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A Review on the New and Old Anticoagulants

Kayla Myers ▼ Abbie Lyden

Anticoagulants serve as the primary strategy for the prevention and treatment of both arterial and venous thromboembolism. Anticoagulants disrupt coagulation by interfering at various points in the coagulation cascade. This class of medications does not lyse clots that already exist; rather, it prevents thrombus formation and prevents or slows the extension of an existing clot. For decades, the standard therapy for patients requiring oral anticoagulation was warfarin. However, due to some of the shortcomings of warfarin, including the need for continuous routine monitoring, longtime onset and offset of anticoagulation effect, major food and drug interactions, and high incidence of bleeding, newer agents, termed direct oral anticoagulants, or DOACs were developed. This article will provide a review of clinically important information regarding the most commonly used anticoagulants and their reversal agents.

Introduction

Warfarin is currently the number one medication-related reason for emergency department visits and adverse effects. However, direct oral anticoagulant (DOAC) use has become prevalent over recent years, with the most common agents prescribed being rivaroxaban and apixaban for atrial fibrillation. Despite their increase in popularity, many practitioners remain reluctant to prescribe DOACs because of their concerns about bleeding and reversibility despite recent evidence of a better safety profile, including nearly half the risk of intracranial bleeding compared with warfarin (Lippi, Mattiuzzi, Cervellin, & Favaloro, 2017). This article will provide a review and clinically important information regarding the most commonly used anticoagulants and their reversal agents.

Anticoagulants disrupt coagulation by interfering at various points in the coagulation cascade (see Figure 1). Anticoagulant medications do not lyse clots that already exist; rather, they prevent thrombus formation and prevent or slow the extension of an existing clot (Abrams Lammon, & Pennington, 2009).

Drugs classified as anticoagulants include parenteral anticoagulants, such as heparin and low-molecular-weight heparins (LMWHs), and oral anticoagulants, such as vitamin K antagonists (VKA) (e.g., warfarin) and DOACs. Direct oral anticoagulants are divided into two classes: direct thrombin inhibitors (DTIs; e.g., dabigatran) and Factor Xa inhibitors (e.g., apixaban, edoxaban, rivaroxaban, and betrixaban; Barnes, Ageno, Ansell, & Kaatz, 2015). They are used for a variety of clinical indications including treatment and prevention of venous thromboembolism (VTE) and stroke prophylaxis in nonvalvular atrial fibrillation (NVAF; Siegal et al., 2015; see Table 1). However, life-threatening bleeding is an important concern for patient taking anticoagulants because the mortality and morbidity in this population can be as high as 66% (Frank Peacock, Gearhart, & Mills, 2012).

The ideal anticoagulant medication is one that does not require frequent monitoring (yet can be monitored if needed), well-defined pharmacokinetics (no need to adjust dose for renal or hepatic impairment), ease of administration (once daily oral dosing), the ability to easily reverse effect if needed, no food or drug interactions, and rapid onset and offset of action and cost-effective therapy. As will be addressed in this article, unfortunately no anticoagulant fulfills all of these advantages. Thus, it is important to understand the safe use of these agents, their mechanisms of action, clinical impact, and existing methods to mitigate bleeding complications in order to choose the correct anticoagulant for a given patient (see Table 2).

Classes of Anticoagulants

Parenteral–Heparin and Low-Molecular-Weight Heparin

Heparin is a rapid-acting anticoagulant that can be divided into two classes: unfractionated heparin (UFH) and fractionated or LMWH. Low-molecular-weight heparins available in the United States include enoxaparin and dalteparin. Heparin products bind to and increase

