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A review of current agents for anticoagulation for the critical care practitioner☆,☆☆

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Abstract There has been a tremendous boom in the arena of anticoagulant therapy recently. Although the indications for these agents reside in the noncritical care environment, over time, the impact of these agents have infiltrated the critical care environment particularly due to devastating complications with associated use. With so many newer agents on the market or coming down the pipeline, it is easy to become overwhelmed. It is important that the critical care practitioner does not ignore these agents but becomes familiar with them to better prepare for the management of patients on one or more anticoagulant agents in the intensive care unit. To equip the critical care practitioners with the knowledge about commonly used anticoagulants, we provide an extensive review of the pharmacology, indications, and adverse effects related to these agents as well as suggestions on preventing or managing complications.

Options for anticoagulant drug therapy to prevent or treat thromboembolic complications have increased significantly over the last several years and have made their way into the critical care environment. A grasp of the various agents available is essential to the critical care practitioner to understand their role in therapy and either avoid or manage complications related to these agents. The purpose of this comprehensive review is to provide the critical care clinician with a working knowledge of currently available anticoagulants.

1. Heparin and heparinoids

1.1. Unfractionated heparin

Unfractionated heparin (UFH), first discovered in 1916 by a second-year medical student, is a glycosaminoglycan

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that is endogenously synthesized and stored in basophilic granules of mast cells, which are found in the highest concentrations in the liver, lung, and intestines. Commercially available UFH is derived from porcine intestinal mucosa and consists of a mixture of polysaccharide chains of various lengths, with molecular weights ranging from 3000 to 30 000 d [1]. Heparin's anticoagulant and antithrombotic effects are modulated indirectly by its ability to bind to antithrombin III (ATIII). It affects the interaction between ATIII and other serine proteases, which results in a decreased production of activated factor X (Xa) and thrombin (IIa), the principal factors responsible for clot formation [1]. Heparin inhibits factors IX, XI, and XII also.

Unfractionated heparin is primarily administered as a continuous intravenous (IV) infusion as the bioavailability is much more predictable in this manner, although it can be administered as a subcutaneous injection, as well [2]. Heparin distributes primarily in the intravascular space, with a volume of distribution similar to that of the whole blood volume as there is endothelial binding of heparin as well as disbursement within the plasma. It binds to a variety of plasma proteins, which is one of the reasons for the variability of anticoagulant response, as well [3]. The half-life of UFH is approximately 60 minutes at standard therapeutic doses; however, this is prolonged with higher doses and longer durations of therapy [3]. The reason for this added complexity is that elimination of UFH has both concentration-dependent (first order, saturable) and concentration-independent processes (zero order, nonsaturable). Although the precise pathways of UFH metabolism are unknown, depolymerization by uptake into endothelial cells (saturable) and the kidneys (nonsaturable) are the prominent routes of elimination [1]. Dosing of UFH is based on weight-based dosing nomograms, although these have limitations due to heparin's complex and unique pharmacokinetic and pharmacodynamic characteristics that make it difficult to determine the appropriate doses and monitoring parameters in individual patients [4]. Monitoring of heparin involves evaluating activated partial thromboplastin times (aPTT). Some of the limitations of the aPTT, however, are its lack of standardization, the impact of collection technique on the test, and alterations related to the pathophysiologic conditions of the patient as it is a global measure of intrinsic coagulation [4]. The heparin assay or anti-Xa assay addresses many of these issues but has some challenges with standardization, cost, and the lack of large randomized controlled trials evaluating its use [5].

Unfractionated heparin is indicated for the prophylaxis and treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), atrial fibrillation with embolization, acute and chronic consumptive coagulopathies, arterial and cardiac surgery, and peripheral arterial embolism and is contraindicated in patients with severe thrombocytopenia or active, uncontrolled bleeding [2]. Significant adverse effects of heparin are bleeding and heparin-induced thrombocytopenia (HIT). Heparin-induced thrombocytopenia is a rare ($\leq 5\%$) but devastating complication and typically presents with thrombocytopenia (50% decrease in platelets from baseline) that can lead to a systemic thrombosis approximately 5 to 10 days after initiation of UFH [6]. Rare patients can present with "rapid-onset" HIT (50% decrease in platelets from baseline within 24 hours), but this occurs when there are circulating antibodies from recent exposure (within previous 100 days). Treatment includes discontinuation of all heparin containing products and initiation of alternative agents for anticoagulation (direct thrombin inhibitors). For a more extensive review of this disease state, please refer to the recent guidelines in the CHEST journal [6].

In regard to bleeding, UFH is one of the few anticoagulants that have a true antidote. Protamine is derived from salmon sperm and works by binding to heparin to form a stable complex. Typical dosing for protamine is 1 mg for every 100 U of heparin, with the maximum dose of 50 mg over 10 minutes [7]. The time that the heparin was administered should be known as lower doses are required the later the protamine is administered. As the half-life of heparin is around 60 minutes, give half of the normal protamine dose 1 hour after administration of heparin, one-quarter the dose 2 hours out, and others [8]. Protamine should be used with caution as an excess can lead to cardiovascular side effects, such as hypotension due to rapid administration and possible histamine release from mast cells as well as anticoagulation via inhibition of platelet aggregation, precipitation of fibrinogen, and impairment of thrombin [9,10].

