Anticoagulants and Treatment of Venous Thromboembolism

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Parenteral Anticoagulants

Indirect Thrombin and/or Xa Inhibitors

Overview

Indirect parenteral anticoagulants include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and fondaparinux. Each of these agents requires binding to endogenous antithrombin (AT) via a unique pentasaccharide sequence to catalyze anticoagulation and inhibit the formation of thrombin. UFH was discovered in canine liver cells around 1916. Commercial preparations are now derived primarily from porcine intestine. LMWHs, which became commercially available in the mid-1980s, are created through controlled depolymerization of UFH molecules and exhibit a higher degree of target specificity within the coagulation cascade. Fondaparinux, first available in the 1990s, is a synthetic analog of the unique pentasaccharide sequence that binds to AT and is designed to specifically inhibit a single target within the clotting pathway (Fig. 17.1). Each of these rapid-acting agents has been shown to be effective in preventing and treating arterial and venous thromboembolism.

Key Concepts

- The indirect parenteral anticoagulants inhibit the formation of thrombin (factor IIa) by binding to and catalyzing endogenous AT via a unique pentasaccharide sequence.
- UFH, with its non-specific binding and nonlinear kinetics, requires frequent monitoring via the activated partial thromboplastin time (aPTT) or the anti-factor Xa assay, using evidence-based, standardized dosing and titration protocols.
- LMWHs and fondaparinux have a more predictable pharmacokinetic profile and may be administered in fixed doses without the need for routine monitoring of anticoagulant activity.

Unfractionated Heparin

Pharmacology

Mechanism of Action

Unfractionated heparin (UFH) is a heterogeneous mixture of naturally occurring, highly sulfated carbohydrate chains stored in secretory granules within mast cells. The molecular weight of UFH polysaccharide chains ranges from 3000 to 30,000 Da (mean 15,000 Da). UFH requires binding with antithrombin (AT), an endogenous anticoagulant produced by the liver, to exert its effect. Binding occurs via a unique pentasaccharide sequence found on only one-third of heparin molecules and induces a conformational change within AT, accelerating enzymatic inhibition of several clotting factors, with factors IIa (thrombin) and Xa being most sensitive to this inhibition and most critical in thrombus formation (Figs. 17.1 and 17.2). UFH inhibits these two factors equally in a 1:1 ratio. FXa inhibition requires only binding of UFH, regardless of chain length, to AT via the pentasaccharide sequence, whereas thrombin inhibition requires higher molecular weight UFH chains (≥5400 Da) for formation of a ternary complex between UFH, AT, and thrombin. Once UFH has catalyzed AT, it disassociates and can catalyze additional AT molecules. UFH only binds free-floating thrombin and does not possess fibrinolytic activity. Thus, it will not lyse existing thrombi but does prevent clot propagation and growth [1–3].

Pharmacokinetics/Pharmacodynamics

UFH is poorly absorbed from the gastrointestinal (GI) tract and must be administered parenterally, with intravenous (IV) infusion or subcutaneous (SC) injection being the preferred

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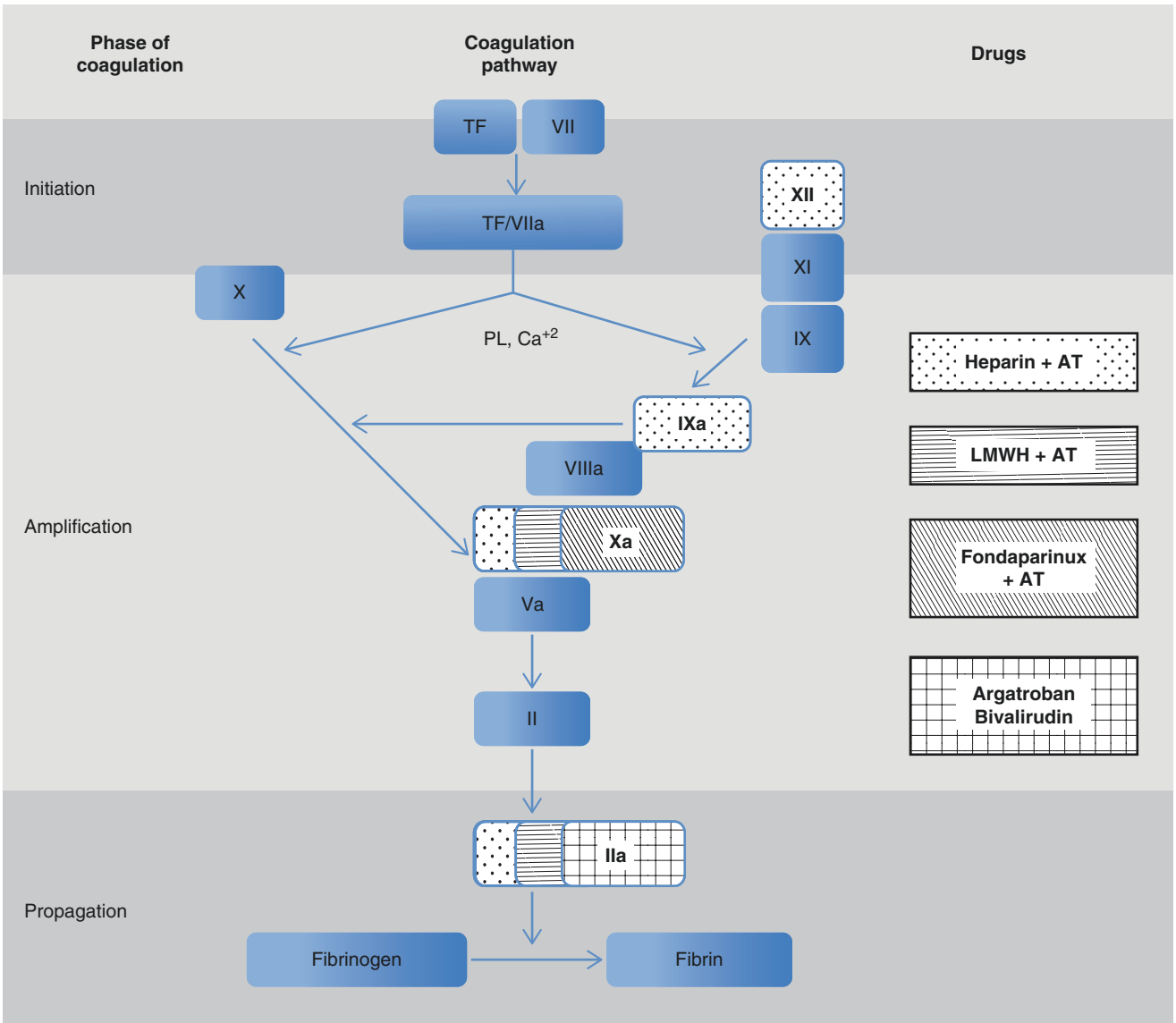

Fig. 17.1 Site of action of parenteral anticoagulants within the coagulation cascade. *AT* anthithrombin, *Ca* calcium, *LMWH* low-molecular-weight heparin, *PL* phospholipid, *TF* tissue factor

routes of administration [1]. The IV route is most commonly employed for therapeutic purposes. An IV bolus followed by a continuous infusion provides an immediate anticoagulant effect and rapid attainment of therapeutic plasma concentrations [4]. When administered SC, bioavailability is reduced to 30–70%, depending on the dose, and the onset of anticoagulation is delayed by 1–2 h. The SC route is most commonly used for venous thromboembolism (VTE) prevention. If the SC route is chosen for treatment of VTE, the dose should be ~10–20% higher than the therapeutic IV dose to overcome the diminished bioavailability [1–3].

UFH binds extensively to the endothelium, macrophages, and plasma proteins other than its intended target, AT, which reduces bioavailability. Plasma levels of heparin-binding proteins vary dramatically over time, particularly in acutely ill patients, rendering the anticoagulant response to heparin unpredictable. Due to intra- and interpatient variability in dose response and changes in patient response over time, UFH requires routine monitoring and dose adjustments via standardized protocols [1, 3].

UFH is cleared from systemic circulation via an initial saturable, macrophage-mediated process and a second, slower non-saturable renal-mediated process. As the initial process becomes saturated with prolonged therapy or higher dosing, clearance becomes dependent on the slower non-saturable process, leading to a nonlinear dose response and a variable half-life (Table 17.1) [1, 2].

Clinical Indications

As the only parenteral anticoagulant for several decades, UFH has gained FDA approval for use in several thromboembolic indications [5], including the following:

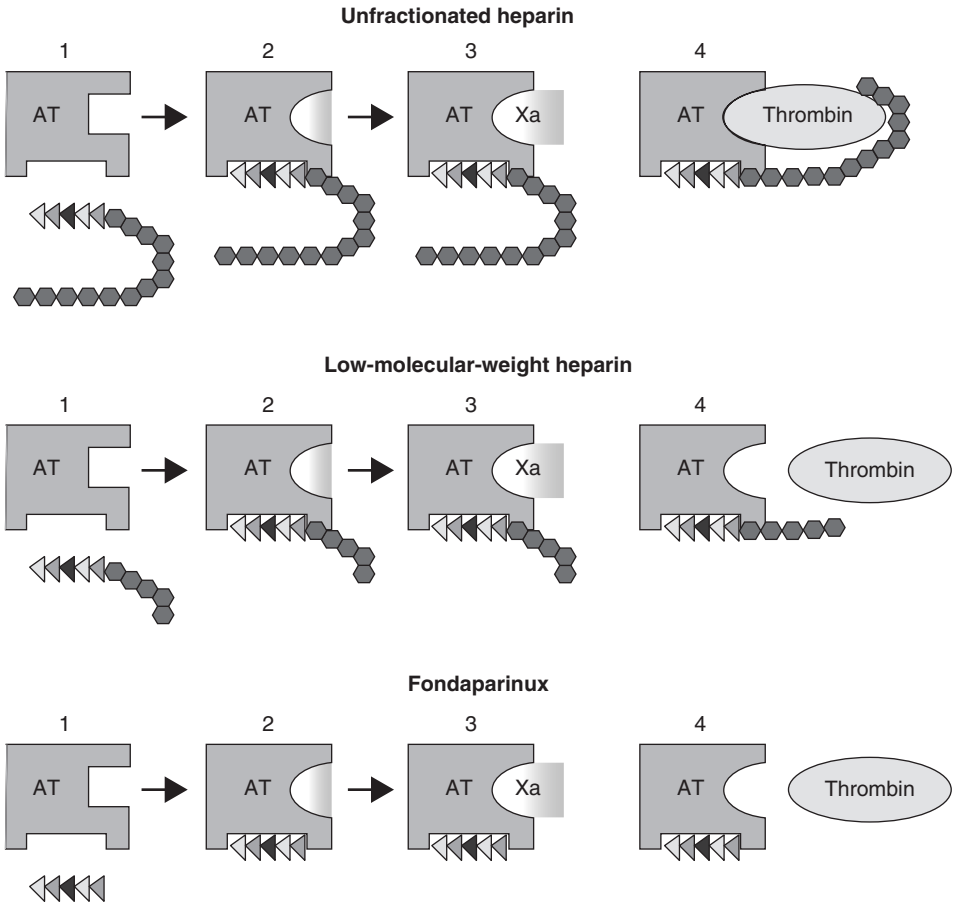

Fig. 17.2 Mechanism of action of indirect parenteral anticoagulants. *AT* antithrombin, *Xa* Factor Xa

- Prevention and treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE)
- Atrial fibrillation and flutter
- Arterial vascular surgery
- Cardiac surgery
- Anticoagulation of device circuits in extracorporeal membrane oxygenation (ECMO) and renal replacement therapies

UFH is generally preferred in patients with severe renal impairment, as it is primarily cleared through non-renal mechanisms and does not require renal dose adjustments. Given its short half-life, it may be preferred in clinical settings that require a rapid offset or reversibility of anticoagulant effect, such as cardiothoracic or vascular surgery [1, 2]. Use of UFH in many settings, such as for treatment of acute VTE, is diminishing with the advent of direct oral anticoagulants (DOACs), which are easier to manage and are safer and more convenient in appropriately selected patients.

