte recruitment [134]. In microvascular endothelial cells of rat brains, thrombin induces inflammatory processes by binding to PAR1 that disrupt the tight junctions and increases the permeability of the blood–brain barrier (BBB) [135]. Also in the lung, PAR1 expression was increased during pneumonia due to *Streptococcus pneumoniae* infection and mediated neutrophil recruitment, thus leading to increased alveolar leakage, both of which were attenuated with a PAR1 inhibitor in mice [136].

The importance of thrombin-induced PAR activation in the host response to infection is supported by the fact that some pathogens have developed defense mechanisms by cleaving these types of receptors. For example, streptococcal virulence factor SpeB is able to cleave PAR1 and thus makes the endothelial cells unresponsive to thrombin and prevents human platelets from thrombin-induced aggregation [137].

Inhibition of the PARs is not only of interest for antiplatelet therapy, but also for inflammation. Blocking PAR1 with vorapaxar showed some anti-inflammatory effects [138], for example by maintaining the endothelial barrier and

proliferation of endothelial cells and thus protecting the endothelial cells [139]. During endotoxemia, PAR-1 inhibition decreased inflammation and endothelial activation [140]. However, the increased bleeding risk due to PAR1 inhibition [120–123] means this strategy is rather not an option for critically ill patients, who nevertheless suffer from an increased bleeding risk as a result of the underlying diseases, stage of sepsis or intensive care procedures as well as surgical interventions. Therefore, the inhibition of thrombin might be more advantageous than PAR inhibition, as thrombin directly and indirectly mediates many inflammatory processes during sepsis, as schematically illustrated in Fig. 1.

Summary

Thrombin not only contributes to clot formation, but also binds to various cell types including platelets, immune cells and the endothelium via the PARs. PARs play a crucial role in coagulation, inflammation, embryogenesis, wound healing and cancer growth.

When thrombin binds to platelets via PAR1, it makes a critical contribution to maintaining and amplifying platelet activation. It also induces the release of heparanase, which forms a procoagulant active complex with TF. This complex is also formed when thrombin binds to PAR1 on granulocytes, for example neutrophils. Furthermore, because thrombin binds to PARs and thus promotes angiogenesis, it plays an important role in regulating wound healing or tumour spread.

PAR activation via thrombin is also a critical mechanism in inflammatory processes. Immune cells such as PBMCs are activated by thrombin via the PAR1 and subsequently release pro-inflammatory cytokines. Thrombin, when binding to the PARs of monocytes, is involved in the regulation of differentiation for scar tissue formation after injury.

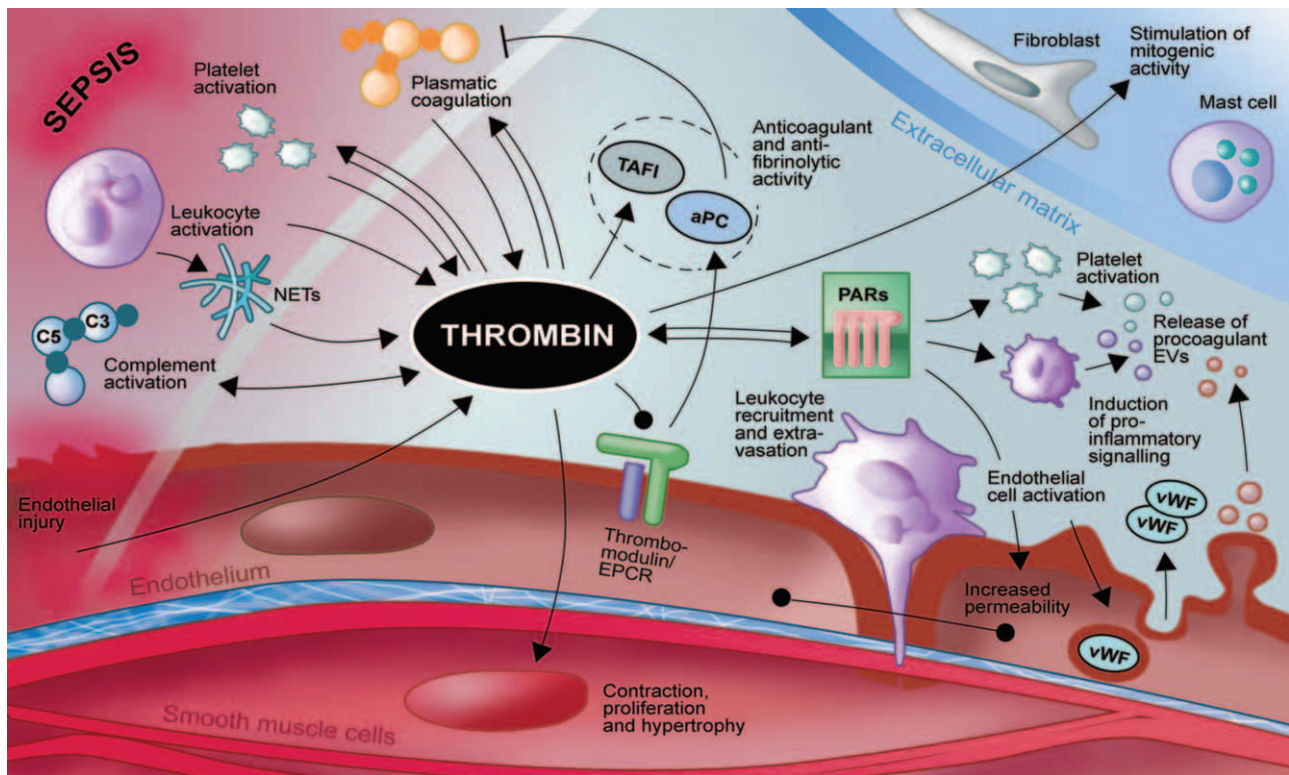
Thrombin also regulates endothelial permeability via PAR binding and is therefore responsible for the development of oedema via the enhancement of leukocyte recruitment and migration and therefore disruption of the tight junctions.