1.2. Low-molecular-weight heparins

Low-molecular-weight heparins (LMWHs) are derived from UFH through chemical or enzymatic depolymerization [11]. The manufacturing process results in smaller heparin fragments with a more predictable dose response and increased bioavailability when compared with UFH. Each commercially available agent has a unique preparation, however, resulting in different drug molecules and dosing for each agent. The drug half-lives of LMWHs are longer than UFH and prolonged in renal dysfunction due to primary elimination by the kidneys. Low-molecular-weight heparins exert their pharmacologic effect similar to UFH by the activation of ATIII. Approximately half of LMWH fragments are long enough to facilitate binding of ATIII to bridge antithrombin to thrombin, while the smaller fragments anticoagulant effects by promoting inactivation of factor Xa. The half-life of LMWHs is longer than UFH due to decreased protein binding to plasma and endothelial cells. The longer half-life allows for once or twice daily dosing and may have an advantage in the ambulatory setting. Of course, this may be less desirable in the critically ill and trauma populations and those with high risk of bleeding. Due to the improved dose response, monitoring of anticoagulant activity is usually not required; however, anti-Xa levels may be measured if monitoring is needed. Although there are

limited data correlating anti-Xa levels with therapeutic outcomes, the following peak anti-Xa levels may be used: 0.6 to 1.0 U/mL (twice daily enoxaparin or nadroparin), 0.85 U/mL (tinzaparin), 1.3 U/mL (once daily nadroparin), and 1.05 U/mL (once daily dalteparin) for the treatment of DVTs [11]. Peak levels should be measured after reaching steady state and collected 4 hours after the dose is administered [11].

Low-molecular-weight heparins have Food and Drug Administration (FDA)–approved indications for the treatment or prophylaxis of DVTs and acute coronary syndromes (ACS). Most data with the use of LMWHs have been in the medical patient population, with limited data on their use outside of orthopedic and abdominal surgery.

Low-molecular-weight heparins are not recommended in patients with any acute bleeding conditions, a high-risk of bleeding, or when there is suspected or documented HIT. Most LMWHs are not recommended in patients with significant renal dysfunction, a creatinine clearance less than 30 mL/min, or those receiving dialysis. Enoxaparin is the only LMWH with specific recommendations on its use in patients with a creatinine clearance less than 30 mL/min. Although there is no FDA-approved reversal agent for LMWH, protamine has been used in the reversal of enoxaparin in the following dose: 1 mg per 1 mg enoxaparin (if administered within 8 hours) and a second dose at 0.5 mg per 1 mg enoxaparin if bleeding continues [11]. The dose of protamine should be reduced if the administration time has been longer than 8 hours. Protamine has variable binding to LMWHs and may result in an incomplete neutralization of their anticoagulant effect [11]. Conventional agents used to treat bleeding such as blood products (fresh frozen plasma [FFP], cryoprecipitate, packed red blood cells) and supportive measures for hemorrhage should be used as initial treatments. In obese patients (>140 kg) and those with renal dysfunction, anti-Xa levels can be measured to optimize anticoagulation and reduce bleeding risk [11].

1.3. Pentasaccharides

1.3.1. Fondaparinux

Fondaparinux sodium is manufactured as a synthetic mimetic of the heparin active site. By containing the same pentasaccharide sequence as UFH and LMWH in its molecular structure, fondaparinux sodium provides a unique mechanism of anticoagulation in comparison with UFH and LMWH [12]. Fondaparinux sodium selectively binds to ATIII leading to inhibition of factor Xa. This causes disruption of the clotting cascade, which further interrupts the formation of activated factor II or thrombin but does not lead to inactivation of thrombin. Fondaparinux sodium also lacks the sugar domain, which is present in UFH and LMWH that complexes with platelet factor 4 leading to the development HIT [12,13]. Therefore, the development of HIT with fondaparinux sodium is rare [12,14,15].

Fondaparinux is routinely administered subcutaneously with 100% bioavailability, although it can be administered intravenously as well. It has a volume of distribution of 7 to 11 L and is highly protein bound, primarily to ATIII. Fondaparinux concentration peaks at 3 hours with an elimination half-life of 17 to 21 hours, in which up to 77% of the drug is excreted unchanged in the urine. Dosing is weight based and can be adjusted based on steady-state plasma concentrations [13].

Fondaparinux sodium is indicated for the prophylaxis of DVTs, specifically in patients undergoing surgery for hip fracture, hip or knee replacement, and abdominal surgery. The prophylaxis dose is 2.5 mg administered subcutaneously once per day, starting no earlier than 6 to 8 hours postoperatively and continued for a minimum of 5 days and up to 24 days depending on the indication. Fondaparinux sodium is also indicated for the treatment of DVT and acute PE when given concomitantly with warfarin. Treatment or prophylaxis with fondaparinux sodium is contraindicated in patients with severe renal dysfunction, defined as a creatinine clearance (CrCl) less than 30 mL/min. Other contraindications include active major bleeding, bacterial endocarditis, and thrombocytopenia associated with a positive antiplatelet antibody to fondaparinux sodium. Prophylaxis with fondaparinux sodium is also contraindicated in patients weighing less than 50 kg [13]. Caution should be exercised when using fondaparinux in patients with spinal or epidural anesthesia due to the risk of developing a hematoma, similar to LMWHs [12,13].

Currently, there are no agents available to reverse the anticoagulation effects of fondaparinux sodium. Fresh frozen plasma and cryoprecipitate can both be used to manage adverse bleeding effects [12,13]. One study conducted in healthy volunteers showed that bleeding complications of fondaparinux sodium can be successfully reversed via the administration of recombinant factor VIIa (rFVIIa) as well [16].