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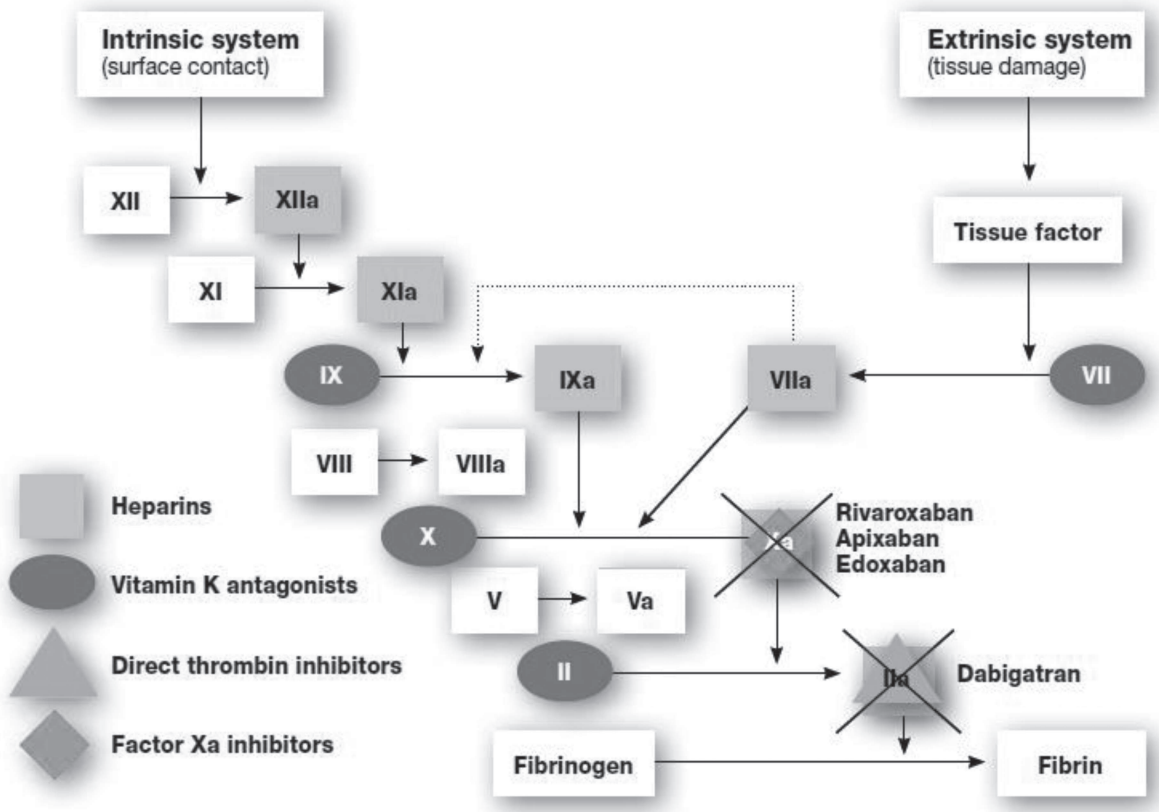

FIGURE 1. How anticoagulants interrupt the coagulation cascade (mechanism of action). See online version of article at https://journals.lww.com/orthopaedicnursing to view figure in color. Copyright © 2018, American Society of Health-System Pharmacists, Inc. (ASHP) All rights reserved. Reprinted by permission of ASHP.

the activity of antithrombin III (AT3). AT3 is an enzyme that inhibits several of the activated clotting factors including 12A, 11A, 9A, and 7A. Thus, heparins inactivate several of the intrinsic activated factors (see Figure 1). As a result of these inhibitions, both ultimately inhibit thrombin activation (Weitz, 2011).

Vitamin K Antagonist—Warfarin

An understanding of vitamin K's role in normal physiological coagulation is important when describing warfarin's mechanism of action. Vitamin K is essential for the hepatic synthesis of clotting Factors II, VII, IX, and X, as well as regulatory factors protein C and S. Warfarin competitively inhibits the vitamin K epoxide reductase complex-1 enzyme (VKOR1), which is a key enzyme for activating the vitamin K available for the body. In short, warfarin depletes functional vitamin K reserves and therefore reduces the synthesis of active clotting factors (Ageno et al., 2012; Patel & Patel, 2018).

Direct Thrombin Inhibitor—Dabigatran

Thrombin is an essential component of the clotting cascade that converts fibrinogen to fibrin. Direct thrombin inhibitors work by inhibiting thrombin, thus preventing the formation of a clot. Currently, there are several DTIs available in the United States including argatroban, bivalirudin, desirudin, and dabigatran. Of the approved agents, dabigatran is the only available oral DTI in the United States (Ageno et al., 2012).

Factor Xa Inhibitors—Apixaban, Rivaroxaban, Edoxaban, and Betrixaban

Factor Xa is the active component of the prothrombinase complex that catalyzes the conversion of prothrombin (Factor II) to thrombin (Factor IIa). Despite the decrease in production, Factor Xa inhibitors do not directly inhibit thrombin or platelet aggregation (Miyares & Davis, 2012).

Dosing and Administration

Heparin and Low-Molecular-Weight Heparin

Both UFH and LMWH are indicated for various conditions including the treatment and prophylaxis of VTE and thrombus prophylaxis in atrial fibrillation (Harter, Levine, & Henderson, 2015; see Table 1). Unfractionated heparin is not orally absorbed and thus must be administered parenterally. Unfractionated heparin can be administered subcutaneously deep-vein thrombosis prophylaxis or as a continuous intravenous infusion when used for therapeutic anticoagulation (Mousa et al., 2007). Derived from UFH, LMWH is administered subcutaneously for both therapeutic and prophylactic indications. Dosing is based on total body weight in kilograms (Harter et al., 2015). When used intravenously, therapeutic efficacy occurs almost immediately with UFH while therapeutic efficacy is reached within 20–60 minutes when administered subcutaneously.