PAR inhibition not only showed anticoagulatory and anti-inflammatory effects, but also increased bleeding events. As critically ill patients nevertheless suffer from an increased potential bleeding risk, because of the underlying diseases, stage of sepsis or intensive care procedures as well as surgical interventions, PAR inhibition might lead to an increase in adverse side effects. Therefore, the inhibition of thrombin might be a more suitable option to prevent the activation of PARs via thrombin.

Thrombosis prophylaxis in critically ill patients with sepsis

The need for effective thrombosis prophylaxis in critically ill patients, especially when they suffer from sepsis,

Fig. 1



The role of thrombin in coagulation and inflammation. aPC, activated protein C; C3, complement factor 3; C5, complement factor 5; EPCR, endothelial protein C receptor; NETs, neutrophil extracellular traps; PARs, protease-activated receptors; TAFI, thrombin activatable fibrinolysis inhibitor; vWF, von Willebrand factor.

cannot be denied. The sepsis guideline recommends a pharmacologic prophylaxis for venous thromboembolism with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) [141]. This guideline also favours LMWH rather than UFH [141], although a look into the rationale for this recommendation shows that only studies comparing LMWH with subcutaneous administration of UFH twice daily were used in medical and postsurgical patients [96] as well as in trauma patients [142]. Contrary to these results, a meta-analysis of 12 trials observed comparable efficacies of UFH administered subcutaneously twice daily and LMWH, whereas UFH showed a tendency to a decreased incidence of major bleeding as compared with LMWH [143]. In a more recent neurosurgical meta-analysis, the rates of venous thromboembolism, postoperative blood transfusion and haemorrhagic stroke were equivalent for prophylactic LMWH and subcutaneous UFH administered twice a day [144]. Overall, LMWH is increasingly used in critically ill patients, although no difference was observed in venous thromboembolism between patients predominantly treated with LMWH or UFH [145].

It was shown that intravenous administration of UFH is superior to subcutaneous administration in preventing

venous thrombotic events (VTEs) [146]. A retrospective review did not find a significant difference between LMWH and heparin infusion with respect to haemorrhagic and general complication rates [147]. Notable in the setting of critical care patients is that the resorption of subcutaneous drugs may be impaired [148,149]. Thus, it may be advisable to make adjustments in monitoring and drugs also when administering heparin subcutaneously in critically ill patients [150].

The advantages of intravenous administration of heparin are obvious. Dose adjustments can be performed quickly, thereby personalizing therapy. Furthermore, an antidote is available for UFH, which is necessary, as this patient population is not only susceptible to thrombosis but also to bleeding.

Despite pharmacological thromboprophylaxis, thrombosis rates in critically ill patients are still high. Therefore, more potent prophylaxis options other than unfractionated or LMWHs may be necessary, especially because heparin administration might become ineffective, which is called heparin resistance, or because it could lead to an even increased thrombosis risk due to the induction of NET formation [151] or to the development of heparin-induced thrombocytopenia (HIT).