1.3.2. Idraparinux

According to clinical trial data, idraparinux sodium (SR34006), also referred to as biotinylated idraparinux (SSR126517E), is a synthetic oligosaccharide that works as an inhibitor of factor Xa. It is currently being investigated for the prevention and treatment of venous thromboembolism (VTE) as well as for stroke prevention in patients with atrial fibrillation [17,18]. Idraparinux is being studied in phase III clinical trials in comparison with currently approved vitamin K antagonists, UFH, and/or LMWHs. Because of its formulation, which results in an elongated half-life of approximately 80 hours, it is dosed as a once weekly subcutaneous injection. Idraparinux is excreted through the kidneys and should be used cautiously in patients with renal dysfunction [19,20]. Because of its once weekly dosing, comparative efficacy with other oral anticoagulants, and lack of evidence of concomitant food and drug interactions, it is considered by investigators as a therapeutic advancement [19]. Patient adherence is anticipated to improve due to convenience of administration, especially when compared

with daily or twice daily dosing and monitoring requirements of other oral and parenteral anticoagulants [18,19]. One potential disadvantage, due to the long half-life of idraparinux, is the lack of antidote if rapid reversal is needed due to acute bleeding and/or need for emergent surgery. Fresh frozen plasma, packed red blood cells, and rFVIIa have all been reported to serve as reversal agents for significant bleeding related to idraparinux [19].

1.4. Factor Xa antagonists

1.4.1. Rivaroxaban

The conversion of factor X to factor Xa plays a vital role in both the intrinsic and extrinsic pathways of the coagulation cascade. Rivaroxaban is a selective inhibitor of factor Xa that currently has FDA approval for DVT prophylaxis in patients undergoing knee or hip replacement; prevention of stroke in patients with atrial fibrillation; and, recently, DVT and PE treatment [21]. The standard prophylaxis dose is 10 mg orally once daily with the initial dose given 6 to 10 hours after surgery. Treatment dosing for DVT/PE is 15 mg twice daily for 21 days, followed by 20 mg daily. Unlike warfarin, rivaroxaban does not require monitoring of coagulation parameters to assess effectiveness or toxicity. Caution should be taken if abruptly discontinuing rivaroxaban as an increased risk of stroke was seen in patients with atrial fibrillation upon discontinuation of rivaroxaban after ROCKET AF study completion. A post hoc analysis was done by the ROCKET AF investigators to evaluate the outcomes of discontinuing rivaroxaban vs warfarin. When looking at temporary discontinuation (mean, 6 days) and permanent discontinuation during the study, there was no difference in thrombotic events compared with warfarin. However, at the completion of the study, there were significantly more thrombotic events in the rivaroxaban group as patients were transitioned to open-label drug, most often warfarin. Although exact recommendations for discontinuation are unclear, it may be beneficial to consider alternate, short-acting anticoagulants in those high-risk patients requiring temporary discontinuation for procedures [22].

Rivaroxaban has a high bioavailability (80%-100%), and maximum concentrations can be seen in plasma 2 to 4 hours after administration. Although high bioavailability is seen when rivaroxaban is administered orally, it should be noted that it has poor absorption when administered into the small intestine via a feeding tube (29%-56% decrease in area under the curve and peak concentration) and should, therefore, be administered via the stomach.

In patients with significant renal impairment (ie, CrCl <30 mL/min), the use of rivaroxaban should be avoided. Dosing of rivaroxaban does not need to be adjusted in patients with a CrCl greater than 30 mL/min. In addition, rivaroxaban should be avoided in patients with moderate to severe hepatic impairment (Child-Pugh class B or C) as a significant increase in rivaroxaban concentrations has been seen [21].

In patients with an epidural catheter, the catheter should not be removed until at least 18 hours after the last dose of rivaroxaban. In addition, this agent should not be restarted any sooner than 6 hours after removal of the catheter [21].

Currently, there is no specific antidote for the reversal of rivaroxaban, although it has been reported that prothrombin complex concentrate (PCC) and rFVIIa may be effective in reversing its effects [21,23].

1.4.2. Apixaban

Apixaban is a reversible, direct inhibitor of factor Xa similar to rivaroxaban [24]. Apixaban was approved in December 2012 for reduction in the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Approval for VTE prevention in patients who have undergone hip and knee replacement is expected soon. Standard dosing of apixaban is 2.5 mg orally twice daily with the initial dose administered 12 to 24 hours after surgery for VTE prevention. The dose recommendation for atrial fibrillation is 5 mg twice daily. As with rivaroxaban, use of coagulation parameters to assess efficacy or toxicity is not required. Apixaban is not recommended in patients with CrCl less than 15 mL/min or those receiving hemodialysis. Caution is recommended in patients with CrCl 15 to 29 mL/min [25].

Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy as clinical trials excluded patients with abnormal liver function tests (alanine aminotransferase/aspartate aminotransferase >2 times and total bilirubin >1.5 times upper limit of normal). In patients with an epidural catheter, the catheter should not be removed until at least 20 hours after the last dose of apixaban, and this agent should not be restarted any sooner than 5 hours after removal of the catheter [23].

Currently, there is no specific reversal agent for apixaban. In patients requiring immediate reversal, surgical hemostasis or transfusion of FFP should be considered. Recombinant factor VIIa can be considered if there is continuing life-threatening bleeding [24].

While receiving apixaban, clotting tests (prothrombin time [PT], international normalized ratio [INR], and aPTT) may be affected. Any changes observed are typically small and subject to a high degree of variability and, thus, are not recommended to assess the effects of apixaban.

1.4.3. Otamixaban

Otamixaban is an IV anti-Xa inhibitor currently unavailable in the United States. Otamixaban reaches maximum concentration in 3 minutes and is effective within 2 to 3 hours of administration [25]. This agent is being studied for use in ACS [26].

1.4.4. Edoxaban

Edoxaban is another oral, reversible factor Xa inhibitor currently in development. Edoxaban has a half-life of 9 to 11 hours allowing for once daily dosing. In July, 2011, edoxaban gained approval in Japan for the prevention of

VTE in patients with total knee arthroplasty, total hip arthroplasty, and hip fracture [25].