Table 1. Anticoagulant Mechanisms, Routes, And Indications

	Heparin (UFH, LMWH)	Warfarin (Coumadin)	Dabigatran (Pradaxa)	Apixaban (Eliquis)	Edoxaban (Savaysa)	Rivaroxaban (Xarelto)
Target for activity		VKOR-1	Factor IIa (thrombin)	Factor Xa	Factor Xa	Factor Xa
Route of administration	iv/sc	po	po	po	po	po
Inpatient/outpatient use	Inpatient	Inpatient, outpatient	Inpatient, outpatient	Inpatient, outpatient	Inpatient, outpatient	Inpatient, outpatient
Indications						
VTE treatment and prevention of recurrence	√	√	√	√	√ (treatment only)	√
VTE prophylaxis (after THR or TKR)	√	√	√ (hip only)	√	0	√
Stroke/systemic embolism prophylaxis in nonvalvular atrial fibrillation	√	√	√	√	√	√
Valve replacement	√	√	0	0	0	0
Reduction in the risk of death, recurrent infarction, and thromboembolic events (e.g., stroke, systemic embolization) after MI, short term	√	0	0	0	0	0

Note. iv = intravenous; LMWH = low-molecular-weight heparin; MI = myocardial infarction; po = orally; sc = subcutaneous; THR = total hip replacement; TKR = total knee replacement; UFH = unfractionated heparin; VKOR-1 = vitamin K epoxide reductase complex-1 enzyme; VTE = venous thromboembolism.

Unfractionated heparin has a short half-life (~90 minutes) and does not require dose adjustment in renal failure (Harter et al., 2015; Weitz, 2011). Compared with UFH, LMWH has a more predictable dose-response curve, whereas UFH must be titrated on the basis of activated partial thromboplastin time (aPTT) or anti-Xa heparin results and thus may take longer than LMWH to achieve therapeutic goals. Enoxaparin and dalteparin reach peak levels approximately 2–4 hours after subcutaneous administration and have a half-life of 3–4 hours. Both enoxaparin and dalteparin are renally eliminated, thus necessitating a dose reduction in patients with renal insufficiency (Douketis, 2010; Harter et al., 2015).

Warfarin

Warfarin dosing is historically complicated due to the large variance in response between patients. The relationship between the dose of warfarin and the response is affected by genetic and environmental factors (e.g., diet, drug interaction, critical illness, etc.); thus, therapeutic doses are difficult to predict. After initiation, warfarin doses are titrated on the basis of international normalized ratio (INR) results; this need for close monitoring and repeat laboratory test results is one disadvantage of warfarin. A wide dosing range is required to maintain a therapeutic INR with relatively low doses often required for the elderly and patients with underlying comorbidities. Warfarin is hepatically metabolized and primarily eliminated as metabolites by the kidney (Alquwaizani Buckley, Adams, & Fanikos, 2013; Patel & Patel, 2018).

Another drawback of warfarin is the delay to reaching full therapeutic effect, which can take 5–7 days. The delay in full anticoagulant effect is due to preexisting clotting factors already in circulation, which must degrade naturally. The delay to therapeutic effect in addition to an initial procoagulant state due to our body's natural anticoagulants protein C and S, warfarin must be started in combination with a parenteral agent with a rapid onset of action. This short-term overlap between warfarin and an LMWH (enoxaparin or dalteparin) is often referred to as "bridging" (Ageno et al., 2012; Patel & Patel, 2018).

Warfarin also carries the disadvantage of having numerous medication and food interactions. Given warfarin works by decreasing the amount of vitamin K in your body, changing the amount of vitamin K you get through food, can affect how warfarin will work. For example, if one were to start eating foods rich in vitamin K, warfarin would become less effective (i.e., making it more difficult to achieve INR goal) (see Table 3). In addition, due to warfarin being hepatically metabolized, medications that interfere with the CYP 450 enzymes can also affect the activity of warfarin (i.e., increasing the INR and increasing the risk for bleeding). Antibiotics, anti-inflammatory drugs (i.e., nonsteroidal anti-inflammatory drugs [NSAIDs]), and antidepressants (i.e., selective serotonin reuptake inhibitors [SSRIs]) are just a few of medication classes that can interfere with warfarin's effectiveness.