Summary

Due to the high thrombosis risk in sepsis patients, the sepsis guidelines recommend pharmacologic prophylaxis for venous thromboembolism with UFH or LMWH. LMWH is recommended over subcutaneous UFH. Here, it is important to note that data comparing continuous intravenous administration of UFH and LMWH are rare, but studies indicate that intravenous administration of UFH is superior to subcutaneous administration in preventing VTEs and that intravenous UFH is as well tolerated as LMWH. The advantage of continuous infusion of UFH is the fast dose adjustment option needed in critically ill patients, who are at risk for developing thrombosis and also bleeding. Nevertheless, the risk for developing heparin-induced thrombocytopenia (HIT) should not remain unmentioned.

Direct thrombin inhibitors in critically ill patients

In critically ill patients, two DTIs for intravenous administration are predominantly used, argatroban and bivalirudin. Bivalirudin is mainly used and approved for patients with cardiac interventions, but its availability is restricted in, for example, Europe, whereas argatroban is widely available and there is a high level of experience with its administration in critically ill patients. Argatroban is a synthetic DTI with a low molecular weight [152]. It is an L-arginine derivative that binds exclusively to the catalytic site of thrombin and inhibits its ability to cleave fibrinogen. Argatroban consequently prevents thrombus formation in a dose-dependent way. Argatroban is metabolized and eliminated by hepatic metabolism. The elimination half-life of argatroban in healthy subjects is about 50 min. Because of the hepatic metabolism, dosing precautions are recommended in patients with hepatic dysfunction, but it can be used without restriction in patients with renal dysfunction [152]. Currently, no antidote is available.

Argatroban has marketing authorization for thromboprophylaxis in patients with induced thrombocytopenia (HIT) for most countries. In Japan, for instance, argatroban is approved for several indications, for example thromboprophylaxis in patients with extracorporeal circuits with antithrombin deficiency. Furthermore, argatroban is used off-label in patients with heparin resistance [153].

Several studies in patients with HIT have confirmed the efficacy of argatroban and showed that it improved patient outcome with regard to thrombotic events and thrombosis-associated mortality [154–158] and also increased platelet count [159].

In critically ill patients, the summary of product characteristics (SmPC) recommends an argatroban starting dose of 0.5 $\mu\text{g}/\text{kg}/\text{min}$ and that the activated (a)PTT assay be used to monitor its efficacy [152], although some studies indicate that lower doses might be sufficient in

critically ill patients [160–163]. Critically ill patients are composed by different heterogeneous patient populations who require individualized treatment. Depending on their disease and comorbidities, some patients are at a higher risk for thrombosis than other patients and some need lower argatroban doses than other patients. These lower doses in critically ill patients might be due to prolonged clearance of argatroban [164], as these patients often have impaired liver function. In critically ill cardiac surgery patients, median argatroban plasma half-life was 2.7 h, and patient age and serum albumin concentration contributed significantly to the prolonged half-life [165]. In addition, argatroban is known to bind to several plasma proteins, mainly to albumin and $\alpha 1$ acid glycoprotein, which may influence the drug's distribution and plasma half-life.

As argatroban has to be given continuously intravenously, it is advantageous for continuous gavage such as, for example, for renal replacement therapies (RRTs), patients on ECMO therapy or patients in high oedematous septic stages, wherein LMWH is not sufficiently resorbed. In patients receiving RRT, argatroban was shown to be well tolerated with regard to bleeding complications and to provide effective anticoagulation [166–168]. Even in patients at high haemorrhagic risk, it was shown to be feasible, although the higher starting dose and the small sample size mean the rate of complication might be overrepresented in this particular study [169]. When monitoring is close and dose titration is strict, argatroban is well tolerated regardless of disease severity or impaired hepatic function [166].

There are indications that critically ill patients with multiple-organ dysfunction syndrome (MODS) require even lower doses of argatroban than recommended in the SmPC [160,161] and very low dosing when hepatic impairment contributes to MODS [160]. A retrospective analysis regarding MODS in critically ill patients revealed that a well tolerated dosage for anticoagulation with argatroban depends on the number of failing organs [170]. It was shown that there is an inverse relationship between the Sequential Organ Failure Assessment (SOFA) Score and the required argatroban dose [171]. In most critically ill patients, a starting dose of 0.2 $\mu\text{g}/\text{kg}/\text{min}$ over 4 h is effective to provide sufficient anticoagulation without bleeding complications [161,163,172].