Clinical Dosing and Management

Note: dosing of IV UFH for interventional procedures varies widely and is beyond the scope of this chapter. Readers are referred to societal guidelines for detailed procedural dosing information. Dosing information presented here is for common indications encountered by providers caring for patients on medical wards, critical care areas, or emergency departments.

Initiation of Therapy

When used for prevention of VTE, UFH is administered SC at a dose of 5000 units SC BID-TID. While no head-to-head trials of these dosing frequencies have been conducted, indirect evidence suggests TID dosing may be more efficacious at the expense of more bleeds [6]. The short half-life of UFH supports more frequent dosing to avoid prolonged drug-free intervals. Although often done in clinical practice, increasing the dose to 7500 units TID in obese patients may not provide increased efficacy and may cause more bleeds [7].

When administered for treatment, use of a bolus and weight-based dosing (using actual body weight) has been shown to rapidly attain therapeutic levels of anticoagulation [4]. Common dosing for acute VTE includes an 80 unit/kg bolus, followed by an 18 unit/kg/h continuous infusion [4]. Though a less commonly employed strategy, therapeutic UFH administered via weight-based, fixed interval SC dos-

Table 17.1 Parenteral anticoagulants

Drug	Pharmacokinetics	Drug interactions	Routine measurement(s)	Reversal	Dosing	Dosage adjustments
Unfractionated heparin	Half-life (h): ~1.5	Concomitant antihrombotics	IV: lab-specific aPTT equivalent to an anti-factor Xa level of 0.3–0.7 units/ml[a]	Protamine 1 mg for each 100 units of UFH administered within the last 2–3 h Alternative: Protamine 50 mg IV over 10 min	*Prophylaxis:* 5000 units SC BID-TID	Use standardized, weight-based dosing protocol to maintain therapeutic aPTT or anti-factor Xa
	Peak effect (h): IV: immediate SC: 1–2 h		SC: consider aPTT 6 h after injection on the third day to confirm therapeutic level		*VTE treatment:* 80 units/kg bolus followed by continuous infusion of 18 units/kg/h or 333 U/kg SC first dose then 250 units/kg SC q12h[b, c] *Acute coronary syndromes:* 60 units/kg bolus followed by continuous infusion of 12 units/kg/h	
	Renal clearance: minimal		Platelet count q 3 days for first for first few weeks to monitor for HIT			
LMWHs Enoxaparin Dalteparin	Half-life (h)[e]: 3–7	Concomitant antithrombotics	Routine measurement of anticoagulant activity not needed	Protamine 1 mg for each 1 mg or 100 anti-Xa units of LMWH given in previous 8 h Alternative: Protamine 50 mg IV over 10 min	VTE prophylaxis: 40 mg SC once daily (moderate risk) 30 mg SC BID (high risk)	Estimated CrCl 15–29 ml/min: VTE prophylaxis 30 mg SC once daily Treatment dosing 1 mg/kg SC q 24 h Estimated CrCl <15 ml/min: Avoid use
	Peak effect (h): 3–5					
	Renal clearance: >50%		May consider anti-factor Xa level if:		Treatment dosing: 1 mg/kg SC q12h or 1.5 mg/kg SC q24 h[b, c, d]	
			Changing/impaired renal function			
			Extremes of weight			
			Pregnant			
			Platelet count q3 days for first few weeks	Only provides ~60% reversal of LMWH activity	VTE prophylaxis: 2500 units SC once daily (moderate risk) 5000 units SC once daily (high risk)	Estimated CrCl <30 ml/min: No specific dose adjustments provided
			Serum creatinine		Treatment dosing: 200 units/kg SC q 24 h or 100–120 units/kg SC q12h[b, c, d]	

Fondaparinux	Half-life(h)[e]: 17–21	Concomitant antithrombotics	Routine measurement of anticoagulant activity not needed	None currently May consider rFVIIa	VTE prophylaxis: 2.5 mg SC once daily	Estimated CrCl 30–50 ml/min: Use with caution
	Peak effect (h): 2–3		Serum creatinine		Treatment dosing: [b, c] 5 mg (<50 kg) 7.5 mg (50–100 kg) 10 mg (>100 kg)	Estimated CrCl <30 ml/min: Avoid use
	Renal clearance: >80%					
Parenteral DTIs						
Argatroban	Half-life: ~40–50 min[f]	Concomitant antithrombotics	aPTT 1.5–3× mean normal	No specific antidote	HIT: 0.5–2 mcg/kg/min, depending on clinical status and hepatic function	
	Peak effect (h): immediate					
	Clearance: primarily hepatic					
Bivalirudin	Half-life[e]: ~25 min		aPTT 1.5–2.5× mean normal	Cessation of infusion is likely sufficient given extremely short half-life	HIT: 0.05–0.15 mg/kg/h, depending on renal function	Use standardized dosing protocol to maintain therapeutic aPTT
	Peak effect (h): immediate					
	Clearance: primarily plasma esterases, minimal renal					

Abbreviations: aPTT activated partial thromboplastin time, *BID* twice daily, *HIT* heparin-induced thrombocytopenia, *IV* intravenous, *LMWH* low-molecular-weight heparin, *SC* subcutaneous, *TID* three times daily, *UFH* unfractionated heparin, *VTE* venous thromboembolism

[a]Therapy target listed is for acute VTE. Therapy target for cardiac indications is approximately 10% lower than for VTE

[b]If a conventional approach with warfarin is used, it should be started as soon as feasible and *overlapped* with parenteral anticoagulant for minimum of 5 days and until INR >2

[c]When used with dabigatran or edoxaban for VTE, a minimum of 5 days parenteral anticoagulant monotherapy; then *switch* to dabigatran or edoxaban immediately once IV UFH infusion stopped or at the time the next dose of LMWH/fondaparinux would be due. *Do not* overlap IV UFH and dabigatran or edoxaban

[d]May be used as monotherapy in VTE patients with active malignancy or pregnancy

[e]In normal renal function

[f]Normal hepatic function

ing at 250 units/kg SC every 12 h has been shown to be effective for acute VTE treatment, as well [8, 9]. In cardiac indications, such as acute coronary syndrome (ACS), dosing is typically lower, with a 60 unit/kg bolus and a 12 unit/kg/h continuous infusion [1]. Bolus dosing is essential to saturate all the intravascular glycosaminoglycan binding sites for heparin to rapidly achieve therapeutic levels but may be deleted if bleeding risk is perceived to be very high (Table 17.1).

Maintenance Dosing and Titration

UFH therapy, but not prophylaxis, requires routine monitoring of anticoagulant activity [1, 3]. UFH may be monitored with the activated partial thromboplastin time (aPTT) or the anti-factor Xa assay. Neither has been rigorously evaluated in clinical trials nor been shown to be superior to the other [1]. The aPTT is not standardized and will vary among laboratory reagents and instrumentation. It is also impacted by variability in plasma proteins and circulating clotting factors [1, 3]. An aPTT range of 1.5–2.5× the mean control aPTT value for the laboratory has traditionally been used [10]. However, variations in reagents and instrumentation across labs require each institution to establish their own therapeutic aPTT range and mean control aPTT for the laboratory. This range should correlate with a plasma heparin concentration of 0.3–0.7 IU/ml by anti-factor Xa assay [1]. Conversely, the anti-factor Xa assay itself may be used to monitor UFH therapy. This assay, which does not depend on thromboplastin reagents, is insensitive to plasma proteins, and may improve monitoring outcomes, has gained in popularity as it has become cost equivalent to the aPTT and is more readily available than in prior years [11]. As with the aPTT, anti-factor Xa assays have yet to be standardized, and results can vary between laboratories. The aPTT and anti-Xa levels are rarely concordant, and routine monitoring of both is discouraged [12]. In patients with heparin resistance (requiring >35,000 units UFH/day to achieve therapeutic aPTT) or with elevated baseline aPTT due to antiphospholipid antibodies, the anti-Factor Xa assay may provide more accurate monitoring of heparin [1] (Table 17.1).

Frequency of Monitoring

Use of the aPTT requires assessment of a baseline value, as it may be elevated even in the absence of anticoagulation, whereas the anti-Xa will be normal (zero) in the absence of anticoagulation. An aPTT or anti-Xa level should be obtained 6 h after initiating an UFH infusion to allow achievement of steady state. Levels should subsequently be measured every 6 h (especially after each dose change) and adjusted per an institution-specific protocol until two sequential therapeutic levels are achieved. Then, monitoring may be decreased to once daily [1, 3] (Table 17.1).

All patients on UFH should have a platelet count performed at least every 3 days for the first 2 weeks of therapy, and periodically thereafter, to monitor for heparin-induced thrombocytopenia (HIT) that has a 1–5% incidence [1, 13].

Managing Invasive Procedures

For procedures requiring minimal to no residual anticoagulant effect, IV UFH should be discontinued 4–6 h prior to the procedure, and twice daily SQ therapeutic UFH should be held for approximately 12 h prior [14]. Interruption of prophylactic UFH varies by procedure and should be discussed with the surgical provider or team. Resumption post-procedurally should be based on achievement of hemostasis, patient's bleeding risk, presence of underlying indication for anticoagulation, and the associated thrombotic risk.

Managing Bleeding and Reversal

Adverse Events

The most common adverse effects of UFH are bleeding and heparin-induced thrombocytopenia (HIT) [1, 2]. Other known complications include osteoporosis and an increase in hepatic enzymes. The risk of bleeding with UFH is associated with the intensity and stability of therapy. Other factors that increase the risk of bleeding with UFH include, but are not limited to, increasing age, renal function, concomitant administration of drugs that affect hemostasis (e.g., antiplatelets, NSAIDS, fibrinolytics), recent surgery, and trauma [1]. In addition to general supportive measures (withdrawal of anticoagulant, hemodynamic monitoring, fluid resuscitation, transfusion of blood products, etc.), patients with serious bleeding may be given protamine sulfate, which binds and neutralizes UFH [15]. Because it is derived from salmon sperm, it should not be used in patients with a fish allergy. Anaphylactoid reactions to protamine sulfate can occur, even in the absence of a fish allergy, and administration by slow IV infusion is recommended to reduce this risk [15]. In clinical practice, for major bleeding associated with UFH, a dose of 50 mg IV protamine may be administered over 10 min, with redosing as needed for refractory bleeding. Because UFH has a short half-life, if more than 4–6 h have passed since the last UFH administration, protamine is unlikely to provide any benefit [15] (Table 17.1). Note that protamine sulfate itself can induce contact activation of factor XII. Overdosing of protamine sulfate can, in fact, induce blood coagulation through contact activation.

Immune-Mediated Heparin-Induced Thrombocytopenia (HIT)

Immune-mediated HIT, a potentially fatal prothrombotic condition, has been reported to occur in up to 5% of patients exposed to UFH. Hallmark signs include a 50% decrease in platelet count from patient's baseline prior to UFH exposure that occurs between days 5 and 15 after exposure. Investigation of HIT should include cessation of any heparin products (UFH, LMWH), calculation of a pretest probability

Table 17.2 4T pretest clinical probability score for heparin-induced thrombocytopenia (HIT)

4Ts category	2 points	1 point	No points
Thrombocytopenia	Platelet count fall >50% and nadir ≥20	Platelet count fall 30–50% or platelet nadir 10-19 K	Platelet count fall <30% or any platelet fall with nadir <10 K
Timing	Clear onset days 5–10 or platelet fall ≤1 day (with prior heparin exposure <30 days)	Unclear onset days 5–10, or >10 days or platelet fall ≤1 day (with prior heparin exposure 30–100 days)	Onset ≤day 4 without previous exposure to heparin
Thrombosis	New confirmed thrombosis or skin necrosis at heparin injection sites or acute systemic reaction following heparin administration	Progressive thrombosis or non-necrotizing skin lesions at heparin injection sites or suspected (unconfirmed) thrombosis	None
O**t**her causes of thrombocytopenia	None	Possible	Definite

Risk strata: 0–3 = low, 4–5 = intermediate, 6–8 = high, $K = 1000$

via the 4T score (Table 17.2), and initiation of an alternative anticoagulant (such as a parental DTI or fondaparinux) in at-risk patients. While associated with significant morbidity and mortality if untreated, accurately selecting patients for HIT testing and treatment via the 4T score, which has a 95% negative predictive value (NPV), is critical, as therapeutically anticoagulating a patient with a true (vs prothrombotic) thrombocytopenia significantly increases their risk of bleeding. For patients with a 4T score of ≤ 3, no antibody testing is indicated. For those with a score >3, additional consideration and possibly antibody testing are warranted [13]. Consultation with an anti-thrombosis expert when HIT is suspected is strongly recommended.