Dabigatran

Dabigatran is administered orally with or without food and is rapidly absorbed. The average half-life of dabigatran is 12–14 hours and is independent of the dose. It

Table 2. Anticoagulants Dosing for Corresponding Indications

	Indications and Dosing of Anticoagulants (Budhiparama, Abdel, Ifran, & Parratte, 2014)					
	Heparin (UFH, LMWH)	Warfarin (Coumadin)	Dabigatran (Pradaxa)	Apixaban (Eliquis)	Edoxaban (Savaysa)	Rivaroxaban (Xarelto)
Dosing (fixed or variable)	Variable	Variable	Fixed	Fixed	Fixed	Fixed
Indications						
VTE treatment and prevention of recurrence	UFH: 80 U/kg bolus, followed by 18 units/kg/hour LMWH: Variable depending on LMWH	INR goal: 2.0–3.0	CrCl > 30 ml/minute: 150 mg bid after 5–10 days of parenteral AC CrCl <30 ml/minute: not recommended	Treatment: 10 mg bid x 7 days, then 5 mg bid Prevention: 2.5 mg bid	Treatment: 60 mg daily CrCl 15-50 or ≤ 60 kg or on p-gp inhibitors: 30 mg daily	Treatment: 15 mg bid x 21 days, then 20 mg daily Prevention: 20 mg daily
VTE prophylaxis (after THR or TKR)	UFH: 5,000 units sc every 8–12 hours LMWH: Variable depending on LMWH	INR goal: 2.0–3.0	THR (CrCl > 30 ml/minute): 110 mg x 1 day, then 220 mg once daily	THR: 2.5 mg bid x 35 days TKR: 2.5 mg bid x 12 days	–	THR: 10 mg daily x 35 days TKR: 10 mg daily x 12 days
Stroke/systemic embolism prophylaxis in nonvalvular atrial fibrillation	UFH: 60–70 units/kg, followed by 12–15 units/kg/ hour LMWH: Variable depending on LMWH	INR goal: 2.0–3.0	CrCl >30 ml/minute: 150 mg bid CrCl 15-30 ml/min: 75 mg bid	5 mg bid Reduce dose to 2.5 mg bid if the patient has 2 out of the 3 following: age ≥80 years, ≥serum creatinine 1.5 mg/dl, and/or body weight ≤60 kg	CrCl ≥ 95 ml/minute: not recommended CrCl 50-95 ml/minute: 60 mg once daily CrCl 15–50 ml/minute: 30 mg once daily	20 mg daily with evening meal CrCl 15-50 ml/minute: 15 mg daily
Valve replacement	UFH: 80 U/kg bolus, followed by 18 units/kg/hour (bridge with warfarin) LMWH**:** Variable depending on LMWH	Atrial: 2.0–3.0 Mitral: 2.5–3.5	–	–	–	–
Reduction in the risk of death, recurrent infarction, and thromboembolic events (e.g., stroke, systemic embolization) after MI (short term)	UFH: 60–70 units/kg, followed by 12–15 units/kg/hour LMWH: Variable depending on LMWH		–	–	--	–

Note. AC= anticoagulation; bid = twice a day; CrCl = creatinine clearance; INR = international normalized ratio; LMWH = low-molecular-weight heparin; MI = myocardial infarction; p-gp = P-glycoprotein; sc = subcutaneous; THR = total hip replacement; TKR = total knee replacement; UFH = unfractionated heparin; VTE = venous thromboembolism.

Table 3. Food and Medication Interactions With Warfarin

	Effect on INR
Vitamin K foods	
Kale	↓
Spinach	
Brussels sprouts	
Parsley	
Green lettuce	
Red cabbage	
Green tea	
Should avoid drinking while on warfarin	
Grapefruit juice	↑
Cranberry juice	
Alcohol	
Drug interactions	
Antibiotics	↑
Fluoroquinolones (ciprofloxacin, levofloxacin)	
Sulfamethoxazole/trimethoprim	
Macrolides (azithromycin, erythromycin, clarithromycin)	
Metronidazole	
Antifungals (e.g., fluconazole)	
Anti-inflammatory (NSAIDs)	
Antidepressants (SSRIs)	

Note: NSAIDs = nonsteroidal anti-inflammatory drugs; SSRIs = selective serotonin reuptake inhibitors.

does not inhibit cytochrome P450; therefore, the potential for drug–drug interactions is low. Unlike warfarin, dabigatran exhibits a predictable dose response and, therefore, does not require routine laboratory coagulation monitoring. It is primarily renally eliminated (80%) and thus requires dosage adjustments in renal impairment (Mekaj, Mekaj, Duci, & Miftari, 2015).