In some dedicated centres, argatroban is widely administered in patients on extracorporeal circuits, for example extracorporeal membrane oxygenation (ECMO), with suspected or confirmed HIT. In acute respiratory distress syndrome (ARDS), patients requiring ECMO, argatroban was shown to be as effective and well tolerated as UFH with regard to bleeding and the need for transfusions [162], but was administered also at low maintenance doses of 0.15–0.26 $\mu\text{g}/\text{kg}/\text{min}$ [162,163] and without putting patients at risk for HIT. The risk for HIT can be as high as 3.7% in this patient population [173].

Summary

Argatroban is a DTI that is continuously intravenously administered and has a short half-life of 50 min. Argatroban holds marketing authorization for parenteral antithrombotic therapy in patients with HIT. Argatroban is proven to be effective in preventing thrombosis in HIT patients in various clinical situations. In addition, in patients with thrombocytopenia, the platelet number may recover during argatroban administration.

In critically ill patients, the starting dose of argatroban has to be low and should be titrated to the targeted anticoagulation level. Some studies indicate an even lower starting dose than recommended in the current SmPCs. It seems that the greater the extent of organ dysfunction is, the lower the required starting and maintenance dose is. When adhering to this, argatroban was shown to be well tolerated even in patients needing extracorporeal circuit treatment such as ECMO.

Evidence FOR the usefulness of argatroban in sepsis

Studies in larger patient populations dealing with the efficacy and safety of argatroban in critically ill patients, especially those with sepsis with and without HIT, are mainly of a retrospective nature.

In comparison to other DTIs such as bivalirudin and lepirudin, the literature also reports conflicting results, particularly regarding effectiveness and safety. Two studies have shown the superiority of argatroban as compared to bivalirudin in terms of the time needed to reach the targeted anticoagulation goal [174,175], while another demonstrated that bivalirudin performed better [176]. In the latter study, bivalirudin had the lowest bleeding rate in patients being treated for HIT, followed by argatroban, whereas lepirudin had the highest bleeding rate, although the patient groups were barely comparable due to their heterogeneity [176].

However, a meta-analysis of largely retrospective studies in mainly critically ill patients demonstrates that the effectiveness of argatroban is similar to that of lepirudin or bivalirudin in patients with HIT and also that the incidence of bleeding was not significantly different [177]. Importantly, when HIT was associated with thrombosis, argatroban seemed to be superior to bivalirudin, as the incidence of thrombosis was lower in patients treated with argatroban [177]. A recently published Bayesian network meta-analysis of retrospective as well as prospective studies with very heterogeneous patient populations with and without HIT seems to confirm this result. This analysis demonstrates that the argatroban patients had the shortest hospitalization and lowest rate of haemorrhage, thromboembolism and mortality as compared to bivalirudin, lepirudin, desirudin and danaparoid [178].

In comparison with heparins such as LMWH or UFH, a retrospective study in critically ill patients diagnosed with HIT showed that argatroban used at doses less than

0.4 µg/kg/min was not associated with an increase in transfusion requirement and furthermore was associated with reduced overall treatment cost as compared to heparin [179]. Although risk factors for bleeding during argatroban are known [180], several retrospective studies have demonstrated that argatroban is well tolerated with bleeding rates comparable to those of heparin in critically ill patients suffering from various diseases other than HIT [181–184].

Not only safety, but also the efficacy of argatroban has been investigated in critically ill patients without HIT. For example, in heparin-resistant critically ill postsurgical patients, in whom the rate of heparin resistance is high probably due to the acute phase reaction [185–188], a retrospective analysis demonstrated that argatroban is an effective alternative prophylactic anticoagulation [189]. There are also some retrospective studies available that deal with the use of argatroban in extracorporeal circuits such as ECMO or RRT. Importantly, it seems that there is no difference in the argatroban dose needed to reach a particular anticoagulation level [190].

In patients with ECMO, argatroban was comparable to UFH with regard to bleeding and thromboembolic complication rates [191]. A propensity score matched study in patients on ECMO without HIT confirmed these results, namely that argatroban was comparable to UFH concerning the occurrence of technical complications, bleeding, thrombosis and costs, but that analysis also demonstrated that argatroban has a platelet-preserving effect [192]. In this study, it was noticed that argatroban doses had to be increased when sepsis improves [192]. Furthermore, several studies in ECMO patients, also in patients with COVID-19 sepsis, showed argatroban to be similar with regard to thrombotic complications and bleeding [162,193,194].