Osteoporosis

UFH therapy has been shown to reduce bone density in up to one-third of patients treated for >1 month, with 2–3% experiencing bone fractures [16]. Alternative agents with a lower incidence of osteoporosis, such as LMWH, are preferred for long-term therapy.

Abnormal Liver Function Tests

UFH, through unknown mechanisms, has been associated with elevations in liver transaminases (AST, ALT) that return to normal upon withdrawal of the drug.

Transitioning Between Anticoagulants

Transitioning to UFH

- When transitioning *to IV/SC UFH* from LMWH, fondaparinux or a DOAC, the IV/SC UFH should be started at the time the next dose of the LMWH, fondaparinux, or DOAC would be due.
- When transitioning *to IV/SC UFH* from warfarin, IV/SC UFH should be started once the INR is <2.

Transitioning from UFH

- Because of UFH's short half-life, when transitioning *from IV UFH* to an alternative rapid-acting anticoagulant (LMWH, fondaparinux, DOAC), the alternative agent may be started at the same time the IV UFH is stopped.
- Because of a longer half-life with SC administration, when transitioning *from SC UFH* to an alternative rapid acting anticoagulant (LMWH, fondaparinux, DOAC), the alternative agent should be started at the time the next dose of SC UFH would be due.
- When transitioning *from IV UFH* to warfarin, the therapies should be overlapped for ≥5 days and until the INR is >2 for at least 24 h.

Low-Molecular-Weight Heparin (LMWH)

Pharmacology

Mechanism of Action

Two LMWHs are currently available in the United States: enoxaparin and dalteparin. The LMWHs are derived via chemical or enzymatic depolymerization of UFH. Like UFH, LMWHs prevent the propagation and growth of formed thrombi but do not break down existing clots. Also like UFH, LMWH are indirect anticoagulants exerting their anticoagulant effect by binding to AT through a unique pentasaccharide sequence (Fig. 17.2). Because of their shorter length and lower molecular weight (4500–5000 Da), LMWHs are unable to bind AT and thrombin simultaneously (Fig. 17.2). The LMWHs thus inhibit factor Xa to a greater degree than thrombin, with an anti-factor Xa-to-IIa activity ratio ranging from 2:1 to 4:1 [1, 2].

Pharmacokinetics/Pharmacodynamics

LMWHs have an improved pharmacokinetic and pharmacodynamic profile compared to UFH. Because they exhibit a lower degree of non-specific binding to plasma proteins, LMWH possesses linear kinetics, a more predictable dose response and more favorable side-effect profile. As a result, these agents can be given in fixed doses without need for routine monitoring of anticoagulation activity. LMWHs are not absorbed from the gastrointestinal tract and must be administered parenterally. Bioavailability of LMWHs fol-

lowing subcutaneous injection is nearly 100%. Peak anti-Xa activity occurs about 3–4 h following administration, and steady state is achieved after 2–3 doses [1, 2].

Enoxaparin and dalteparin are metabolized in the liver by desulfation and/or depolymerization to lower molecular weight substances with minimal biologic activity. LMWHs are predominantly (>50%) cleared via renal elimination. In normal renal function, the elimination half-lives of dalteparin and enoxaparin range from 3 to 7 h after repeat dosing and attainment of steady-state plasma concentrations. In reduced renal function, the half-life will be prolonged, and a dose reduction or avoidance may be required to avoid accumulation and increased risk of bleeding (Table 17.1) [1, 2].

Clinical Indications

Dalteparin [17] is FDA-approved for:

- VTE prophylaxis in patients undergoing abdominal surgery and hip replacement surgery or with acute medical illness
- Extended treatment of cancer-associated VTE
- ACS

Off-label uses of dalteparin [17] include:

- Acute treatment of non-cancer-associated VTE
- Pregnancy-associated VTE
- Bridging therapy for mechanical prosthetic cardiac valve

Enoxaparin [18] is FDA-approved for:

- VTE prophylaxis in patients undergoing hip or knee arthroplasty and abdominal surgery or with acute medical illness
- Acute treatment of non-cancer-associated VTE
- ACS

Off-label uses of enoxaparin [18] include:

- Bridging therapy for mechanical prosthetic cardiac valve
- Pregnancy-associated VTE
- VTE prophylaxis in bariatric, general, gynecologic, or cancer surgery
- VTE prevention and treatment in pediatric patients
- Bridging therapy during temporary interruption of vitamin K antagonists (VKAs), such as warfarin, in patients at high risk for thromboembolism

Clinical Dosing and Management

Dosing

Prophylactic or treatment doses vary depending on the LMWH preparation. Dalteparin dosing is based on anti-Xa units, whereas enoxaparin is dosed in milligrams (mg). One milligram of LMWH is equivalent to 100 anti-Xa units.

For prophylaxis, dalteparin is dosed at 2500 or 5000 units SC once daily, depending on the patient's VTE risk [17]. Enoxaparin prophylactic dosing is 30 mg SC BID for high-risk patients and 40 mg SC once daily for moderate-risk patients [18]. Optimal VTE prophylaxis dosing in obesity is not known, but increasing the dose by 25–30% has been suggested and is reasonable [3, 19]. In low-weight patients (<45 kg women, <57 kg men), enoxaparin has been shown to accumulate which may increase bleed risk and may warrant a dose reduction or avoidance [3, 18].

When used for treatment, dalteparin may be dosed at either 100–120 units/kg twice daily (BID) or 200 units/kg once daily, and enoxaparin may be dosed at either 1 mg/kg BID or 1.5 mg/kg once daily, using actual body weight and depending on indication [1, 3, 17, 18]. Dose capping of LMWH in obesity is not recommended [19]. Whenever possible, once-daily LMWH is recommended for patient convenience, adherence, and cost. However, use of more frequent BID dosing may be preferred in select populations, such as those with extensive thrombus burden, obesity, or active cancer [3]. Also, BID dosing should be preferred in patients with an increased risk of bleeding, such as in the postoperative setting, as this will avoid the higher-peak anti-Xa activity seen with once-daily dosing. The wide therapeutic index of LMWHs allows for dose rounding, preferably to the nearest commercially available syringe size, to simplify administration as well as reduce risk for dosing errors.

Due to differences in molecular weight and charge, dalteparin exhibits less accumulation in renal dysfunction than enoxaparin. No renal dose adjustments are provided for dalteparin, but it is suggested to monitor anti-Xa levels for patients with an estimated creatinine clearance (CrCl) of <30 ml/min by Cockroft-Gault equation. Enoxaparin prophylaxis and treatment should be dose-reduced for patients with an estimated CrCl of <30 ml/min (along with consideration for anti-Xa monitoring for accumulation) and avoided in those with severe renal impairment (estimated CrCl <15 ml/min) [1–3].

Administration

Both dalteparin and enoxaparin come in pre-filled syringes, which increase the feasibility and convenience of outpatient therapy. LMWHs should be administered subcutaneously in the abdomen once or twice daily. If administration in the abdomen is not possible, these agents may be administered in other areas with appreciable amounts of subcutaneous fat, such as the lateral aspect of the upper arm or thighs.

Monitoring

Routine monitoring of LMWHs is not recommended but may be considered in select populations, such as those with

extremes of weight, changing renal function, or altered pharmacokinetics (e.g., pregnancy, burns, pediatrics, etc.) [1–3, 19]. It is important to note optimal anti-Xa ranges for LMWHs have not been established and observed ranges have not been strongly correlated with clinical outcomes. If monitoring is employed, a chromogenic anti-factor Xa assay calibrated to LMWH should be used. When assessing for accumulation, trough anti-Factor-Xa levels, taken just prior to the next dose, may be used with a target of <0.5 IU/ml. Peak levels of LMWH should be drawn 4 h post-dose, with an expected range of 0.2–0.5 IU/ml for prophylaxis, 0.6–1.0 IU/mL with BID treatment dosing, and 1–2 IU/mL with once-daily treatment dosing [1]. The clinical significance of elevated anti-factor Xa levels is unknown, and there are no suggested dose adjustments to achieve a specific anti-factor Xa level.

Managing Invasive Procedures

The last dose of prophylactic LMWH should be administered at least 6 h prior to procedure and up to 12–24 h prior. Postoperatively, prophylactic LMWH should be resumed no sooner than 6 h after the procedure to mitigate bleed risk [14]. Also, postoperative prophylaxis should not be excessively delayed (e.g., >24 h), in the absence of contraindications, as this may lead to postoperative VTE complications.

For patients receiving therapeutic LMWH, the last dose should be given ~24 preoperatively. Resumption postoperatively should occur at ~24 h for low bleed risk procedures and ~48–72 h for higher bleed risk procedures. Use of step-up approach, with prophylactic dosing at 24 h, is reasonable for prevention of post-op DVT and minimization of bleeding via avoidance of therapeutic anticoagulation in the immediacy [14, 20].

Managing Bleeding and Reversal

Adverse Effects

As with any anticoagulant, bleeding is the most common complication of LMWHs. Risk may be reduced via careful consideration of renal function, safe and appropriate timing of doses, and avoidance of concomitant agents that may alter coagulation status, such as antiplatelets [1, 15]. In the event of a significant bleed, general approaches should be employed, and protamine sulfate should be considered. Renal function should be rapidly assessed to determine if significant accumulation may have contributed to the bleeding event and aid in estimation of remaining duration of drug exposure. Due to limited binding to LMWH, protamine only neutralizes about 60% of LMWH anticoagulant activity. A dose of 50 mg IV may be given if the last dose of LMWH was given in the previous 8 h, with a repeat dose if bleeding is not controlled. If >8 h has passed since last LMWH administration, protamine is not likely to provide benefit.

Heparin-Induced Thrombocytopenia

LMWHs have less interaction with the heparin-binding protein platelet factor 4 (PF4) and consequently are associated with an approximate five- to tenfold lower rate of HIT compared to UFH. However, LMWHs do cross-react with heparin antibodies in vitro and should not be used as an alternative anticoagulant in patients with suspected or confirmed HIT. Platelet counts should be monitored every few days during the first 2 weeks of LMWH therapy and periodically thereafter [1, 13].

Transitioning Between Anticoagulants

Transitioning from LMWH

- When switching *from an LMWH* to an alternative anticoagulant with a rapid onset of action, such as UFH, fondaparinux, or a DOAC, the alternative anticoagulant should be started at the time the next dose of LMWH would have been due.
- When transitioning *from an LMWH* to warfarin, such as in acute VTE or HIT, the LMWH should be overlapped with warfarin for a minimum of 5 days and until the INR is >2 for approximately 24 h. This is due to the long half-life (~40 h) and slow onset of effect of warfarin, coupled with the long half-life of pre-existing, circulating thrombin (~60 h).

Transitioning to LMWH

- When transitioning *to an LMWH* from a DOAC, the LMWH should be started at the time the next DOAC dose would have been due.
- When transitioning *to an LMWH* from IV UFH, the LMWH may be started as soon as the IV UFH is stopped.
- When transitioning *to an LMWH* from SC UFH, the LMWH should be started at the time the next SC UFH dose would have been due.
- When transitioning *to an LMWH* from warfarin, the LMWH should be started when the INR is <2.

Fondaparinux

Pharmacology

Mechanism of Action

Fondaparinux is a synthetic analog of the of the unique pentasaccharide sequence found within porcine-derived UFH and LMWH chains and has a molecular weight of 1728 Da. Like UFH and LMWH, fondaparinux is an indirect anticoagulant, requiring binding to AT to exert its effect (Fig. 17.2). This interaction with AT induces a conformational change that catalyzes targeted binding and inhibition of FXa. Fondaparinux is then released and available to catalyze other AT molecules. Due to its short length compared to UFH, fondaparinux is unable to bind and inhibit thrombin [1].