1.4.5. Betrixaban

Betrixaban is an oral, competitive factor Xa inhibitor. Betrixaban primarily undergoes biliary excretion with minimal renal excretion, which may be favorable in patients with renal impairment [25]. Currently, this drug is being evaluated in patient undergoing elective knee arthroplasty and those with atrial fibrillation [27].

2. Vitamin K antagonists

2.1. Warfarin

Warfarin has been used as an anticoagulant for more than 50 years and has been the standard for long-term anticoagulation [28]. Although it is a standard, the dosing of warfarin is complicated by a relatively high incidence of drug interactions and interpatient variability. Patient diet, alcohol intake, body mass, concomitant drug treatment, coexisting diseases, compliance, and genetic factors can all affect the anticoagulant activity of warfarin [29].

Warfarin inhibits the production of vitamin K–dependent clotting factors II, VII, IX, and X as well as protein C and S. Although factor VII is quickly affected, anticoagulation is not achieved for several days until the longer half-life factors are inhibited.

Warfarin is an agent with a relatively long half-life of 36 to 42 hours [30]. Varying individual responses and drug interactions necessitate patient-specific dosing, titrated to a goal INR. Warfarin is indicated for the treatment of VTE, prophylaxis of embolic complications from atrial fibrillation, and after insertion of a nonbiological cardiac valve. For most patients, the goal INR is between 2.0 and 3.0, but the goal INR may be 3.5 or greater in patients with nonbiologic cardiac valves and coagulation disorders.

The annual rate of major bleeding is approximately 1.3% in patients treated with warfarin. In addition, the risk of bleeding with warfarin is increased in patients older than 65 years and in those with a history of a bleeding disorder, cerebrovascular disease, and hepatic insufficiency [31].

Reversal agents for warfarin include vitamin K (phytonadione), FFP, factor VIIa, and PCC. The American College of Chest Physicians has developed recommendations for managing an elevated INR or bleeding associated with treatment with warfarin [28].

Recombinant factor VIIa has been used to treat severe hemorrhage in patients who are taking warfarin [32,33]. Although it has a rapid onset, it does have a short duration of action. Patients with severe or life-threatening bleeding should also receive vitamin K and an agent with a longer duration of effect such as FFP or PCC as they will exhibit a rebound in anticoagulation when factor VIIa begins to wear off (approximately 7 hours). Prothrombin complex concentrate may be a better option for reversal of warfarin in patients who are unable to receive the large volume of fluid required with the administration of FFP [34-36].

3. Antiplatelet agents

3.1. Cyclooxygenase inhibitors

The first documented prescribing of nonsteroidal anti-inflammatory drugs (NSAIDs) was by Hippocrates in 400 BC, when willow bark extract was prescribed for fever and inflammation. It was not until the 1600s, however, that salicin, the active ingredient of willow bark extract, was identified. In 1899, acetylsalicylic acid (aspirin), the prototypical NSAID, became commercially available [37]. In 1971, it was subsequently discovered that the mechanism of action of aspirin and other NSAIDs was through prostaglandin inhibition via the cyclooxygenase (COX) enzyme [38]. Two isozymes of COX have since been identified, COX-1 and COX-2. Cyclooxygenase 1 is expressed in most tissues throughout the body, including platelets, endothelium, gastric mucosa, and kidney. Cyclooxygenase 2 is usually undetectable in most tissues but is inducible in response to inflammation and may increase more than 20-fold during an inflammatory reaction [39]. The beneficial effects of NSAIDs are related to inhibition of COX-2 resulting in its antipyretic, analgesic, and anti-inflammatory properties. Inhibition of COX-1 by NSAIDs is the cause of unwanted renal, gastric, and bleeding adverse effects.

Aspirin is FDA approved for a wide variety of indications, including rheumatic diseases (rheumatoid arthritis, osteoarthritis, and arthritis and pleurisy of systemic lupus erythematosus), vascular diseases (ischemic stroke, myocardial infarction [MI], and angina pectoris), post revascularization procedures (coronary artery bypass graft [CABG], percutaneous transluminal coronary angioplasty, and carotid endarterectomy) [40]. Although all NSAIDs inhibit the COX enzyme, the effects of aspirin are irreversible. This results in an inhibition of platelet aggregation for the 8 to 10 day lifespan of the platelet, and as such, aspirin should be held 1 week before elective surgery [41,42]. In the event of emergent surgery or if the risk of cardiovascular events outweighs the benefits of discontinuing aspirin before surgery, options for reversing anticoagulation include platelet transfusion or the administration of de-amino d-arginine vasopressin (desmopressin), both of which reverse the anticoagulant effect of aspirin within 30 minutes [9,43,44].

Unlike aspirin, the antiplatelet effect of other NSAIDs is temporary due to the reversible binding of COX. Nonsteroidal anti-inflammatory drugs are indicated for the treatment of inflammation, fever, and pain but should be discontinued at least 5 half-lives before surgery to ensure restoration of platelet function [42]. Nonsteroidal anti-inflammatory drugs have varying pharmacokinetic and pharmacodynamic

Table 1 Pharmacokinetic profiles of NSAIDs [44-46]

Drug	Ratio [a]	Half-life (h)	Recommended anti-inflammatory dose	Time to hold before elective surgery [b] (h)
Aspirin	3.12	0.25	1200-1500 mg TID	168-240
Celecoxib	0.11	11	100-200 mg BID	33-55
Diclofenac	0.05	1.1	50-75 mg QID	3-5
Etodolac	0.11	6.5	200-300 mg QID	20-33
Flurbiprofen	10.27	3.8	300 mg TID	11.5-19
Ibuprofen	1.69	2	600mg QID	6-10
Indomethacin	1.78	4-5	50-70 mg TID	15-25
Ketoprofen	8.16	1.8	70 mg TID	5.5-9
Ketorolac	1.64	4-10	10 mg QID	30-50
Meloxicam	0.09	20	7.5-15 mg daily	60-100
Nabumetone	0.64	26	1000-2000 mg daily	78-130
Naproxen	1.79	14	375 mg BID	42-70
Piroxicam	0.79	57	20 mg daily	171-285

[a] Expressed as the ratio of the 50% inhibitory concentration of COX-2 to the 50% inhibitory concentration of COX-1 in whole blood. Nonsteroidal anti-inflammatory drugs with a ratio of less than 1 indicate selectivity for COX-2.