In patients requiring RRT, for instance following cardiac surgery, the effectiveness and safety of argatroban were comparable to those of heparin when argatroban was closely monitored and carefully titrated, regardless of disease severity or impaired hepatic function [166]. In critically ill COVID-19 patients in whom UFH failed to prevent early clotting of the dialysis circuit, LMWH and argatroban were compared and the use of LMWH resulted in the longest circuit life spans, although the sample size was probably too small to permit a solid conclusion to be drawn [195].

In actual fact, there are almost no clinical trials that investigate the effectiveness of argatroban in patients with or without HIT in a solely septic patient population. There is one prospective randomized controlled clinical trial in heparin-resistant critically ill, mainly sepsis patients without HIT that demonstrates the superiority of argatroban over an increased UFH dose with regard to effectiveness as measured by reaching the targeted aPTT range [153]. Also, regarding safety, no significant

difference in the bleeding incidence was seen between argatroban and UFH [153].

In critically ill patients, regardless of sepsis but with HIT, a multicentre clinical trial proved that the platelet count recovered rapidly after argatroban initiation and that argatroban is a well tolerated therapeutic option in HIT patients at high haemorrhagic risk and with renal failure [169]. It is important to know that in patients with HIT and thromboembolic events a delay of one or more days in the administration of argatroban was accompanied by a significant increase in the incidence of further thromboembolic complications [196].

Summary

Several retrospective and some prospective studies have demonstrated the efficacy and safety of argatroban in critically ill patients with and without HIT in comparison to heparins. Also, in patients on extracorporeal circuits, such as RRT or ECMO, the use of argatroban seems to be comparable to heparins regarding efficacy and safety. Studies in solely septic patient populations that investigate different anticoagulatory strategies with clinical outcomes such as thromboembolic rate or bleeding complication are missing.

Bleeding risk during argatroban treatment

The bleeding risk associated with argatroban needs to be addressed, as there is no antidote available. However, in the case of UFH, for example ECMO therapy and subsequent bleeding, the use of heparin's antagonist protamine is also very critical. Thus, the bleeding risk for argatroban might be relative. When compared to other anticoagulatory therapies in HIT patients, most studies did not show patients receiving argatroban to have an increased bleeding risk [162,166–169] and in some settings even showed a decreased bleeding risk [158,197]. During therapy of arterial thrombi in rats with LMWH, the bleeding risk was actually higher than with argatroban [198]. In humans, a similar situation was observed in patients undergoing elective percutaneous coronary interventions (PCIs), wherein major bleeding was present only in patients receiving UFH (3.0%) [197]. In patients with stroke, the occurrence of haemorrhagic complications did not differ significantly between the argatroban and the control group, which was defined as patients receiving any other anticoagulatory therapy [199].

The bleeding risk on argatroban therapy is increased when, for example major surgery is performed prior to or during argatroban therapy, especially when at the same time, the dosage is adapted to a body weight of more than 90 kg, bilirubin levels are elevated (>3 mg/dl), or when thrombocytopenia (≤ 70 G/l) is present at the start of argatroban therapy [180].

If bleeding occurs when on argatroban and acute reversal of argatroban is necessary, treatment with prothrombin complex concentrate (PCC) might reverse the anticoagulant effect of argatroban [200].

Summary

As with every anticoagulatory drug, there is a certain bleeding risk, although studies have indicated that the bleeding risk is not higher than for other anticoagulation substances. Nevertheless, caution is advised with regard to dosing, as some risk factors that could be present, especially in critically ill patients, can increase the bleeding rate. Close monitoring of argatroban with an appropriate method can reduce the bleeding risk.

Argatroban monitoring

Administration of argatroban in patients with critical illness, increased bleeding risk or increased potential need for urgent procedures requires close monitoring. In patients with moderate or severe hepatic dysfunction (Child-Pugh Classes B and C), it is advisable to start treatment with a reduced dose. The activated partial thromboplastin time (aPTT) is the most widely available monitoring assay for measurement of the anticoagulatory effect of argatroban [201–203]. Whether the aPTT assay is the appropriate tool for monitoring, argatroban treatment is the subject of considerable controversy [204–206]. Furthermore, studies indicate that the aPTT does not correlate well with plasma levels in critically ill patients [207,208]. Also, close aPTT monitoring might be challenging in daily ICU routine [209].