Apixaban

Apixaban is rapidly absorbed after oral administration and may be given with or without food. It has a half-life similar to the other DOACs of approximately 8–15 hours; however, compared with the other DOACs it has the smallest amount of renal clearance (25%; Mekaj et al., 2015). Dosing depends on the indication for treatment, the age of the patient, serum creatinine, and body weight. In patients with two out of the three of the following, the dose should be reduced:

- Age 80 years or older
- Serum creatinine of 1.5 mg/dl or greater
- Body weight of 60 kg or less

Despite having the lowest amount of drug renally eliminated, clinical efficacy and safety studies did not include patients with end-stage renal disease (ESRD) on dialysis. Therefore, it is not recommended in the drug label as an anticoagulant of choice in patents with ESRD (Agrawal & Manna, 2018).

Edoxaban

Edoxaban is rapidly absorbed after oral administration (Yin, Tetsuya, & Miller, 2014). Unlike rivaroxaban, the systemic absorption of edoxaban does not seem to be affected by food. It has dual mechanisms of elimination. Approximately one-third is eliminated via the kidney and the reminder via feces (Eikelboom & Weitz, 2010). Similar to the other DOACs, renal dose adjustments are recommended (Stacy, Call, Hartmann, Peters, & Richter, 2016).

Rivaroxaban

Rivaroxaban is rapidly absorbed and oral bioavailability is dependent on the dose administered and food intake. Higher bioavailability (≥80%) of 15 mg and 20 mg is achieved when taken with food, most often with the evening meal, whereas 10 mg may be taken with or without food (Kubitza, Becka, Wensing, Voith, & Zuehlsdorf, 2005). Metabolism of rivaroxaban occurs primarily through the liver via the CYP isozyme CYP 3A4. Approximately 30% of rivaroxaban is excreted unchanged in the urine and through fecal elimination (Turpie, 2007). Rivaroxaban is dosed once daily, which is could be advantageous in patients who are less complaint with medication therapy (Frost et al., 2014).

Betrixaban

Betrixaban was recently approved in 2017 and is the only DOAC approved for extended duration prophylaxis for VTE in acute medically ill patients. Betrixaban should be taken with food to ensure adequate absorption at the same time every day. Patients with severe renal impairment or patients concomitantly taking P-gp inhibitors (e.g., amiodarone, verapamil) require dose reduction (Skelley, Thomason, Nolen, & Candidate, 2018).

Side Effects

Bleeding is the most concerning adverse event related to all anticoagulants. Minor types of bleeding include nosebleeds and excessive bleeding from minor abrasions or bruises. Major bleeding, such as gastrointestinal (GI) bleeding and intracranial hemorrhage (ICH), can be life-threatening and rapid reversal may be warranted. Excessive anticoagulation may be the result of drug interactions, disease states (renal, liver, or cardia impairment), and higher doses of the anticoagulant. That being said, an individualized approach is necessary to balance the risks for bleeding and thromboembolism in patients receiving anticoagulants. Strategies to minimize the risk for bleeding include evaluating the need for medications that could increase bleeding risk (e.g., SSRIs and NSAIDs), cautioning patients to avoid excessive alcohol intake, and educating patients to be aware for the signs/symptoms of bleeding (Alquwaizani et al., 2013).

Given the influence of environmental factors, drug interactions, and the narrow therapeutic index, major bleeding is also a concern with the VKA antagonist. The most important risk factors for hemorrhage in VKA therapy include intensity of anticoagulant effect, time within therapeutic range, and patient characteristics. Higher INRs (INR >3) have been directly associated with increased rates of hemorrhage (Alquwaizani et al., 2013). Recent clinical trials have compared the efficacy and safety of DOACs with warfarin for the prevention of

stroke and systemic embolism with NVAF or prevention or treatment of VTE addressing differences in the risk for GI bleeding and ICH. Of the DOACs, apixaban is superior for NVAF with reduced rates of ICH and major bleeding for deep-vein thrombosis/pulmonary embolism (see Table 4).

One unique but rare adverse effect of heparin is heparin-induced thrombocytopenia (HIT; 1%–5%). Heparin-induced thrombocytopenia is an antibody-mediated adverse reaction of heparin, associated with the production of heparin-dependent antibodies, development of thrombocytopenia, and venous and atrial thrombosis (Hirsh, Guyatt, Albers, Harrington, & Schünemann, 2008). Monitoring platelet counts throughout therapy can help assess for HIT as it typically occurs in patients exposed to UFH or LMWH for 5–7 days, or sooner if the patient was previously exposed. The incidence of HIT is approximately one-tenth lower with LMWH than with UFH. Patients receiving UFH for a longer period of time (e.g., 1 month) are also at an increased risk of osteoporosis and development of vertebral fractures (Alquwaizani et al., 2013).