Pharmacokinetics/Pharmacodynamics

Fondaparinux is >95% bound to AT, exhibits linear pharmacokinetics, and has a highly predictable dose response across a wide range of studied doses. This predictability, along with high bioavailability and a long half-life, minimizes inter- and intra-patient variability and allows fondaparinux to be given in fixed, once-daily doses without the need for routine monitoring and reduced potential for adverse effects. Fondaparinux is not absorbed through the gastrointestinal mucosa. SC administration provides rapid and complete absorption of fondaparinux with 100% bioavailability. Peak plasma concentrations are achieved at approximately 2–3 h after subcutaneous administration, and steady state is achieved after 3–4 doses of once-daily fondaparinux (Table 17.1) [1, 3, 19].

Decreased binding to macrophages and endothelial cells increases the plasma half-life of fondaparinux compared to UFH and LMWH. Fondaparinux is heavily dependent on renal elimination, with up to 77% of drug excreted unchanged in the urine. The terminal half-life is 17–21 h in healthy volunteers, and this will be prolonged in acute or chronic kidney injury. Age (>75 years) and low body weight (<50 kg) are associated with reduced clearance of fondaparinux. In patients with multiple factors that may affect fondaparinux clearance, the effect is likely to be cumulative, and use of an alternative anticoagulant may be indicated. After stopping fondaparinux, the anticoagulant effect will persist for up to 4 days and even longer in patients with reduced clearance [1, 3, 19]. As it does not affect pre-existing circulating thrombin, it is theorized that fondaparinux may afford some degree of residual hemostatic function, should it be needed, at a site of injury. As a synthetic agent, fondaparinux may be used in patients with a documented pork allergy or with religious beliefs precluding pork products.

Clinical Indications

Fondaparinux [21] is FDA-approved for VTE prevention in patients undergoing hip, knee, or abdominal surgery. Based on results from the MATISSE DVT and PE trials [22, 23], fondaparinux is also FDA-approved for acute treatment of VTE in conjunction with warfarin. The most recent CHEST 2016 guidelines recommend VTE treatment with a direct oral anticoagulant (DOAC) over conventional approaches of warfarin overlapped with a rapid-acting parenteral agent such as UFH, LMWH, or fondaparinux [24]. When a patient is not a DOAC candidate, the ACCP 2012 guidelines on antithrombotic therapy for VTE recommend fondaparinux (or LMWH) over UFH for initial parenteral therapy for acute VTE [9].

Off-label uses include:

- Treatment of acute superficial venous thrombosis of the leg
- Acute coronary syndromes (ACS)
- VTE prevention in general surgery
- Heparin-induced thrombocytopenia (HIT)
  - Fondaparinux may be preferred in stable HIT patients with normal renal function as it greatly simplifies management compared to other therapies, such as argatroban and bivalirudin.

Clinical Dosing and Management

Dosing

The prophylactic dose of fondaparinux is 2.5 mg SQ once daily. Prophylactic use in patients <50 kg is contraindicated, as orthopedic studies have shown increased risk for bleeding in low-weight patients. For obese patients, the same 2.5 mg prophylactic dose may be used without need for dose adjustment [1, 21, 25].

When used for treatment, fondaparinux is given in fixed doses based on the patient's weight category (Table 17.2). For obese patients, a standard dose of 10 mg SQ once daily may be used without need for upward dose adjustment. Because it is primarily renally eliminated, it is contraindicated in patients with an estimated CrCl of <30 ml/min by Cockroft-Gault equation, and caution is recommended in those with an estimated CrCl of 30–50 ml/min [1, 3].

Administration

Fondaparinux comes in pre-filled syringes of 2.5, 5, 7.5, and 10 mg strengths, which increases convenience and facilitates outpatient therapy. It is administered subcutaneously in the abdomen once daily. As with LMWHs, if administration in the abdomen is not possible, fondaparinux may be administered in other areas with appreciable amounts of subcutaneous fat, such as the lateral aspect of the upper arm.

Monitoring

While not routinely recommended, if measurement of fondaparinux is indicated (e.g., changing renal function, extremes of weight, or age), plasma concentration is most accurately assessed by use of a chromogenic anti-factor Xa activity assay calibrated to fondaparinux. It is important to note optimal anti-Xa ranges for fondaparinux have not been established and observed ranges have not been strongly correlated with clinical outcomes [1, 3].

Managing Invasive Procedures

Because of its long half-life, prophylactic fondaparinux should be held for at least 48–72 h and therapeutic fondaparinux held for at least 72–96 h prior to invasive procedures requiring minimal to no residual anticoagulant effect. Resumption post-procedurally should be based on achievement of hemostasis, patient's bleeding risks, presence of underlying indication for anticoagulation, and the associated thrombotic risk.

Managing Bleeding and Reversal

Adverse Effects

The most common adverse effect of fondaparinux is bleeding. Risk may be mitigated by administering a first post-procedural prophylactic dose at least 6 h after the procedure or even the next morning, which will not compromise efficacy [26]. Clinicians must ensure a patient has adequate renal function prior to and throughout fondaparinux therapy to avoid bleeding complication associated with accumulation. Concomitant use of fondaparinux and drugs that affect coagulation (e.g., antiplatelets, NSAIDs) poses a pharmacodynamic drug interaction that may potentiate bleeding risk and should be avoided whenever possible. If a patient on fondaparinux does experience a bleed, it is important to rapidly evaluate their current renal function to estimate how long the anticoagulant effect of fondaparinux will persist. Also, clinicians should employ assertive fluid resuscitation to promote renal elimination of fondaparinux if possible. Currently there is no specific antidote for fondaparinux (Table 17.1). It cannot be reversed with protamine, possibly due to its charge, sulfate content, molecular size, or a combination of these factors. Fresh-frozen plasma (FFP) or factor concentrates such as prothrombin complex concentrate (PCC) or recombinant factor VIIa (rFVIIa) have been used, but none of these have been adequately studied. Additionally, factor concentrates have been associated with a risk of thrombosis and should be reserved for clinical situations refractory to general approaches to bleeding management.

Transitioning Between Anticoagulants

Transitioning from Fondaparinux

Clinical situations that might involve transitioning from fondaparinux to an alternative anticoagulant include a desire for a shorter-acting anticoagulant (e.g., UFH, LMWH) prior to an invasive procedure or need for longer-term oral anticoagulation therapy.

- When switching *from fondaparinux* to an alternative anticoagulant with a rapid onset of action, such as UFH, LMWH, or a DOAC, the alternative anticoagulant should be started 24 h after the last dose of fondaparinux.
- When transitioning *from fondaparinux* to warfarin, such as in acute VTE or HIT, fondaparinux should be overlapped with warfarin for a minimum of 5 days and until the INR is >2 for approximately 24 h.

Transitioning to Fondaparinux

The most common clinical situation wherein a transition to fondaparinux from another anticoagulant might occur is HIT.

- Patients with suspected or confirmed HIT who have been receiving UFH (either SQ or IV) or LMWH should have fondaparinux initiated as soon as safely possible, regardless of the timing of the previous dose of UFH or LMWH, to minimize the risk for HIT-associated thrombosis.
- This obviously may place patients at risk of over-anticoagulation if UFH or LMWH has been recently administered and underscores the importance of using the 4T score to determine pretest probability of HIT to most accurately identify at-risk patients warranting a change in therapy.
- For patients with suspected or confirmed HIT that have recently been started on warfarin, vitamin K should be administered, and a parenteral DTI should be initiated.

Direct Thrombin Inhibitors (Argatroban and Bivalirudin)

Overview

Hirudin is a naturally occurring direct thrombin inhibitor (DTI) derived from leech saliva that has high affinity for thrombin. It binds to both the active site and the exosite 1 region on thrombin. Although a recombinant form was once approved for clinical use (lepirudin), it was removed from the market due to excessive bleeding. Two synthetic direct thrombin inhibitors, argatroban and bivalirudin, are currently available for clinical use. Unlike indirect anticoagulants that require binding with AT, DTIs bind specifically and directly to thrombin [1, 27, 28] (Fig. 17.1).

Key Concepts

- Parenteral DTIs are administered via continuous infusion and monitored via the aPTT using standardized dosing and titration protocols.
- Parenteral DTIs are not usually first-line anticoagulant therapies but rather are used in clinical situations that require a parenteral anticoagulant but preclude the use of UFH or LMWH, such as HIT.

Pharmacology

Mechanism of Action

Bivalirudin (2180 Da) is a bivalent synthetic peptide DTI that reversibly binds to thrombin at both the active site and exosite 1. Argatroban (508 Da) is a monovalent non-peptide mimetic DTI and reversibly binds thrombin at the active site only (Fig. 17.3) [28].

Pharmacokinetics/Pharmacodynamics

Argatroban and bivalirudin are administered parenterally and thus do not require absorption. Due to their short half-lives, they are administered via continuous infusion. Both agents produce an immediate anticoagulant effect, and steady-state plasma concentrations are achieved within a few

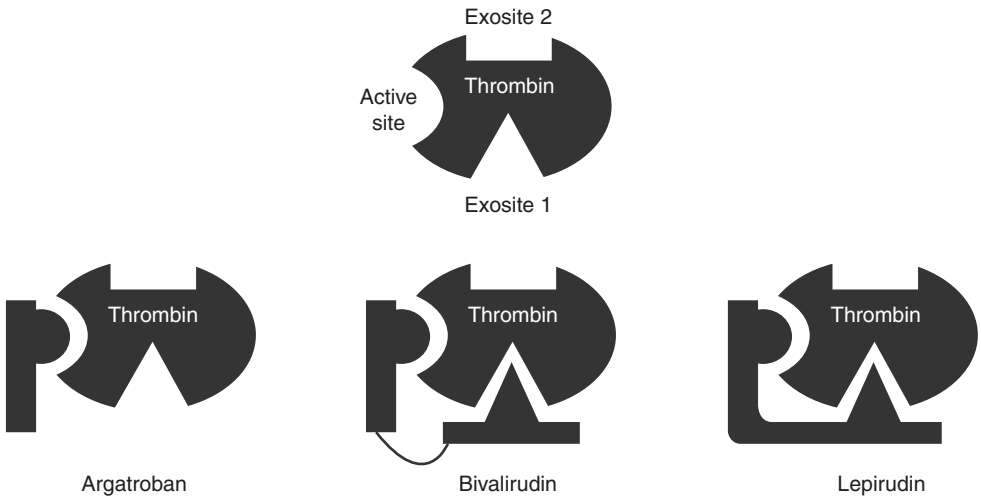

Fig. 17.3 Mechanism of action of parenteral direct thrombin inhibitors (DTIs). The activity of DTIs is produced by direct interaction with the thrombin molecule. Bivalirudin (a bivalent DTI) simultaneously binds exosite 1 and the active site. Argatroban (a univalent DTI) binds only the active site. (Adapted from Baetz et al. [29])

hours of initiation of therapy. The parenteral direct thrombin inhibitors do not bind to plasma proteins or cells and thus produce a more linear and predictable anticoagulant response than unfractionated heparin [1, 27, 28].

Argatroban is metabolized primarily in the liver and excreted in the feces through biliary secretion. Patients with impaired hepatic function have a fourfold decrease in clearance and require dose adjustments. Bivalirudin is metabolized primarily via blood proteases and broken down into the amino acid pool. Approximately 20% of bivalirudin is excreted via the kidneys as unchanged drug. In diminished renal function, the half-life will be prolonged, and dose adjustments are indicated (Table 17.1) [1, 27, 28].

Clinical Indications

FDA-approved indications for argatroban [30] include:

- HIT
- Percutaneous coronary intervention (PCI) with HIT

FDA-approved indications for bivalirudin [31] include:

- Percutaneous coronary interventions with or without HIT

Common off-label use of these two therapies includes circuit patency in cardiopulmonary bypass (CPB) surgeries and extracorporeal membrane oxygenation (ECMO) and renal replacement therapies in patients with a contraindication to UFH, such as HIT.

Heparin-Induced Thrombocytopenia

Due to their mechanism of action, argatroban and bivalirudin have become the mainstays of initial HIT treatment. They do not interact with platelet factor 4 (PF4), and their direct inhibition of thrombin reduces platelet activation and prevents thrombus formation.