Especially in critically ill patients, confounding factors can cause the aPTT to be prolonged without there being any real clinical bleeding tendency. Prolongation of the aPTT may lead to inadequate thrombo-prophylactic drug dosing, or in the worst case to the administration of no anticoagulation therapy at all [210]. For instance, the aPTT of patients with lupus anticoagulants overestimates the argatroban concentration [211].

In general, increased aPTT is sensitive to decreased levels of FVIII, FIX, FXI and FXII as well as to the intake of anticoagulants, antiphospholipid antibodies and von Willebrand disease [212–214]. As aPTT measurement is often misused as a predictor for bleeding in critically ill patients [215], the detection of prolongation may lead to insufficient or no antithrombotic therapy or even result in the indiscriminate use of coagulation factors or blood products, especially fresh frozen plasma (FFP). Moreover, it may even cause urgently required surgical interventions to be postponed [216,217].

Major problems in critically ill patients are the presence of lupus anticoagulants or contact pathway factor deficiencies, such as prekallikrein or FXII deficiency without any increased risk for bleeding [217–219], which may prolong the aPTT. A study revealed that FXII levels

below 42.5% are most likely to confound the aPTT assay, resulting in a prolongation of aPTT, and this extent of FXII deficiency was seen quite frequently in critically ill patients [220].

Therefore, the aPTT might not be the best tool for monitoring DTIs such as argatroban in critically ill patients. Other global coagulation assays are available and may be more suitable for monitoring anticoagulation. Thrombin time (TT) adds a certain amount of thrombin to measure the time needed for plasma clot formation. When DTIs are present, thrombin clotting time is prolonged. When a high level of anticoagulation is required, this lies outside the measurable range of the TT assay, as the TT is very sensitive to small concentrations of DTI. For this situation, a modified or diluted TT (dTT) is more practical [207].

A similar test is the ecarin-activated clotting time (ECT) or ecarin-activated chromogenic assay (ECA), which uses the snake venom ecarin from *Echis carinatus* to convert prothrombin to fibrinogen-activating meizothrombin. Similar to thrombin, meizothrombin is also inhibited by DTIs.

Indeed, the aPTT showed discordance with an ECA and dTT [221]. The TT has a linear dose–response profile [222] and, contrary to the aPTT, a strong correlation to the plasma concentrations of argatroban in critically ill patients [207].

Anti-IIa assays are based on either modified or dTT assays or ECT, wherein the time until clot formation is converted to concentration units of argatroban ($\mu\text{g/ml}$). When comparing the results, it is important to know which type of anti-IIa, namely based on TT or ECT, was used, as both tests are not superimposable [223].

The advantage of these thrombin-based tests is that they activate the clotting cascade at the level of thrombin generation and none of these tests contain phospholipids. Therefore, neither antiphospholipid antibodies nor kallikrein deficiency, nor FXII deficiency confounds these tests. Their disadvantage is that they have a lack of defined prophylactic and therapeutic target ranges.

Colucci *et al.* [224] investigated a small patient series with HIT and showed that a median aPTT of 44.2–59.7 s, which is often used as a prophylactic range, is equivalent to a median of 0.2–0.67 $\mu\text{g/ml}$ argatroban as measured with an anti-IIa assay developed in-house, while therapeutic aPTTs of 64.6 and 70.4 s were equal to 0.88 and 1.01 $\mu\text{g/ml}$ argatroban levels, respectively. The authors pointed out that each hospital has to define its own target ranges based on the type of assay being used, for example their in-house target anti-IIa therapeutic range was set at 0.4–0.8 $\mu\text{g/ml}$ [224].

The fact that many hospital laboratories do not provide anti-IIa assays required for proper argatroban monitoring

is a problem. Here, the possible monitoring tools are the viscoelastic tests such as TEG, ROTEM or ClotPro. Viscoelastic tests give more detailed information about the functional formation of the clot, interaction and total sum effects of different aspects of the coagulation system such as clot firmness and clot lysis. These tests are conducted with whole blood, which also gives information on the involvement of blood cells, especially platelets. Whereas ECATEM, EXTEM and FIBTEM CT correlate very well with plasma concentrations of DTIs such as hirudin, argatroban and bivalirudin, INTEM and HEPTTEM CT show a weaker correlation [207,225–229]. Therefore, EXTEM, FIBTEM or ECATEM CT should be preferred. Especially the commercially available ClotPro ECA test (ecarin-based assay) appears to be a promising argatroban bedside monitoring tool. However, here, too, well defined prophylactic and therapeutic-targeted ranges are lacking and further studies are needed.