Adverse events specific to dabigatran include dyspepsia, dizziness, headache, and dyspnea. If a patient experiences these adverse effects, it may be improved by taking with food (Rybak, Ehle, Buckley, & Fanikos, 2011). Other than the risk of bleeding, the Factor Xa inhibitors are well tolerated and have otherwise minimal side effects.

Monitoring

Each anticoagulant varies in its effect on routine and specialty coagulation assays and each drug may require distinct laboratory assay(s) to measure drug concentration or activity (Samuel et al., 2016). The routine need to monitor and titrate medications is a noted drawback of some of the anticoagulant medications, most notably with warfarin. However, there are circumstances when clinically reliable laboratory tests are of great importance, as in the setting of life-threatening bleed or the need for urgent surgery.

Unfractionated Heparin

Currently, the two most common methods for monitoring UFH are the aPTT and anti-Factor Xa (anti-Xa) heparin assay. Both methods are generally obtained every 6 hours while the patient is on a continuous infusion; however, monitoring may be extended if the patient remains therapeutic for a period of time (e.g., laboratory every 24 hours). Of the two, aPTT is used more frequently because of its ease of automation, accessibility, and cheaper cost than anti-Xa. The goal therapeutic range is set at 1.5–2.5 times the control aPTT. The main drawbacks of using aPTT for monitoring UFH infusion are constant fluctuating results, delay in reaching therapeutic range, and the need for multiple-dose adjustments and blood samples, as compared with anti-Xa assay. The American College of Chest Physicians and the College of American Pathologists recommend using anti-Xa as it better correlates with heparin concentrations targeting a goal of 0.3–0.7 unit/ml (Samuel et al., 2016).

Low-Molecular-Weight Heparin

Therapeutic monitoring is not routinely indicated in patients on LMWH, although there are clinical scenarios within certain patient populations that may warrant monitoring. Patients with renal insufficiency, obesity, and pregnancy, or when overdose is of concern, anti-Xa levels can be used to monitor LMWH. Ideally, the anti-Xa level should be obtained 4 hours after the administration of LMWH.

Warfarin

The laboratory parameter used to monitor warfarin for safety and efficacy is the prothrombin time (PT) and the INR. The PT measures the number of seconds it takes for the blood to clot and the INR allows for the standardization of the PT measurement. A patient's INR who is not on warfarin therapy is approximately 1.0. If a patient has an INR of 2.0 or 3.0, that would indicate that it takes two or three times longer for that individual's blood to clot compared with someone who is not on anticoagulation. The therapeutic INR goal is dependent on the indication, patient's environmental factors and history, and provider's preference. For most indications, the goal INR is 2–3. Achieving goal INR is a dynamic process and requires chronic monitoring (sometimes multiple times per week, particularly at the beginning of therapy or at times of acute illness in which there may be INR variability). The frequent monitoring has the potential to impair patients' quality of life and also imposes a significant cost to the healthcare system and increased provider burden (Patel & Patel, 2018).

Table 4. DOAC Safety and Efficacy Compared With Warfarin[a]

		Dabigatran	Apixaban	Edoxaban	Rivaroxaban
NVAF	Efficacy	Superior	Superior	Noninferior	Noninferior
	GIB	↑	↔	↑	↑
	ICH	↓	↓	↓	↓
DVT/PE	Efficacy	Noninferior	Noninferior	Noninferior	Noninferior
	Major bleeding	↔	↓	↔	↓

Note. DVT/PE= deep-vein thrombosis/ pulmonary embolism; GIB = gastrointestinal bleed; ICH = intracranial hemorrhage; NVAF = nonvalvular atrial fibrillation; ↔ = no difference compared with warfarin; ↓ = statistically significant difference in favor of DOAC; ↑ = statistically significant increase in risk with DOAC.
[a]Data from Agnelli et al. (2013), Connolly et al. (2009), Bauersachs et al. (2010), Büller HR et al. (2010), Granger et al. (2011), Patel et al. (2011), & Schulman et al. (2009).

Direct Oral Anticoagulants

Routine monitoring is not required during DOAC therapy, regardless of body weight, age, sex, race, or demographic variations. Indeed, this is one of the initial advantages cited for the development of DOACs, that is, the lack of need for INR (or other) monitoring. Direct oral anticoagulants may be a good choice for patients with unstable INRs on warfarin or complicated interacting drug regiments on warfarin. These medications have fixed dosing, that is, the dose is not intended to be adjusted on the basis of any coagulation laboratory parameter. As a result of Factor Xa inhibition, apixaban, rivaroxaban, and edoxaban prolong other clotting tests including PT/INR and aPTT. However, these changes are small and subject to variability and thus not useful in the monitoring of these medications (Ten Cate, Henskens, & Lancé, 2017).