Argatroban is FDA-approved and ACCP guideline-recommended for treatment of HIT. Though not FDA-approved, use of bivalirudin for immune-mediated HIT has increased over the last decade, as evidence suggests that target aPTTs are achieved more quickly with a similar or reduced incidence of bleeding as compared to other parenteral DTIs. Additionally, bivalirudin has several practical advantages over argatroban, including less impact on the INR, less reliance on organ elimination, and potentially lower cost. While bivalirudin is not specifically recommended as a treatment option for HIT in the ACCP guidelines, it is noted that "factors such as drug availability, cost, and ability to monitor the anticoagulant effect may influence the choice of agent" [13].

Clinical Dosing and Management

Note: dosing of parenteral DTIs for interventional procedures varies widely and is beyond the scope of this chapter. Readers are referred to societal guidelines for detailed procedural dosing information. Dosing information presented here is for common indications encountered by providers caring for patients on medical wards, critical care areas, or emergency departments.

Initiation of Therapy

Dosing of both argatroban and bivalirudin for HIT is provided in Table 17.1. As discussed previously, both bivalirudin and argatroban may require initial dose adjustments based on their primary method of elimination and individual patient characteristics. Both are administered as a continuous infusion.

Maintenance Dosing and Titration

Use of a standardized, evidence-based protocol for initiation, titration, and maintenance of parenteral DTIs is recommended for HIT treatment. In HIT, argatroban and bivaliru-

din are typically monitored via the aPTT, with a target of 1.5–3× and 1.5–2× the institution-specific control aPTT, respectively. If a patient's baseline aPTT is elevated to within the target range, it may preclude either the use of a DTI or use of the aPTT for monitoring. In these instances, use of an alternative anticoagulant (e.g., fondaparinux) or an alternative assay (e.g., a DTI-specific assay) should be considered. While some institutions have developed DTI-specific assays, they are not commercially available for widespread use. HIT protocols should also incorporate monitoring of other laboratory parameters (e.g., hemoglobin, hematocrit) in order to assess for bleeding [1, 13].

Frequency of Monitoring

The aPTT is typically drawn 2–4 h after start of the DTI infusion (to allow achievement of steady-state plasma concentrations), after any dose adjustments and every 2–4 h until therapeutic. Once the patient has two consecutive therapeutic aPTTs, monitoring may be decreased to once or twice daily.

Bivalirudin mildly affects the INR, with a mean increase of 0.6, whereas argatroban imparts a more pronounced effect [32]. It should be noted this is only a lab artifact and does not convey the same increased bleed risk as an elevated INR with warfarin therapy. It can, however, make transitioning to warfarin very challenging. (See section on transitioning to oral anticoagulation below.)

Managing Invasive Procedures

Based on their short half-lives, parenteral DTIs should be held 2–4 h prior to invasive procedures requiring minimal to residual anticoagulant effect. Note that the half-lives of argatroban and bivalirudin may be prolonged in patients with hepatic and renal impairment, respectively, and require earlier cessation prior to a procedure to allow adequate offset of drug effect. Resumption post-procedurally should be based on achievement of hemostasis, patient's bleeding risks and underlying indication for anticoagulation, and the associated thrombotic risk.

Transitioning Between Anticoagulants

Transitioning to a Parenteral DTI

As with fondaparinux, a common clinical situation wherein a transition to a parenteral DTI from another anticoagulant might occur is HIT.

- Patients with suspected or confirmed HIT who have been receiving UFH (either SQ or IV) or LMWH and cannot be transitioned to fondaparinux (e.g., severe renal impairment) should have a parenteral DTIs initiated as soon as safely possible, regardless of the timing of the previous dose of UFH or LMWH, to minimize the risk for HIT-associated thrombosis.
- This obviously may place patients at risk of over-anticoagulation if UFH or LMWH has been recently administered and underscores the importance of using the 4T score to determine pretest probability of HIT to most accurately identify at-risk patients warranting a change in therapy (Table 17.2).

Transitioning from a Parenteral DTI

After initial therapy with a non-heparin parenteral anticoagulant, HIT patients are usually transitioned to oral anticoagulation (OAC) for longer-term treatment in the outpatient setting. Direct oral anticoagulants (DOACs), such as dabigatran, apixaban, rivaroxaban, and edoxaban, have not been extensively studied in HIT, and thus warfarin remains the preferred OAC in this setting. The ACCP guidelines recommend starting warfarin once the platelet count has recovered to $>150 \times 10^3$/microliter (or to patient's baseline) and to continue overlap with the chosen parenteral non-heparin anticoagulant for ≥5 days and until INR is within a target range for a period of time during the overlap. The INR should then be rechecked after discontinuation of the parenteral anticoagulant to determine an INR based solely on the warfarin [13].

Argatroban

Argatroban significantly prolongs the PT/INR, which makes transitioning to warfarin a challenging process. Argatroban labeling does not recommend a specific duration of overlap; however, it recommends to continue the overlap with a goal INR of >4 if the argatroban infusion rate is ≤2 mcg/kg/min. For rates >2 mcg/kg/min, it is recommended to temporarily reduce the rate to 2 mcg/kg/min to determine the INR at that rate. However, if a patient has required infusion rates >2 mcg/k/min in order to maintain a goal INR, decreasing the rate may put the patient at risk of undertreatment. Thus, it is suggested that providers may use the chromogenic factor X activity assay if available (not to be confused with an anti-FXa LMWH or UFH assay) to monitor warfarin during the transition with a goal target range of 20–40% factor X activity (corresponds to an INR of 2–3). Unfortunately, this assay is often not readily available or is a send-out lab with a prolonged turnaround time that is not conducive to acute care. An alternative approach on days 4 or beyond (when warfarin should begin to have some effect) or once the INR is >4–5, one can shut off the argatroban for 2 h and then collect a blood sample for an accurate INR that reflects warfarin activity alone. The argatroban infusion should be resumed as soon as possible once the INR is drawn and continued while awaiting results to avoid any significant gaps in therapy.

Bivalirudin

Bivalirudin also impacts the INR but much less so than argatroban [32]. Aiming for an INR goal of 1.0 greater than the planned warfarin target INR is likely sufficient, without need

for interruption of bivalirudin therapy. For example, bivalirudin and warfarin should be overlapped ≥5 days and until the INR is >3 for at least 24 h.

Managing Bleeding and Reversal

Adverse Events

Bleeding is the most serious adverse effect associated with the parenteral DTIs. Concomitant use of other antithrombotics (antiplatelet agents, etc.) poses a pharmacodynamic interaction that may potentiate bleed risk. General approaches to bleeding management (e.g., looking for and controlling the source of the bleed) and supportive measures, such as resuscitation and monitoring, should be employed. There are no specific antidotes for argatroban or bivalirudin. Cessation of the infusion during recognition of a bleed is the most prudent intervention given their short half-lives and rapid elimination from the body [15]. In healthy subjects, coagulation parameters return to baseline 1–2 h after stopping a parenteral DTI infusion. The ACCP guidelines suggest that activated recombinant factor VIIa may potentially be used to reverse the effects of argatroban and bivalirudin in urgent situations, but this has not been studied in humans [1].

Oral Anticoagulants

Vitamin K Antagonists

Overview

Dicoumarol, the first vitamin K antagonist (VKA), was isolated from spoiled sweet clover in 1939–1940 by Professor Karl Paul Link [33]. Warfarin was subsequently synthesized (1942) and developed as a rodenticide but then went into clinical use in the 1950s. The VKAs were the only oral anticoagulants until the development of the direct oral anticoagulants (DOACs) introduced in 2010. Warfarin is the major VKA worldwide and the principal formulation used in North America. Other formulations with different pharmacokinetics are in use outside of the United States. Approximately 1–2% of the population of first-world countries is prescribed an oral anticoagulant. The VKAs work indirectly by interfering with the synthesis of the vitamin K-dependent coagulation factors (factors II, VII, IX, and X) leading to impaired coagulation (Fig. 17.4) [34]. The VKAs have many drawbacks, require considerable dose management to maintain a patient in a therapeutic range, and result in undertreatment as a consequence.

Key Concepts

- The vitamin K antagonists inhibit the synthesis of the vitamin K-dependent coagulation factors II, VII, IX, and X. Warfarin is the most common vitamin K antagonist.
- Warfarin therapeutic levels are affected by multiple factors including diet, drugs, genetics, and concomitant illnesses and, as such, require careful and frequent monitoring and dose adjustment.
- The prothrombin time, reported as an international normalized ratio (INR), equilibrates results from different thromboplastin reagents and is the common measure of therapeutic efficacy.
- Specialized programs referred to as anticoagulation clinics provide the most effective therapy by patient education, focused proactive dose management, and keeping patients within a specified therapeutic range.

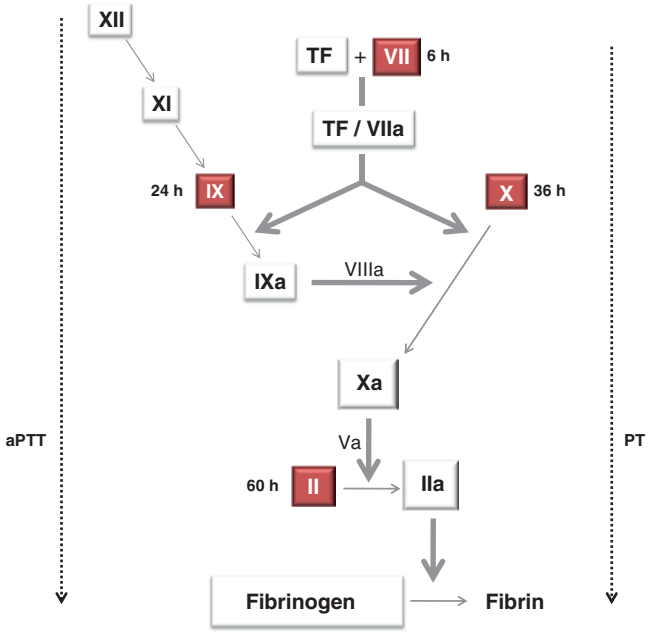

Fig. 17.4 Simplified scheme of the coagulation cascade indicating those factors that are vitamin K dependent for their normal synthesis (shaded) and their natural metabolic half-lives. Warfarin interferes with vitamin K-dependent factor synthesis; its effect on the coagulation cascade can be measured by the prothrombin time (PT) as well as the activated partial thromboplastin time (aPTT), although the PT is the more responsive and clinically useful measure of warfarin's effect

Pharmacology

Mechanism of Action

Vitamin K is an essential cofactor in the posttranslational γ-carboxylation of several glutamic acid residues in the vitamin K-dependent coagulation factors II, VII, IX, and X (Fig. 17.5), as well as proteins C and S [34, 35]. With reduced or absent γ-carboxylation, these proteins are unable to bind cell membranes, calcium, and phospholipid, and they manifest a reduced coagulant or enzymatic activity. Warfarin produces its anticoagulant effect by interfering with the cyclic interconversion and regeneration of reduced vitamin K from its 2,3-epoxide (oxidized vitamin K) by inhibiting the enzyme vitamin K oxide reductase complex 1 (VKORC1) responsible for this interconversion (Fig. 17.5). The enzyme,

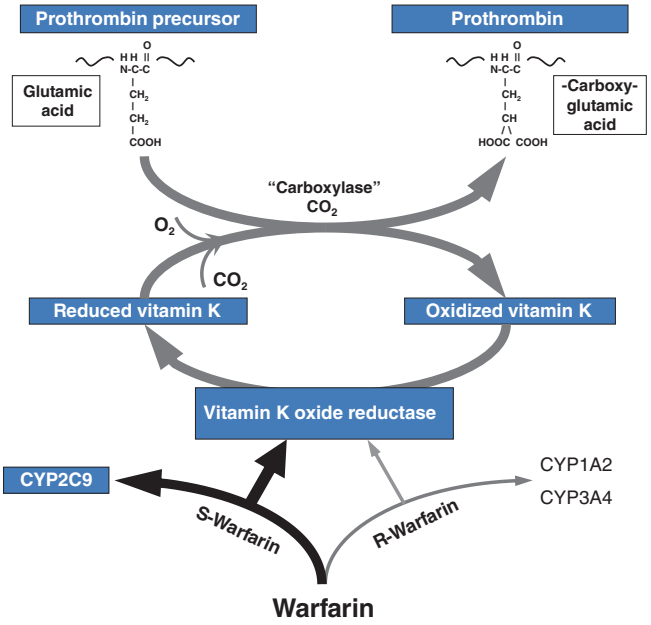

Fig. 17.5 The vitamin K cycle. Reduced vitamin K participates in a carboxylation reaction to gamma carboxylate a number of glutamic acid moieties in the prothrombin precursor leading to the synthesis of functional prothrombin. In the process, reduced VK is oxidized. The latter moiety is recycled via a vitamin K oxide reductase enzyme (VKOR). VKOR is the target of warfarin (mainly the S isomer of warfarin) leading to an accumulation of oxidized vitamin K. S-warfarin is metabolized mainly by the liver cytochrome P450 enzyme, 2C9 [78]

carboxylase, then utilizes reduced vitamin K along with oxygen and CO_2 to create carboxyglutamic acid on the vitamin K proteins to prepare the ideal protein forms to participate in the kinetically fast hemostatic reactions of tenase and prothrombinase (see Chap. 10).