Summary

For effective and well tolerated use of argatroban, the anticoagulatory status must be properly monitored. The aPTT is recommended for monitoring and is still widely used, although the aPTT does not correlate well with argatroban plasma levels in critically ill patients. In addition, this particular patient population develops contact pathway factor deficiencies such as FXII deficiency or also lupus anticoagulants, which confounds the aPTT assays and can result in prolongation.

Some tests are available that are not confounded by these factors, as they directly activate thrombin, and the time of fibrin formation is converted into plasma argatroban levels. These so-called anti-IIa tests are based on either dTT or ecarin time (ECT). If these tests are not performed in a hospital laboratory, confounding factors of the aPTT need to be considered and the results should be carefully interpreted.

Argatroban and platelet aggregation

Argatroban appears to be superior to other anticoagulants in the therapy of arterial thrombotic events. Argatroban binds monovalently to the active centre of thrombin, although, for example, bivalirudin additionally bivalently binds to the fibrin binding site of thrombin. Consequently, contrary to argatroban, bivalirudin cannot bind to fibrin-bound thrombin. Thus, argatroban is able to inhibit clot- or fibrin-bound thrombin better than hirudins or heparins [230]. Consequently, it can attenuate thrombin-induced platelet aggregation of the clot or fibrin network better than can hirudin or LMWH [231].

Even when platelets are activated by means of collagen, argatroban can attenuate platelet aggregation more effectively because it inhibits thrombin-induced enhancement of platelet activation [232,233]. Furthermore, argatroban reduces thrombin-induced P-selectin expression on platelets [234]. These thrombin-mediated effects

of argatroban on platelets contribute to the superior efficacy of argatroban over that of heparin in the treatment of arterial thrombi, which are generally platelet-rich thrombi. This inhibition of thrombin-induced platelet activation and aggregation is a feature of the therapeutic doses of argatroban [235].

The superior role of argatroban in the therapy of arterial thrombi was confirmed in an animal experiment showing that argatroban is more effective in treating arterial thrombosis than is UFH [236], whereas LMWH and argatroban were similarly effective in treating venous thrombi [198]. Furthermore, argatroban inhibited the formation of microthrombi in a rat model [237], whereby such thrombi are formed by both plasmatic coagulation and platelet aggregation initiated by TF expressing PBMCs [238]. Not only platelet aggregation might be inhibited by argatroban, but also neutrophil migration [239], which, *inter alia*, can lead to improved microcirculation [240].

Summary

Argatroban inhibits fibrin-bound thrombin. In comparison to other anticoagulants, argatroban binds monovalently to the active site of thrombin. For this reason, argatroban can attenuate further platelet aggregation in an already formed clot. This makes argatroban an effective anticoagulation therapy option in patients with thrombosis.

Argatroban and beyond anticoagulation

Because it inhibits thrombin, argatroban also has anti-inflammatory properties. It has been shown that thrombin only in low concentrations protects from endothelial barrier disruption and also attenuates the expression of cell adhesion molecules on endothelial cells and therefore inhibits leukocyte migration and adhesion to the endothelium [241]. Furthermore, the production of pro-inflammatory cytokines such as TNF- α and IL-6 may be inhibited [241].

Therefore, argatroban can reduce thrombin-induced inflammatory reactions. Here, it must be stated that thrombin is a very potent pro-inflammatory substance, being much more pro-inflammatory than, for example, classical pro-inflammatory substances such as LPS. Thus, argatroban may have potent anti-inflammatory properties, not only caused by the indirect inhibition of, that is, IL-6, but mainly by direct thrombin inhibition. Such antiinflammation properties of argatroban were proven in synovial cells obtained from patients with osteoarthritis and rheumatoid arthritis [242]. In animal studies, argatroban was seen to attenuate diabetic cardiomyopathy (DCM) in chronic diabetes [243] or reduce hepatic inflammation with established fatty liver disease in mice [93].

Furthermore, argatroban prevents injuries caused by thrombin on endothelial cells [244] and it attenuates

reperfusion injuries by reducing thrombin-induced interactions between leukocytes, platelets and endothelial cells [245]. In an experimental sepsis model in rats, the use of argatroban was able to improve intestinal microcirculation by preserving functional capillary density (an indicator of microvascular perfusion) and by reducing leukocyte adherence to the endothelium in submucosal venules [246].