[b] Estimated time based on 3 to 5 times the elimination half-life. May vary depending on type of surgical intervention, dose, and underlying organ function.

profiles (see Table 1), which is important to note when predicting the duration and extent of platelet inhibition. No studies have demonstrated differences in anti-inflammatory and analgesic effects based on COX selectivity. Conversely, NSAIDs with COX-2 selectivity have demonstrated a reduction in the incidence of adverse gastrointestinal events with short-term use; however, the benefits of COX-2 selectivity on such events seem to be lost with prolonged use (celecoxib is the only one on the market) [47].

Nonsteroidal anti-inflammatory drugs are contraindicated in patients with known hypersensitivity to a particular agent as well as in patients who have a history of bronchospasm, angioedema, or nasal polyps that was precipitated by aspirin or other NSAIDs [48]. In addition, aspirin is contraindicated in children and teenagers with viral infections due to the risk of Reye's syndrome [40]. In addition, celecoxib is contraindicated in patients with known hypersensitivity to sulfonamides as well as for use during the perioperative period when CABGs are performed [49].

3.2. Adenosine diphosphate antagonists (thienopyridines)

3.2.1. Ticlopidine

Ticlopidine hydrochloride prevents platelet aggregation via irreversibly inhibiting the formation of the platelet-fibrinogen complex through an adenosine diphosphate–mediated pathway. As with clopidogrel, antiplatelet effects are rapid, with peak plasma concentrations being achieved within 2 hours of administration. Elimination of ticlopidine hydrochloride is prolonged after repeated dosing, extending from 12 hours initially to 5 days. Steady-state plasma concentrations of ticlopidine hydrochloride are attained after 14 to 21 days of consecutive daily dosing, and the agent undergoes extensive breakdown in the liver [50,51].

Ticlopidine hydrochloride is indicated for prevention of stroke in patients at risk for or with a history of thrombotic stroke, primarily in patients allergic to aspirin. Hypersensitivity, active bleeding, preexisting neutropenia or thrombocytopenia, history of thrombotic thrombocytopenic purpura, history of aplastic anemia, and severe hepatic dysfunction are all contraindications to its use. It is recommended that ticlopidine hydrochloride be discontinued in the 10 to 14 days before elective surgical procedures. With a prolonged bleeding time, administration of 20 mg of IV methylprednisolone will correct this within 2 hours. Another method to reverse bleeding is the administration of platelet transfusions [51].

3.2.2. Clopidogrel

Clopidogrel is an adenosine diphosphate receptor antagonist with specific affinity for the $P2Y_{12}$ receptor. Through its irreversible binding to this receptor, platelet activation and aggregation are directly inhibited. This agent indirectly inhibits the activation of glycoprotein (GP) IIb/IIIa complex leading to antiplatelet effects that remain for 7 to 10 days, the lifespan of the platelet, once again [50,52,53].

Clopidogrel is indicated for use in ST-segment and non–ST-segment elevation MI. In addition, studies have shown clopidogrel to be useful in preventing new ischemic stroke, MI, and death from recent stroke or peripheral arterial disease. The recommended dose is 75 mg/d, with various loading doses of 300 to 600 mg given based on specific indications. Clopidogrel should be given concomitantly with daily aspirin [52,53].

Contraindications for use of clopidogrel include active bleeding and anaphylactic hypersensitivity to the drug. Precautionary use should be used with concomitant cytochorome P (CYP) 450 2C19 inhibitor use (ie, omeprazole, chloramphenicol, fluconazole, fluoxetine, oxcarbazepine), and therapy should be discontinued 5 days before elective

surgical procedures, unless the benefit of continued platelet inhibition outweighs the risk of bleeding. Currently, there are no sound recommendations concerning reversal agents for clopidogrel [52,53].

3.2.3. Prasugrel

In contrast to clopidogrel and ticlopidine, newer thienopyridines were designed to have more favorable pharmacodynamic effects and safety. Prasugrel is an irreversible thienopyridine prodrug that is metabolized to its active form via esterases and 1 CYP-mediated oxidative step unlike clopidogrel that requires 2 steps [54]. For this reason, it is thought that prasugrel is associated with fewer drug interactions and interactions with genetic polymorphisms. Prasugrel is administered as a 60-mg loading dose followed by 10 mg daily in conjunction with aspirin 75 to 325 mg daily and is indicated for patients with ACS who are undergoing revascularization [55,56]. Prasugrel use is not recommended in elderly patients (>75 years old) except in high-risk situations such as diabetes mellitus or prior MI and is contraindicated in patients with a prior stroke or transient ischemic attack [55,56]. In addition, prasugrel should be dose adjusted to 5 mg daily in patients weighing less than 60 kg. In the event of major bleeding, no specific reversal agent for prasugrel exists, although functioning platelets can be administered. Prasugrel should be held 7 days before a planned CABG [56,57].