Dietary vitamin K enters the body in a partially reduced state, bypassing the warfarin-sensitive reductase and replenishing fully reduced vitamin K stores in the presence of warfarin therapy. In response to warfarin, the vitamin K-dependent factors decline according to their natural half-lives with factor VII declining most rapidly (~ 6 h) and prothrombin (factor II) least rapidly (~ 60 h) (Fig. 17.4). Factor IX has a half-life of 24 h; factor X has a half-life of 48–60 h. The prothrombin time, a measure of the extrinsic and common pathways of coagulation, is most sensitive to this change and is initially influenced by the rapid fall of factor VII (see Chap. 11).

Pharmacokinetics/Pharmacodynamics

Warfarin is highly water soluble, rapidly absorbed from the gastrointestinal tract with peak absorption in 60–90 min and highly protein bound by albumin after absorption. Warfarin is a racemic mixture of stereoisomers (*R* and *S* enantiomers), each with distinctive metabolic pathways, half-lives, and potencies. Racemic warfarin has an average plasma half-life

$$\text{INR} = \left(\frac{\text{PT}}{\text{mean of normal}}\right)^{\text{ISI}}$$

Fig. 17.6 The derivation of the international normalized ratio (INR) from the prothrombin time ratio. The international sensitivity index (ISI) is derived by each manufacturer of thromboplastin by simultaneously comparing the PT result with their new thromboplastin with that from an international standard thromboplastin in 60 patients receiving warfarin therapy

of 36–42 h (range of 15–60 h). Differences in metabolism, disease- and/or drug-induced alterations in metabolic fate, or the sensitivity of the VKORC1 enzyme to warfarin account for much of the variation in an individual's initial response to, and maintenance requirement for, warfarin. The S enantiomer of warfarin (five times more potent than the R enantiomer) is metabolized primarily by the CYP 2C9 enzyme of the cytochrome P-450 (CYP450) system. A number of genetic polymorphisms (single-nucleotide polymorphisms, or SNPs) in this enzyme lead to a reduced activity of the enzyme and may influence both the dosage required to achieve a therapeutic level and the bleeding risk with warfarin therapy. Specifically, the *CYP2C9*2* and *CYP2C9*3* alleles are associated with lower-dosage requirements and higher bleeding complication rates compared with the wild-type *CYP2C9*1*. The prevalence of these polymorphisms varies in different populations. Renal impairment has no direct impact on warfarin since only its metabolites are excreted by the kidney and these have little or no anticoagulant activity. However, renal impairment may impair the function of CYP2C9 leading to accumulation of warfarin, thus enhancing its effect.

The "anticoagulant" effect of warfarin is related to a reduction of the vitamin K-dependent coagulation factors and is reflected by an elevation of the prothrombin time (PT) and the activated partial thromboplastin time (aPTT) (Fig. 17.4), both of which are most sensitive to reductions of factor VII and factor IX, respectively. However, the "antithrombotic" effect is most dependent on a reduction of prothrombin (factor II) and factor X in the common pathway of coagulation. The pharmacodynamic effect is most commonly measured by the PT as expressed as an international normalized ratio (INR), a derived result that corrects for different sensitivities of thromboplastin (tissue factor), the reagent used in the PT assay (see Fig. 17.6 for calculation of the INR) [36]. A safe and effective therapeutic INR range was first developed empirically but has since been confirmed by a number of large prospective trials [37, 38]. Table 17.3 summarizes the therapeutic range established for the different indications for which warfarin is used.

Table 17.3 The recommended indications for warfarin therapy and the recommended therapeutic range

Treatment of venous thrombosis	2.5 (2.0–3.0)
Treatment of pulmonary embolism	2.5 (2.0–3.0)
Prevention of systemic embolism	
Atrial fibrillation	2.5 (2.0–3.0)
Recurrent systemic embolism	2.5 (2.0–3.0)
After myocardial infarction[a]	3.0 (2.5–3.5)
Bioprosthetic heart valves (M or Ao position)[b]	2.5 (2.0–3.0)
Mechanical prosthetic heart valves	
Bileaflet valve in Ao position	2.5 (2.0–3.0)
Bileaflet or tilting valve in M position	3.0 (2.5–3.5)
Mechanical valve + atrial fibrillation (any position)	3.0 (2.5–3.5)
Mechanical valve + additional risk factors	3.0 (2.5–3.5) + aspirin (81 mg daily)

Abbreviations: *Ao* Aortic valve, *INR* international normalized ratio, *M* mitral valve

[a]For prevention of recurrent MI, an INR of 3.0 (2.5–3.5) is recommended

[b]For St. Jude or CarboMedics bileaflet or Medtronic-Hall tilting-disk valve

Warfarin pharmacodynamics is also dependent on the sensitivity of warfarin's target, the *VKORC1* enzyme. The *VKORC1 gene* also has a number of SNPs that lead to varying sensitivities of the enzyme to warfarin inhibition and have been shown to have a major impact on the pharmacodynamics of warfarin. A combination of SNPs leads to various haplotypes of the gene and gene product. Some of these haplotypes result in an enzyme that is more sensitive to warfarin inhibition so that a lower dosage of warfarin is required, whereas others are more resistant, so that a higher dosage (and maintenance dosage) of warfarin is needed to achieve a therapeutic INR. The prevalence of these haplotypes varies in different populations. A combination of genetic alterations in either the *CYP2C9* or *VKORC1* genes has been shown to account for as much as 20–50% of the variability in warfarin maintenance dosing, but as discussed below, pharmacogenetic testing is not routinely recommended to guide initiation or maintenance dosing.

Clinical Indications

The FDA-approved indications for warfarin include the following:

- Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism
- Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement
- Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction

As primary prophylaxis for venous thromboembolism (VTE), warfarin is commonly used after major hip or knee replacement surgery, although other agents such as aspirin or DOACs are rapidly replacing warfarin for this indication. Similarly, for stroke prevention in atrial fibrillation, the DOACs are rapidly gaining on warfarin's market share for this indication. Warfarin remains the principal oral anticoagulant for patients with mechanical heart valves. Finally, warfarin is used to varying degrees after myocardial infarction, although the DOACs are also being studied for this indication. Warfarin has been the mainstay of treatment for the secondary prevention of VTE following an acute episode of VTE, but this indication is also being challenged by the DOACs.

Clinical Dosing and Management

Initiation of Therapy

During the initiation of therapy, warfarin has the potential to create a brief hypercoagulable state before it produces a hypocoagulable state. This is due to a reduction in protein C and S, both vitamin K-dependent proteins, the former of which has a short half-life similar to factor VII. As a result, protein C levels decline faster than prothrombin or factor X potentially leading to a hypercoagulable state. This is most problematic in patients who may already have low protein C levels. Consequently, in patients with an underlying thrombogenic condition such as a VTE, a rapid-acting anticoagulant such as heparin or low-molecular-weight heparin is started simultaneously with warfarin.

Warfarin therapy should be initiated using an average maintenance dose of about 5 mg for the first 2 or 3 days. Heparin or low-molecular-weight heparin (LMWH) should be given concurrently with warfarin when an immediate anticoagulant effect is required such as in the treatment of VTE, and treatment should overlap for a period of 4–5 days since it takes that long to lower levels of prothrombin and factor X, those factors mostly responsible for the antithrombotic effect of warfarin. Heparin is discontinued when the INR has been in the therapeutic range on two measurements taken at least 24 h apart. Using a 10 mg starting dose for outpatients is recommended by the 2012 American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines [35]; however, a recent Cochrane Database Systematic Review [39] of the optimal initial dose for warfarin failed to identify an optimal method or dosing schedule between an initial 5 and 10 mg dose. A starting dose lower than 5 mg may be appropriate in the elderly, in patients with impaired nutrition or liver disease, and in patients at high risk of bleeding.

Maintenance Dosing

Estimation of the maintenance dose is based on observations of the INR response following administration of a fixed dose

of warfarin over an interval of a few days [34]. An individual who rapidly achieves an elevated INR (above 1.5) after two doses of warfarin is likely to require a low maintenance dose. The opposite holds for a patient who shows little elevation of the INR (below 1.5) after two doses.

The patient's genotype for CYP2C9 and VKORC1 has been shown to influence dose (as much as 50% of the variability of the INR) and bleeding outcomes in a number of retrospective or observational trials, but prospective trials have shown mixed results for the benefit of pharmacokinetic [40, 41] dosing. In 1015 patients randomized to pharmacogenetic vs standard dosing, the North American COAG trial failed to show a difference in time-in-range between groups in the first 15 days or at 4 weeks or a significant difference in rates of the combined outcome of an INR of 4 or more, major bleeding, or thromboembolism [40]. Black patients managed by genotype-guided dosing actually had significantly less time-in-range than non-black patients managed by standard care. A number of other randomized controlled trials showed mixed results as have a number of systematic reviews [41].

The value of pharmacogenetic-guided dosing is limited by availability of rapid turnaround genetic assays, cost of genetic assays, complex algorithms needed to utilize genetic information, and conflicting trial results about the usefulness of such information and the overall cost-effectiveness. All of these must be compared with the relative in expense and value of frequent monitoring of a simple INR test. At the present time, pharmacogenetic-based dosing is not recommended by the ACCP guidelines [35].

Frequency of Monitoring

Monitoring is performed frequently when warfarin is initiated – every day or two until a therapeutic INR is achieved – and then the interval of monitoring is gradually extended depending on stability of dosing. Stable patients are usually monitored once every 4 weeks although some studies have shown that intervals of 6–12 weeks are safe in patients who are stable.