Reversal

Reversal of the anticoagulant effects may be needed for patients experiencing life-threatening bleeding such as, ICH, or patients undergoing emergent, elective, or invasive procedures. The reversal strategy depends on the setting (e.g., emergency department, operating room, intensive care unit) and urgency. The presence of bleeding, the site, and the severity are all important considerations. Here we list a number of different therapies or antidotes (neutralize the anticoagulants activity) that are used when reversal is indicated (see Table 5). These therapies do not work for all anticoagulants, so the selection on reversal agent depends on the medication that was prescribed. Of note, there are serious risks with "reversing" anticoagulation, most importantly, clotting in patients that at baseline requires anticoagulation. Indeed, the risk of thrombosis often leads practitioners to not reverse the specific anticoagulant and instead just hold the medication for a few doses, particularly in the setting of minor bleeding.

Table 5. Anticoagulants and Their Reversal Agents[a]

Anticoagulant	Reversal Agents
Heparin (UFH, LMWH)	Protamine
Warfarin	Withhold drug (if minor bleeding) Vitamin K PCC4 (Kcentra) aPCC (FEIBA) FFP
Dabigatran	Withhold drug Hemodialysis Idarucizumab PCC4 (Kcentra) aPCC (FEIBA)
Apixaban, rivaroxaban, edoxaban	Withhold drug Andexxa (apixaban and rivaroxaban only) PCC4 (Kcentra) aPCC (FEIBA)

Note. aPCC = activated prothrombin concentrate complex; FEIBA = factor eight inhibitor bypass activity; FFP = fresh frozen plasma; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.
[a]Adapted from "Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals From the Neurocritical Care Society and Society of Critical Care Medicine," by J. A. Frontera, J. J. Lewin III, A. A. Rabinstein, I. P. Aisiku, A. W. Alexandrov, A. M. Cook, … C. L. Zerfoss, 2016, Neurocritical Care, 24(1), 6–46.

Protamine

In the event of a major bleed and if rapid reversal of the anticoagulant is necessary, heparin products can be reversed with the administration of protamine sulfate. Protamine, a strong basic molecule derived from salmon, reverses the anticoagulant effects when it binds to the strong acidic molecule heparin, forming a neutralized salt. Protamine has a rapid onset of action, inhibiting heparin effects within 5 minutes of administration. Slow administration (maximum of 5 mg/min) is recommended to avoid any infusion-related reactions as well as hypotension and bradycardia. Caution is warranted in patients with allergies to salmon and/or if sensitive to neutral protamine Hagedorn insulin. Dosing is based on the amount and time of UFH administered. A dose of 1 mg of protamine will reverse 100 units of UFH. Because of LMWH having a higher affinity for Factor Xa rather than IIa, protamine will only partially reverse LMWH, maximally neutralizing only 60%–75% of the anti-Xa activity (Garcia, Baglin, Weitz, & Samama, 2012).

Vitamin K (Phytonadione)

Vitamin K leads to the production of functional coagulation Factors II, VII, IX, and X, which are normally depleted by warfarin. Vitamin K works to reverse only warfarin and does not neutralize the activity of other anticoagulants. The onset and duration of activity are related to the route of administration. If rapid reversal is necessary, as is in life-threatening bleeding such as ICH, 10 mg intravenous is recommended. Intravenous administration has a faster onset (1–2 hours) versus oral (10 hours). The duration of oral vitamin K may last multiple days, thus decreasing the ability to become therapeutic on warfarin once anticoagulation is restarted. It is not recommended to give vitamin K subcutaneously, given its erratic absorption and variable pharmacokinetics. When deciding to administer vitamin K for elevated INR or bleeding, the practitioner must weigh the benefit of INR reversal versus the risk of clot by giving too much vitamin K (Hemphill et al., 2015).

Fresh Frozen Plasma

Fresh frozen plasma (FFP) contains all the anticoagulation factors and proteins present in whole blood and reverses warfarin's anticoagulant effects by replacing the vitamin K–dependent clotting Factors, II, VII, IX, and X. It has a variable onset between 1 and 4 hours and a variable duration lasting between 6 and 8 hours. Dosing is based on milliliter per kilogram and the large volume of fluid administration is a potential disadvantage of using FFP. Additional barriers to its use include the need for blood-type matching (must be ABO compatible) and the need to unthaw the product, potentially delaying the administration to the patient (Hemphill et al., 2015).