3.2.4. Ticagrelor

Ticagrelor is a reversible P2Y12 receptor inhibitor due to its cyclo-pentyl-triazolo-pyrimidine structure that is different from the thienopyridine structure of the other agents. Ticagrelor is direct acting so this agent does not require biotransformation to an active form via the CYP450 enzyme pathways, although the CYP3A4 enzyme is necessary for metabolism of ticagrelor into its inactive form [54,56]. Ticagrelor has a half-life of 7 to 9 hours, and a loading dose of 180 mg followed by 90 mg is administered orally twice daily [56,58]. Currently, this agent is indicated to reduce the rate of thrombotic events in patients with ACS [56,58]. It was initially thought that ticagrelor would need to be discontinued just 2 days before CABG due to its short half-life; however, postmarketing data regarding bleeding risk have led to label changes that now state to hold this agent 5 days before CABG or any surgery if possible [58]. Besides bleeding, ticagrelor has adverse effects that are different from other agents in this class. Bradyarrhythmias (6% with ventricular pauses) and dyspnea (14%) have been demonstrated to occur at higher rates than patients receiving clopidogrel [58]. Dyspnea is often related to the first few doses and resolves without discontinuation of the agent. There are no specific reversal agents for this drug, and platelets should be administered with caution in patients with severe bleeding because this agent is reversible and can inhibit newly administered platelets in theory.

3.3. Glycoprotein IIb/IIIa inhibitors

The agents in this class (abciximab, eptifibatide, tirofiban) inhibit platelet aggregation by specifically binding to the GPIIb/IIIa receptor, the major surface receptor involved in the final common pathway for platelet aggregation. There are approximately 80 000 of these receptors on the surface of each platelet. By binding to the GPIIb/IIIa receptor, these agents prevent fibrinogen, von Willebrand factor, and other adhesive molecules from binding to the receptor, thereby inhibiting platelet aggregation. Unlike other antiplatelet agents, the GPIIB/IIIA receptor inhibitors (GPI) antagonize platelet aggregation, not platelet activation, and they are regarded as the most potent FDA-approved antiplatelet agents. All 3 available agents have the potential to cause thrombocytopenia, although the risk is slightly higher with abciximab (up to 6.5%) [59]. Platelet counts generally recover several days after the infusion is stopped. The GPIs are only available parenterally, and they are highly used in the setting of ACS.

In ACS patients in whom CABG is selected after angiography, the GPI (eptifibatide or tirofiban) should be discontinued 4 hours before operation. There is no direct reversal agent for the GPIs. In the event of serious or uncontrolled bleeding, platelet function can be recovered by transfusion of platelets. Because abciximab binds irreversibly to the platelet, platelet transfusion can be performed shortly after discontinuation of the drug; however, the irreversible nature of the small molecule GPIs precludes the immediate administration of platelet transfusion as they will be inhibited by the drug. Fibrinogen supplementation in the form of FFP or cryoprecipitate can be considered to compete with the small molecule GPIs for the GP binding site and, perhaps, overcome the effects of the drugs while they are still active [59]. Below are some of the details related to each specific GPIIb/IIIa inhibitor.

3.3.1. Abciximab (Reopro)

Abciximab was the first drug of this class to be FDA approved. It is a chimeric, human-murine Fab fragment of a monoclonal antibody. Abciximab is an irreversible, noncompetitive inhibitor that is unlike the small molecule inhibitors because it works through steric hindrance of the receptor site, thereby blocking the binding of fibrinogen and von Willebrand factor to the GPIIb/IIIa receptor complex. Abciximab is not specific for the GPIIb/IIIa receptor because it also binds with equal affinity to the vitronectin receptor on platelets, vascular endothelial cells, and smooth muscle cells. Abciximab may have anti-inflammatory properties also, although the clinical relevance of this binding is unknown.

The half-life of abciximab is biphasic in that concentrations decrease rapidly within 10 minutes after bolus administration and then decrease again at 30 minutes. This is probably due to the rapid binding to platelet receptors. Platelet function generally recovers after 48 hours, although platelet-bound abciximab can remain in the circulation for the life of the platelet. The drug is ultimately cleared by platelet degradation.

Because abciximab is not renally cleared, no dosage adjustments are necessary in renal failure, unlike the other GPIIb/IIIa inhibitors. Effective half-life is 18 to 24 hours. Abciximab is administered as a bolus of 0.25 mg/kg over 10 to 60 minutes before the start of percutaneous coronary intervention (PCI) followed by a continuous infusion of 0.125 μg/kg per minute (maximum dose of 10 μg/min) for 12 hours [60].

Abciximab is contraindicated in patients with known hypersensitivity to the drug or to murine proteins. Because abciximab increases the risk of bleeding, it is contraindicated in clinical scenarios that increase a patient's risk such as thrombocytopenia, history of a cerebrovascular accident, recent major surgery or trauma, and recent genitourinary or gastrointestinal bleeding [60].

3.3.2. Eptifibatide

Eptifibatide is a small molecule, cyclic heptapeptide based on a peptide recognition sequence from barbourin, a disintegrin found in snake venom. This molecule irreversibly and competitively inhibits the GPIIb/IIIa receptor binding site. Eptifibatide's plasma half-life is only 2.5 hours. Recommended dosing for this drug is 2 IV push bolus doses (180 μg/kg) 10 minutes apart followed by the maintenance infusion of 2 μg/kg per minute. Eptifibatide is cleared by the kidneys and requires dose adjustment in patients with a CrCl less than 50 mL/min [61]. Because eptifibatide increases the risk of bleeding, it is contraindicated in clinical scenarios that increase a patient's risk such as thrombocytopenia, history of a cerebrovascular accident, need for dialysis, and recent major surgery or trauma [61].