However, a comparison of argatroban and heparin in patients undergoing percutaneous transluminal coronary angioplasty with stable angina pectoris showed no difference with regard to the inflammatory, haemostatic and endothelium-derived markers [247].

It is also known that argatroban has neuroprotective properties [248,249] and this appears to result from attenuation of the PAR1-dependent VEGF secretion [250], as argatroban seems to inhibit not only thrombin, but also the expression of PAR1 itself [243,251]. Thrombin not only influences VEGF secretion, but also has a positive feedback-loop to express TF. In synovial cells, the expression of TF and VEGF as well as IL-6 and MMP-3 secretion was reduced by argatroban [242].

As PARs and VEGF play a role in cancer, argatroban might inhibit thrombin-supported tumour growth. This has already been proven in studies where argatroban attenuated tumour cell migration, which resulted in reduced melanoma-derived metastases [252] and inhibited the spread of bone metastases in breast cancer [251]. The systemic use of argatroban even reduced tumour mass and neurological deficits while also prolonging survival in rats with glioma [253].

One disadvantage could be that anticoagulation promotes bacteria dissemination by inhibiting immunothrombosis, but studies have shown that argatroban is even able to reduce the number of bacteria in the spleen, while the amount of bacteria were at least not increased in the liver or lung [254], although the mechanism needs further study.

In summary, argatroban is a well established, highly effective and well tolerated anticoagulant for HIT in the critical care setting. Beyond this, the inhibition of thrombin also has anti-inflammatory effects including endothelial protecting effects that might contribute to an attenuation of complement activation as well as organ dysfunction. Consequently, argatroban might be a suitable anticoagulation agent for sepsis patients with confirmed or suspected HIT.

Summary

Because it inhibits thrombin and subsequently attenuates thrombin binding to PARs, argatroban also has anti-inflammatory properties. Animal models have shown that argatroban attenuates endothelial barrier disruption and leukocyte migration as well as the release of

pro-inflammatory cytokines. Furthermore, argatroban was able to protect against reperfusion injury and improved microvascular perfusion during sepsis in animal experiments. The net anti-inflammatory effect is still not proven in humans because there has been a lack of studies in critically ill patients with and without sepsis. Concomitant anti-inflammatory properties of antithrombotic drugs should be further investigated and not neglected, especially in critically ill patients.

Conclusion

In inflammatory diseases, such as sepsis or COVID-19, coagulation and inflammation interact closely mutually reinforcing each other. Here, thrombin plays a key role since thrombin is not only a main driver for clot formation, but also acts as a strong pro-inflammatory trigger by activating different cell types such as platelets, leukocytes and endothelial cells via PAR-binding.

For both highly pro-inflammatory and pro-coagulatory diseases, sepsis and COVID-19, LMWHs or UFHs are recommended for thromboprophylaxis. However, in these particular diseases, conditions can occur that require enhanced anticoagulation. Such conditions can be HIT, HIT-like conditions such as vaccine-induced immune thrombotic thrombocytopenia (VITT), platelet-activating effect of heparin and subsequent platelet consumption, recurrent clotting of extracorporeal circuits and heparin resistance. Especially in critically ill patients with COVID-19, heparin resistance is a common problem that ICU physicians have to deal with. Therefore, a switch to DTIs should be considered in patients suffering from one of these conditions.

DTIs do not only efficiently inhibit thrombin generation and fibrin-bound thrombin, and also improve fibrinolysis, but they also influence inflammation and protect endothelial integrity, as thrombin can no longer bind to PAR receptors.

A further advantage of DTIs is the monitoring of these substances via different anti-IIa assays such as dTT, ECT or ECAs, which is simpler than, for example, for heparins as the thrombin-inhibiting action cannot be measured by anti-Xa assays, which are the state-of-the-art methods for heparins.

However, clinicians should be aware that argatroban is an effective anticoagulant, which may induce a bleeding tendency, among other mechanisms, by inactivating clot-bound thrombin. Cautious, closely monitored and titrating dose escalation is recommended.

In conclusion, the authors of this review recommend enhanced anticoagulation with DTIs as possible thromboprophylactic substance in sepsis and COVID-19 patients with suspected or confirmed HIT, HIT-like conditions, low platelet counts due to heparin use,

impaired fibrinolysis, as well as in patients on extracorporeal circuits and patients with heparin resistance.

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