Managing Out-of-Range INRs

Out-of-range INRs are not uncommon. When an out-of-range INR is obtained, patients should be queried about diet (INR varies inversely with the amount of vitamin K in diet), medications (new starts or discontinuations), concomitant illnesses (e.g., heart failure, liver disease), and adherence to dosing. An elevated INR can be managed by briefly discontinuing warfarin, administering vitamin K, or infusing fresh-frozen plasma (FFP) or factor concentrates (Table 17.4). The choice is based largely on the severity of the clinical situation (e.g., degree of elevation of the INR, presence of severe bleeding). Assuming an ongoing normal food intake and reasonable hepatic function, when warfarin is stopped, it takes about 4–5 days for the INR to return to the normal range in patients whose INR is between 2.0 and 3.0. The INR will return to normal more quickly in patients requiring a larger daily maintenance dose than in those requiring a lower daily maintenance dose. Because the absolute daily risk of bleeding is low even when the INR is excessively prolonged, many physicians manage patients with INR values of 4.0–9.0 by simply holding warfarin and monitoring more frequently, unless the patient is at a higher risk of bleeding or bleeding has already developed. Vitamin K should be given orally or by the intravenous route. Intravenous injection rarely may be associated with anaphylactic reactions, but it does lead to

Table 17.4 Recommendations for managing elevated international normalized ratios (INRs) or bleeding in patients receiving warfarin

Condition*	Description
INR above therapeutic range but <5.0; no significant bleeding	Lower dose or omit dose, monitor more frequently, and resume treatment at lower dose when INR therapeutic; if only minimally above therapeutic range, no dose reduction may be required (Grade 2C)
INR ≥5.0 but <9.0; no significant bleeding	Omit next one or two doses, monitor more frequently, and resume treatment at lower dose when INR in therapeutic range. Alternatively, omit dose and give vitamin K (≤5 mg orally), particularly if at increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, vitamin K (2–4 mg orally) can be given with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, additional vitamin K (1–2 mg orally) can be given (Grade 2C)
INR ≥9.0: no significant bleeding	Hold warfarin therapy, and give higher dose of vitamin K (5–10 mg orally) with the expectation that the INR will be reduced substantially in 24–48 h. Monitor more frequently, and use additional vitamin K if necessary. Resume therapy at lower dose when INR is therapeutic (Grade 2C)
Serious bleeding at any elevation of INR	Hold warfarin therapy, and give vitamin K (10 mg by slow IV infusion), supplemented with fresh plasma or prothrombin complex concentrate, depending on the urgency of the situation; recombinant factor VIIa may be considered as alternative to prothrombin complex concentrate; vitamin K can be repeated every 12 h (Grade 1C)
Life-threatening bleeding	Hold warfarin therapy, and give prothrombin complex concentrate supplemented with vitamin K (10 mg by slow IV infusion); recombinant factor VIIa may be considered as an alternative to prothrombin complex concentrate; repeat if necessary, depending on INR (Grade 1C)

Abbreviations: *IV* Intravenous

*If continuation of warfarin therapy is indicated after high doses of vitamin K, then heparin or low-molecular-weight heparin can be given until the effects of vitamin K have been reversed and the patient becomes responsive to warfarin therapy. It should be noted that INR values of >4.5 are less reliable than values in or near the therapeutic range. Thus, these guidelines represent an approximate guide for high INRs

reversal of the INR more quickly than oral or subcutaneous administration of vitamin K. The response to subcutaneous vitamin K may be unpredictable and sometimes delayed. Ideally, vitamin K should be administered in a dose that will quickly lower the INR into a safe, but not subtherapeutic range, without causing resistance when warfarin is reinstated. High doses of vitamin K, although effective, may lower the INR more than is necessary and lead to warfarin resistance persisting for up to 1 week.

Outpatient management of warfarin therapy should aim for simplicity and clarity. It is recommended that a single or limited number of warfarin tablet strengths be used and that patients clearly understand the various dosing patterns that are used, such as alternate-day doses or dosing levels based on days of the week. One must also be aware that several different warfarin preparations are on the market, which can lead to confusion for the patient.

Managing Drug Interactions

Drug interactions commonly occur by affecting the pharmacokinetic or pharmacodynamic behavior of warfarin [42]. Drug interactions may interfere with GI absorption of warfarin or interfere with the metabolism of warfarin (via P450 2C9 hepatic enzyme) leading to a reduction or increase in clearance and, consequently, higher or lower plasma warfarin levels. The latter mainly affects the S enantiomer of racemic warfarin. Some drugs or disease states (liver disease, hyperthyroidism) can alter the metabolism of coagulation factors, inhibit coagulation factor interactions by other mechanisms (heparin), or inhibit other aspects of hemostasis (aspirin effect on platelet function) and lead to a greater risk of bleeding. Generally, interactions are most problematic when interacting drugs are added to or deleted from a patient's regimen, or a dose change is made. Once a patient has achieved stability on warfarin and an interacting medication, there should be little problem in maintaining stability of warfarin dosing. Managing drug interactions requires more frequent monitoring of the INR. This can be done prospectively when there is a planned drug addition or deletion and certainly when a patient presents with an abnormal INR resulting from a drug interaction or change in concomitant medications.

Dietary supplements and herbal preparations are also responsible for interacting with warfarin and may require special vigilance and questioning on the part of the clinician to reveal patient use of these products. For a listing of various drug interactions, the reader is referred elsewhere [42].

Managing Invasive Procedures

It is not uncommon for patients to require invasive procedures during warfarin therapy. Whether minor dental work or major surgery, the physician needs to assess the following questions [14]:

- Do I need to stop warfarin, i.e., what is the risk of bleeding during the procedure if warfarin is continued?
- If warfarin is stopped, do I need a short-acting anticoagulant to cover the pre- and post-procedure period, i.e., what is the risk of thromboembolism when warfarin is stopped for a few days?
- What is the risk of bleeding post-procedure with a short-acting anticoagulant?

Historically, clinicians often stopped warfarin and used bridging anticoagulation (LMWH) to protect against thromboembolism during the periprocedural period. Now, however, mounting evidence suggests that this is not needed and in fact may lead to an increase in bleeding in patients with low or moderate risk of thromboembolism off warfarin for a short period. There is not only a risk of major bleeding but also a risk associated with the delayed reinstitution of long-term therapy because of the bleeding. Investigators have shown a 3-month cumulative risk of major post-procedure bleeding of approximately 3% with bridging versus 1% without such bridging. In a recent study, 1884 patients with atrial fibrillation at low to moderate risk of thromboembolism off anticoagulants were randomized to either LMWH bridging or no [43] bridging. The outcome of arterial thromboembolism was the same in each group (0.3% vs 0.4%, respectively; $p = 0.01$ for non-inferiority). The incidence of major bleeding was 3.2% in the bridging group vs 1.3% in the no bridging group ($p = 0.005$). Similar results were found in a large retrospective analysis of 1178 Kaiser Permanente Colorado patients, mostly with venous thromboembolism as opposed to atrial fibrillation (AF) (2.7% major bleeding in bridged patients vs 0.2% in non-bridged patients). There was no difference in the rate of venous thromboembolism.

If bridging therapy is implemented in those at very high risk of thromboembolism, warfarin is usually discontinued 4 or 5 days before the procedure, and the INR is allowed to decline. LMWH is started 2 or 3 days before the procedure, usually at a full-treatment dose (100–150 anti-factor Xa U/kg subcutaneously) once or twice daily depending on the risk of thrombosis, with the last dose omitted the morning or night of the day before the procedure (approximately 12–24 h before the procedure). Most authorities recommend cessation of LMWH 24 h prior to surgery. It is then restarted about 12 h after the procedure along with warfarin. If the risk of postoperative bleeding from the procedure is high, LMWH can be restarted in 24–48 h, rather than in 12 h. When the INR becomes therapeutic, LMWH administration is stopped. Table 17.5 summarizes the author's approach integrated with various guideline recommendations for management of oral anticoagulation during invasive procedures.

Table 17.5 An approach for managing anticoagulation therapy in patients requiring an invasive procedure [78]

Risk of thromboembolism or bleeding	Example	Recommendation or suggestion[a]
Low risk of thromboembolism off anticoagulants with moderate to high risk of bleeding	Bileaflet mechanical aortic valve without AF; AF with $CHADS_2$ score < 2; VTE >12 month ago	Stop warfarin approximately 5 days before procedure; allow the INR to return to normal; no need to bridge with rapid-acting anticoagulant; resume warfarin after procedure
Intermediate risk of thromboembolism off anticoagulants with moderate to high risk of bleeding	Bileaflet mechanical aortic valve with other risk factors such as AF, prior stroke, heart failure, and hypertension; VTE 3–12 months ago; recurrent VTE; active cancer	Approach is based on individual patient and surgery-related factors. Based on results of the BRIDGE trial [76], bridging is generally not required. In some instances, one might use a prophylactic dose of LMWH
High risk of thromboembolism off anticoagulants with moderate to high risk of bleeding	Mechanical mitral valve; old-style aortic valve; AF with high $CHADS_2$ score (5 or 6); CVA/TIA <3 months; rheumatic valvular heart disease; recent (<3 month) VTE	Stop warfarin approximately 5 days before procedure; allow the INR to return to normal; begin therapy with full-dose UFH or LMWH approximately 3 days before procedure; stop UFH approximately 6 h before procedure; omit last one or two doses of LMWH; restart UFH or LMWH ~12–24 h after procedure or when patient is in hemostatically stable condition
Low risk of bleeding on anticoagulants	Dental work; screening colonoscopy; cataract surgery	Continue warfarin without adjusting dose or INR if within therapeutic range; alternatively omit a dose or two of warfarin and allow INR to fall to a lower range (~1.5–2.0) and restart after procedure

Note: These guidelines represent the author's approach and are an amalgam of guideline recommendations and recent clinical trial results. The risk of thromboembolism with discontinuation of anticoagulants vs the risk of bleeding during the procedure if anticoagulants are continued must be assessed for each patient; restarting a rapid-acting anticoagulant too soon after a procedure can lead to bleeding, which will then prolong resumption of warfarin anticoagulation and put the patient at risk of thromboembolism; deciding on a final course of action often requires a discussion with the physician performing the procedure

Abbreviations: AF Atrial fibrillation, *$CHADS_2$* system for scoring thromboembolic risk in non-valvular AF that assigns points for congestive heart failure, hypertension, age ≥75, diabetes mellitus, and prior stroke or transient ischemic attack, *CVA* cerebrovascular accident, *INR* international normalized ratio, *LMWH* low-molecular-weight heparin, *UFH* unfractionated heparin, *TIA* transient ischemic attack, *VTE* venous thromboembolism

[a]Based on recommendations of the American College of Chest Physicians Consensus Conference on Antithrombotic Therapy

Adverse Events: Managing Bleeding and Reversal of Therapy

Warfarin consistently ranks in the top three drugs to bring patients to an emergency room with an adverse event (hemorrhage), leading to hospitalization. In a recent report warfarin ranked #1 representing 15% of visits to an emergency room for a drug-related adverse event [44].

Patients with warfarin-related major bleeding must be supported hemodynamically (fluids and RBC transfusions if needed), receive intravenous vitamin K to maintain normal vitamin K-dependent factor levels by endogenous production, have their anticoagulation reversed (infusions of fresh-frozen plasma (FPP) or prothrombin complex concentrates (PCCs)), and lastly, have the site of bleeding identified and treated (if possible).

FFP has been the standard approach to correct a long INR for patients with bleeding on warfarin. The usual problem with FFP correction is that the tolerable dose is insufficient to correct the degree of defect. If FFP is used, it should be given at a dose of 15–30 mL/kg to have a significant impact on factor replenishment. However, many patients cannot tolerate that dose in the short period of time needed to correct a bleeding state or stop an intracerebral hemorrhage. PCCs are concentrates of the vitamin K-dependent factors (II, VII, IX, and X). Their principal advantage compared with FFP is their ability to restore normal coagulation in minimum time (15–30 min) without infusions of large volumes of FFP over hours which may also stress the heart in patients who may already be compromised [45]. Preparation time also is shorter than for FFP. PCCs do carry a small risk of enhancing the risk of thrombosis. Their efficacy has been studied prospectively in clinical trials [46]. PCCs are often dosed in a range of 25–50 IU/kg, but the specific dose will depend on degree of INR prolongation and desired level of correction.

Small studies have also shown that recombinant factor VIIa (rFVIIa) can reverse the coagulopathy and associated bleeding induced by warfarin, as well as other coagulopathies. However, how to dose has not been studied critically, and the range of dosing is reported empirically to range from approximately 20 μg/kg to more than 100 μg/kg.

Although factor concentrates are shown to return the INR to normal more rapidly than with FFP, there is still debate as to how beneficial they are over FFP in terms of outcome. Meta-analysis data suggest that they are efficacious [47, 48]. Both PCCs and rFVIIa have the potential to induce a prothrombotic state, and such thromboembolism has occurred as a result of therapy. Table 17.4 outlines the 2008 ACCP recommendations for managing patients receiving coumarin

Table 17.6 Comparative pharmacokinetics, pharmacodynamics, and other features of direct oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target(s)	IIa	Xa	Xa	Xa
Prodrug	Yes	No	No	No
Bioavailability (%)	6.5 (pH dependent)	80	50	62
Peak effect	1.5–3 h	2–4 h	1–3 h	1–2 h
Half-life[a]	12–17 h	5–9 h	9–14 h	10–14 h
Renal elimination (unchanged drug)	80%	33%	25%	50%
Protein binding (%)	35	90	87	55
Dialyzable	Yes	No	No	Possible
Interactions	P-gp	CYP 3A4, P-gp	CYP 3A4, P-gp	CYP 3A4 (minimal), P-gp
Monitoring	No	No	No	No
Dosing	Twice daily	Once daily	Twice daily	Once daily
Antidote	Idarucizumab	Andexanet alfa	Andexanet alfa	Andexanet alfa
		Ciraparantag (in development)	Ciraparantag (in development)	Ciraparantag (in development)
Lab measure	aPTT, TT, ECT	PT, Anti-Xa	Anti-Xa	Anti-Xa

Abbreviations: *P-gp* P glycoprotein, *3A4* cytochrome P450 3A4, *INR* international normalized ratio, *PT* prothrombin time, *aPTT* activated partial thromboplastin time, *TT* thrombin time, *ECT* ecarin clotting time
[a]Normal renal function

anticoagulants who need the INR lowered because of actual or potential bleeding. These recommendations have not significantly changed in the most recent guidelines.