3.3.3. Tirofiban

Tirofiban is a small molecule, nonpeptide (peptidomimetic) tyrosine derivative that reversibly inhibits the platelet GPIIb/IIIa receptor. Unlike abciximab, tirofiban has less affinity for the GPIIb/IIIa receptor and dissociates more rapidly (seconds), thus leading to a shorter plasma half-life of approximately 2 hours. Various dosing regimens of tirofiban have been investigated in different clinical scenarios, the most common being a loading dose of 0.4 μg/kg per minute infused over 30 minutes followed by a maintenance infusion of 0.1 μg/kg per minute. More than 90% platelet inhibition is achieved after the 30 minute bolus infusion. Because this agent is cleared by the kidneys, the dose should be reduced by 50% in patients with a CrCl less than 30 mL/min [62].

Because tirofiban increases the risk of bleeding, it is contraindicated in clinical scenarios that increase a patient's risk such as thrombocytopenia, history of a cerebrovascular accident, and recent major surgery or trauma.

4. Direct thrombin inhibitors

Direct thrombin inhibitors (DTIs) bind directly to thrombin and inhibit both soluble and fibrin-bound thrombin. Direct thrombin inhibitors block the action of thrombin by binding to 1 (univalent) or 2 (bivalent) of its 3 domains including the following: the active site or catalytic site and exosite 1, the substrate binding site [63-65]. Direct thrombin inhibitors currently available in the Unites States are bivalirudin, argatroban, and dabigatran. Lepirudin, a recombinant form of hirudin, was available for the treatment or prophylaxis of thrombosis complicating HIT but was removed from the market in May 2012.

4.1. Bivalirudin

Bivalirudin is a synthetic, 20-amino acid analogue of hirudin. Although it is also bivalent like lepirudin, the binding of bivalirudin to thrombin is reversible because, once bound, it is slowly cleaved by thrombin, thus allowing recovery of thrombin activity [66]. Bivalirudin is approved as an alternative to heparin in patients with or without HIT undergoing PCI and percutaneous transluminal coronary angioplasty. It is administered as a bolus of 0.7 mg/kg followed by an infusion of 1.75 mg/kg per hour to maintain an activated clotting time greater than 300 seconds for the duration of the procedure and up to 4 hours postprocedure, if needed. If anticoagulation is needed after 4 hours, the infusion may be continued at 0.2 mg/kg per hour for up to additional 20 hours [11]. Bivalirudin has a fast onset of action and a half-life of only 25 minutes making it an effective and safe option during PCI. Although only 20% of the dose is cleared by the kidneys, the dose must be adjusted in patients with moderate to severe renal insufficiency (CrCl <30 mL/min). The main mechanism of bivalirudin clearance is by proteolytic cleavage and hepatic metabolism, and unlike lepirudin, it is not immunogenic [67]. Because of its improved safety profile, bivalirudin is being explored as an alternative to heparin in patients undergoing cardiopulmonary bypass surgery [11].

4.2. Argatroban

Argatroban is a competitive, univalent DTI that binds noncovalently to the active site of thrombin forming a reversible complex [65]. Argatroban is approved for the prevention or treatment of HIT-associated thrombosis and as an alternative to heparin in patients with a history of HIT undergoing PCI. It has a half-life of approximately 45 minutes and is metabolized in the liver via the CYP450 3A4/5 enzyme system. As a result, dose adjustments are necessary in patients with hepatic, but not renal impairment [68]. Argatroban is given as a continuous infusion at an initial rate of 2 μg/kg per minute in patients with normal hepatic function and 0.5 μg/kg per minute in patients with hepatic insufficiency (defined as a Child-Pugh score of >6), heart failure, multiple organ system failure, severe anasarca, or after cardiac surgery (ie, conditions associated with hepatic congestion/dysfunction). The dose of argatroban is titrated to

achieve a goal aPTT of 1.5 to 3.0 times the patient's baseline, which is monitored every 4 hours until steady state within the reference range is achieved. Activated clotting time can also be used to monitor its effect and is maintained more than 300 seconds [6]. Although all DTIs may increase the INR as well as other thrombin-dependent coagulation tests, argatroban raises it the most (argatroban > bivalirudin > lepirudin), which creates a challenge when transitioning from argatroban to a vitamin K antagonist. The usual practice is to aim for an INR of 4 or higher while on warfarin and argatroban together. Once the INR is at 4 or higher, it can be rechecked after stopping the argatroban infusion for 4 to 6 hours to ensure it is within the usual therapeutic goal of 2 to 3 [69,70].

4.3. Dabigatran

Dabigatran etexilate is the only oral DTI currently available in the United States. It is a double prodrug that is rapidly converted by plasma and hepatic esterases into its active metabolite, dabigatran, via 2 intermediates. It reversibly inhibits both clot-bound and free thrombin by binding to its active site [71]. The oral bioavailability of dabigatran is low (3%-7%) and is dependent on the presence of an acidic environment. It has a fast onset of action (~1-2 hours) with a half-life of 8 hours after a single dose, which extends up to 17 hours with continued use. Although metabolized in the liver, dabigatran has no effect on CYP450 enzymes and has a low potential for drug-drug interactions. Reduction of the dose of dabigatran, however, is recommended when coadministered with amiodarone and strong P-GP inhibitors (ie, verapamil), and the agent is contraindicated with quinidine use. Most of the drug (80%) is excreted unchanged via the kidneys; therefore, the dose must be adjusted in patients with renal impairment and is not recommended in severe renal disease (CrCl <15 mL/min) due to the prolonged half-life that results (up to 28 hours) [71]. In addition, dabigatran should be discontinued 1 to 2 days (if CrCl ≥ 50 mL/min or greater) or 3 to 5 days (if CrCl <50 mL/min) before invasive or surgical procedure if possible due to the increased risk of bleeding. Longer times should be considered in patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be necessary, and anticoagulant therapy should be reinitiated as soon as possible after procedure [72]. Currently, dabigatran is licensed in the United States for use in patients with nonvalvular atrial fibrillation to prevent stroke and systemic embolism at a dose of 150 mg twice daily, with a reduced dose of 75 mg twice daily in patients with a CrCl less than 30 mL/min [73]. Clinical advantages of dabigatran include oral administration, predictable and reliable pharmacokinetic and pharmacodynamic profiles, lack of need for routine monitoring, minimum drug-drug interactions, potentially safer side effect profile, and fixed dose administration. The safety of this agent, however, will need to be confirmed as its usage increases, especially in elderly patients.