Table 6. Prothrombin Concentrate Complex Products

Reversal Agent	Type	Coagulation Factors
Profilnine SD, Bebulin	Inactivated PCC, 3-factor	II, IX, X
Kcentra	Inactivated PCC, 4-factor	II, **VII,** IX, X
FEIBA	Activated PCC, 4-factor	II, **VIIa,** IX, X
NovoSeven	Activated factor VIIa	VIIa

Note. FEIBA = factor eight inhibitor bypass activity; PCC = prothrombin concentrate complex. Boldface indicates main difference between the two products.

Prothrombin Concentrate Complex

Prothrombin concentrate complexes (PCCs) are intermediate pooled plasma products containing high concentrations of clotting factors when compared with FFP (Franchini & Lippi, 2010). The differences between the PCC products lie among the factors they contain as well as whether these factors are activated or inactivated (see Table 6). For example, both Factor Eight Inhibitor Bypass Activity, or FEIBA, and Kcentra contain four Factors: II, VII, IX, and X. The main difference between these two products is that Kcentra contains all inactivated factors whereas FEIBA contains the activated form of Factor VII. Prothrombin concentrate complex products have a rapid onset of action and duration of action of approximately 12–24 hours. Pharmacologic effects are dependent on the half-lives of the factors that begin to wane after 12–24 hours after dosing. Kcentra also contains proteins C and S as well as heparin. Therefore, it is an absolute contraindication if the patient has an intolerance to heparin products and/or a history of HIT. Potency of the PCC product is based on the factor of 9 units and the maximum infusion rate should not exceed 3 units/kg/min.

Idarucizumab (Praxbind)

Idarucizumab (Praxbind) is a humanized monoclonal antibody fragment that binds to both free and thrombin-bound dabigatran. Idarucizumab is the antidote to dabigatran because it binds dabigatran specifically to completely reverse the anticoagulation effect, making it unable to interact with free thrombin. It is structurally similar to thrombin and has 350 times greater affinity for dabigatran than for thrombin. Once the idarucizumab–dabigatran complex is formed, it is then cleared by the kidneys. It has an immediate onset of action and the recommended dose is 5 g. Idarucizumab is administered intravenously (Frontera et al., 2016).

Coagulation Factor Xa (Recombinant), Inactivated—ZHZO (Andexxa)

Andexxa is a modified activated human Factor Xa that acts as a decoy, binding to Factor Xa inhibitors such as rivaroxaban and edoxaban and neutralizing their activity. It has a rapid onset of activity (~2 minutes) and the effects last up to 5–7 hours. Dosing is based on the anticoagulant used, the timing of the last dose, and the mount of the last dose. Reversal involves both an intravenous bolus and continuous infusion given for more than 2 hours (Sartori & Cosmi, 2018). Pre- and post-anti-Xa levels after receiving Andexxa may be taken to observe hemostatic efficacy. The most common adverse reactions in patients receiving Andexxa include thrombosis, urinary tract infections, and pneumonia (Rogers & Finks, 2018).

Table 7. Advantages and Disadvantages of Anticoagulants

	Warfarin	DOAC
Onset	Slow: 5–7 days	Fast: immediate
Offset	Half-life: 20–60 hours	Shorter half-lives
Dosing interval	Daily	Depends on agent
Dose	Patient-dependent (must be titrated)	Fixed dose
Food interactions	Many	Minimal
Drug interactions	Many	Fewer
Safe in pregnancy	No	No
Cost	Cheap but requires INR monitoring, thus added costs (e.g., clinic appointments)	Expensive but increasingly covered by insurances
Safe for patients with significant renal dysfunction	Yes	No
Monitoring required	Yes: INR for dose titration	No
Reversal (antidote available)	Yes: vitamin K, PCC	Yes: depends on agent

Note. DOAC = direct oral anticoagulant; INR = international normalized ratio; PCC = prothrombin concentrate complex.

Conclusion

Both oral anticoagulation and parenteral anticoagulation are essential for arterial and VTE diseases. For decades, the standard for patients requiring oral anticoagulation was warfarin. However, due to some of the shortcomings of warfarin, including the need for continuous routine monitoring, long-time onset and offset of anticoagulation effect, major drug and food interactions, and high incidence of bleeding, especially in our elderly patients, newer agents termed DOACs were developed (see Table 7). The advantages of DOACs, which consist of dabigatran, apixaban, rivaroxaban, and edoxaban, are their lower incidence of major bleeding, convenience of use, minor food and drug interactions, shorter half-life, and lack of the need for laboratory monitoring. Understanding the use of these agents, their mechanism of action, clinical impact, and existing methods to reverse their anticoagulation effects is essential as life-threatening bleeding is an important concern for all patients taking anticoagulants.

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