4.4. Comments on DTIs

Although there are multiple therapeutic options for DTIs, there are no established antidotes for them. Given the short half-lives of parental DTIs (bivalirudin, and argatroban), discontinuation of these agents and establishment of hemostasis (ie, transfusion of blood products) may be all that are necessary to control severe bleeding [11]. On the other hand, dabigatran has a longer half-life, which creates a challenge when trying to reverse its anticoagulant effects. Discontinuation of the drug, surgical hemostasis, and transfusion of blood products are still first-line therapies to control bleeding. Use of clotting agents such as rFVIIa and prothrombin complex concentrate is being investigated as potential therapy for the rapid reversal of dabigatran's effect [74].

5. Fibrinolytic agents

Fibrinolytic agents effectively lyse thrombi through conversion of plasminogen to plasmin, which then degrades fibrin. This causes a dissolution of clots and restoration of blood flow to ischemic tissues. Streptokinase and urokinase, the first-generation plasminogen activators, are fibrin nonspecific and cause systemic fibrinolysis. Therefore, they cause increased bleeding, are associated with allergic reactions, and have limited efficacy. This led to the development of fibrin-specific agents with better safety and efficacy profiles [75,76]. Currently, the 3 commercially available fibrinolytics approved by the FDA are as follows: alteplase (Activase and Cathflo), reteplase (Retavase), and tenecteplase (TNKase). Common indications for fibrinolytics include acute ST-segment elevation MI (alteplase, reteplase, and tenecteplase), acute ischemic stroke (alteplase, reteplase-unlabeled use), PE (alteplase, reteplase-unlabeled use), peripheral arterial occlusion (alteplase, reteplase-unlabeled use), and occlusion of a central venous catheter (alteplase, reteplase-unlabeled use) [77-79].

All 3 agents are recombinant direct tissue-type plasminogen activators with varying degrees of fibrin specificity. Alteplase, a second-generation fibrinolytic, which is structurally identical to endogenous tissue-type plasminogen activator, was the first to be developed. Unlike first-generation fibrinolytics, the activity of alteplase is enhanced in the presence of fibrin, resulting in thrombus-specific lysis and minimal systemic effect. Alteplase's structure consists of several domains with each having a specific function. The half-life of alteplase in the circulation is only 4 minutes, which necessitates its administration as a weight-based bolus injection, followed by a short continuous infusion. Because alteplase is approved for use in multiple conditions, its dosing and duration of infusion will depend on the

indication. Despite a short plasma elimination half-life, the physiologic effect may last longer due to its tight fibrin binding effect [80].

Reteplase is a truncated variant of alteplase with a prolonged half-life (13 minutes) and less fibrin specificity and binding than alteplase. It is the first of the third-generation fibrinolytics to become commercially available. A lower affinity for fibrin binding allows reteplase to activate plasminogen on the surface of the clot as with alteplase and within the clot, also. Although in vitro and animal studies have demonstrated a faster clot lysis and greater patency with reteplase than alteplase, this has not translated into clinical outcomes with both agents having similar efficacy. The longer half-life allows for administration of reteplase by a fixed dose, double-bolus infusion [81].

Tenecteplase is another recombinant variant of alteplase and varies from tissue-type plasminogen activator by 3 amino-acid substitutions. These substitutions result in a longer half-life, highest degree of fibrin specificity and binding, and resistance to plasminogen activator inhibitor-1. Increased fibrin specificity may be associated with a lower risk of noncerebral bleeding because fibrinogen degradation is restricted to the fibrin surface. Because its longest elimination half-life (22 minutes), tenecteplase can be administered as a single weight-based bolus injection [82,83]. Although there are no direct comparative studies, published data suggest that all agents have similar efficacy in establishing reperfusion [75,76,83].

Bleeding (intracranial bleeding, hemorrhagic stroke, other systemic bleeding, and superficial bleeding from a puncture/catheter or surgical sites) is the most common adverse event associated with fibrinolytic therapy and is a major safety concern. The incidence of major bleeding, including intracerebral hemorrhage, associated with each fibrinolytic agent varies depending on the indication and dose administered. With all of the fibrinolytics, the risk of intracerebral hemorrhage increases with advanced age, the concurrent use of heparin, and the presence of hypertension. Overall, each patient should be evaluated for any disease or condition associated with an increased risk of bleeding, and the decision should be based on patient's underlying risk without treatment, risk from treatment, and benefits from treatment [75,76]. Currently, there are no antidotes for the fibrinolytic agents, and with such short half-lives, supportive care is the only way to manage patients who develop significant bleeds.

6. Conclusion

A growing number of agents targeted to interfere with coagulation have or will become commercially available. Research is ongoing to develop drugs that target novel sites such as factors VIIa, VIIIa, and IXa of the clotting cascade and thromboxane A_2 and protease-activated receptors (PAR 1) on platelets [71]. It is imperative for the critical care clinician to have a fundamental understanding of all such agents to appropriately manage patients receiving such therapies.

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