Other adverse events rarely seen with warfarin therapy include a condition of acute skin and fat tissue necrosis due to the induction of a hypercoagulable state discussed above. Rarely, therapy can be associated with cholesterol crystal embolization to peripheral extremities resulting in a condition called purple toe syndrome.

Cessation of Therapy or Transition to Other Oral Anticoagulants

When a course of therapy has ended, warfarin can simply be stopped without a need for dose tapering. If the patient is to be transitioned to a DOAC, the general rule is to hold warfarin until the INR declines to approximately 2.0 and then start the DOAC. Because of its rapid onset of action, the latter will provide therapeutic anticoagulation within 2 h.

Systems of Anticoagulation Management

Because of the labor intensiveness of VKA management, specialized anticoagulation management services (clinics) have been established to handle large numbers of patients and to optimize dosing. These services are differentiated from usual care by their proactive and focused attention to warfarin dosing and patient education [49]. There is abundant evidence that these programs achieve a higher time in INR range and better outcomes [50]. With the development of point-of-care, handheld, INR monitors, patients are now able to monitor their own INR at home with dose management handled by their provider or, with proper training, manage their own dosing [51, 52].

Direct Oral Anticoagulants

Overview

Warfarin therapy presents the clinician with several management problems in that the therapeutic level is affected by many factors, including diet, other medications, illnesses, and genetics. Therapy is hampered by a high degree of poor treatment with only approximately 50% of patients maintained in a therapeutic INR during therapy resulting in a high incidence of bleeding or thrombosis. The new direct oral anticoagulants are free of many of warfarin's drawbacks. These drugs include a direct thrombin (IIa) inhibitor (dabigatran etexilate) and three direct Xa inhibitors (apixaban, edoxaban, and rivaroxaban) (Table 17.6). When these factors are inhibited, fibrin and clot formation are impaired (Fig. 17.7). These small molecules directly block either factor Xa or thrombin (factor IIa) at their catalytic pocket. They promise to be more convenient and possibly safer than warfarin because they are given in fixed dosages, have a predictable anticoagulant effect, do not require monitoring, have few or minimal interactions with drugs or diet, and have a rapid onset of action that eliminates the need for parenteral anticoagulation in many situations.

Key Concepts

- The direct oral anticoagulants (DOACs) are small molecules that bind to the active enzymatic pocket of their specific target (either factor IIa or Xa) and neutralize the target, thus impairing coagulation.
- The DOACs have favorable pharmacokinetics that make them easier to manage than the vitamin K antagonists including a rapid onset and offset of action, predictable dose response, and few or no interactions with drugs or diet.

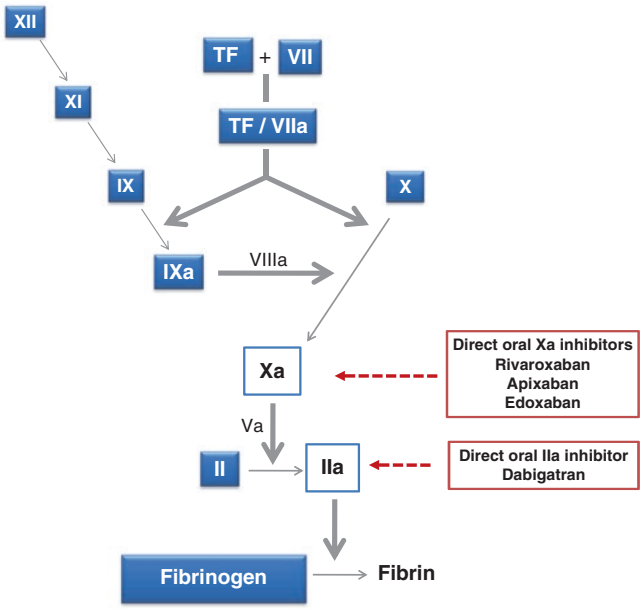

Fig. 17.7 Site of action of the direct oral anticoagulants. *TF* tissue factor

- The DOACs are all dependent to a greater or lesser extent on renal elimination of unchanged drug so that knowledge of renal function is important when initiating DOAC therapy.
- DOACs have been compared to the VKAs in large clinical trials of stroke prevention in atrial fibrillation and for the treatment and prevention of venous thromboembolism. In all cases, they have been found to be as effective as the VKAs and, overall, safer than the VKAs, especially with regard to intracranial bleeding.

Pharmacology

Mechanism of Action/Pharmacokinetics/Pharmacodynamics

Dabigatran etexilate (Pradaxa®, Boehringer Ingelheim) is a direct, selective, and oral thrombin inhibitor administered once or twice daily [53]. Dabigatran etexilate is an oral prodrug that is rapidly converted by a serum esterase to dabigatran, a potent, direct, competitive thrombin inhibitor. By inhibiting thrombin, it interferes with the fibrinogen to fibrin reaction and clot formation. It also impairs the activation of platelets by thrombin. Dabigatran has a 2-h onset of action, 14–17-h half-life, and 6.5% bioavailability. Eighty percent of dabigatran is excreted via the kidney unchanged, and renal function is an important determinant of therapeutic levels. Table 17.6 reviews dabigatran's relevant properties.

Rivaroxaban is a direct, selective, and oral factor Xa inhibitor administered mostly once daily [53]. It has an onset of action of 2–4 h and a half-life of 5–9 h and is partially eliminated by the kidney (approximately 33% unchanged drug) with the remainder metabolized by CYP450 enzyme 3A4. By binding to activated factor Xa, rivaroxaban interferes with Xa's ability to catalyze the conversion of prothrombin to thrombin and leads to impaired clot formation. Rivaroxaban has no effect on platelet function. Table 17.6 summarizes rivaroxaban's relevant properties.

Apixaban is a direct, selective, and oral factor Xa inhibitor administered twice daily [53]. It has a 1–3 h onset and 9–14 h half-life. Approximately 25% of apixaban is eliminated via the kidney with the rest metabolized by CYP 3A4. Similar to rivaroxaban, apixaban interferes with factor Xa's ability to generate thrombin from prothrombin. It has no effect on platelet function. Table 17.6 reviews apixaban's relevant properties.

Edoxaban is a third direct, selective, and oral factor Xa inhibitor administered once daily [53]. Similar to the other Xa inhibitors, it has a rapid onset of action within 1–2 h after oral administration with a half-life of approximately 10–14 h. Edoxaban has negligible CYP 450 metabolism and approximately 50% is excreted unchanged by the kidney. It impairs coagulation similar to the other factor Xa inhibitors. Table 17.6 reviews edoxaban's relevant properties.

Clinical Indications

The FDA-approved indications for the four DOACs are as follows:

Dabigatran Etexilate

- To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- For the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5–10 days
- To reduce the risk of recurrence of DVT and PE in patients who have been previously treated
- For the prophylaxis of DVT and PE in patients who have undergone hip replacement surgery

Rivaroxaban

- To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- For the treatment of DVT and PE and for the reduction in the risk of recurrence of DVT and of PE
- For the prophylaxis of DVT, which may lead to PE, in patients undergoing knee or hip replacement surgery

Apixaban

- To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- For the treatment of DVT and PE and for the reduction in the risk of recurrent DVT and PE following initial therapy

- For the prophylaxis of DVT, which may lead to PE, in patients who have undergone hip or knee replacement surgery

Edoxaban

- To reduce the risk of stroke and systemic embolism (SE) in patients with non-valvular atrial fibrillation. Edoxaban should not be used in patients with creatinine clearance (CrCL) >95 mL/min because of increased risk of ischemic stroke compared to warfarin at the highest dose studied (60 mg).
- For the treatment of DVT and PE following 5–10 days of initial therapy with a parenteral anticoagulant.

Clinical Dosing and Management

Dosing for VTE, AF, Orthopedic Surgery

Based on the results of large randomized clinical trials [54–62], DOACs are now recommended as first-line therapy for stroke prevention in AF and for the treatment of acute VTE. However, individuals with certain characteristics should not be considered for DOAC therapy. Table 17.7 summarizes general and specific criteria that should be considered in prescribing a DOAC.

Table 17.7 Considerations for selection of patients for direct oral anticoagulant therapy with atrial fibrillation or venous thromboembolism

Indication	Patient selection	Clinical considerations that may influence choice of therapy or exclude therapy with a DOAC
Stroke prevention in non-valvular atrial fibrillation	All patients with non-valvular AF, persistent, intermittent, or paroxysmal meeting specific risk factor criteria Non-valvular AF excludes patients with mitral stenosis or artificial heart valves and/or valve repair	Significant drug-drug interactions
		Significant renal impairment
		Significant liver impairment
		History of gastrointestinal bleeding
		Mechanical heart valve (excludes use of DOACs)
		Pregnancy/breast feeding (excludes use of DOACs)
		Extremes of body weight
		History of poor drug adherence
		Inability to pay for drug
Treatment of acute venous thromboembolism	All patients with VTE	Above considerations plus:
Prevention of recurrent VTE for extended treatment		Strong thrombophilic state
		Antiphospholipid syndrome
		Active cancer

Each DOAC has specific dose and dose modification recommendations for their major indications. These are summarized in Table 17.8. For the treatment of acute VTE, both rivaroxaban and apixaban can be started at the time of diagnosis without a lead-in phase with a parenteral anticoagulant (i.e., heparin or LMWH). However, both drugs are started at a higher dose for an initial period (Table 17.8) and then de-escalated to a lower maintenance dose for the duration of therapy. Both edoxaban and dabigatran require a lead-in phase of heparin or LMWH for at least 5 days before the DOAC is started based on the design of their clinical trials.

Monitoring Therapy and Coagulation Assays

Routine monitoring of the anticoagulant effect of DOACs is not necessary because they have a wide therapeutic window and their dose effect is predictable and is minimally influenced by drugs or diet. However, one would want to know their impact on coagulation in situations of major bleeding, trauma, or emergent surgery. In such situations a widely available, sensitive, and rapid turnaround assay would be desired [63]. Unfortunately, such assays are not clinically available. Table 17.9 summarizes both qualitative and quantitative assays that reflect drug concentration and/or drug effect on the coagulation cascade [64]. In clinical situations, the manufacturers currently recommend aPTT for measuring the effect of dabigatran and PT to determine the anti-Xa activity of rivaroxaban, apixaban, and edoxaban. Neither of these assays is ideal, all are reagent-dependent in their ability to reflect drug activity, and none are sensitive enough to exclude the presence of drug. For dabigatran, only the thrombin time (TT) is sensitive enough to exclude significant drug present when it is normal. The TT is not as widely available as the other assays noted above, and it may not be available during the 24 h cycle in those hospitals that do provide a TT. Thus, in patients taking dabigatran, an elevated aPTT suggests meaningful levels of dabigatran, but a normal aPTT cannot definitively exclude important levels of drug onboard.

The PT is more sensitive than the aPTT for assessing the effect of the factor Xa inhibitors and is recommended by the manufacturers. Like the aPTT, the result is reagent dependent and is most sensitive to rivaroxaban and much less sensitive to apixaban. The chromogenic anti-factor Xa assay with appropriate calibrators for each drug is an excellent quantitative assay, but it has very limited on-site availability in US hospitals, and the turnaround time from reference laboratories is obviously not suitable for emergent situations. Thus, the PT is helpful if elevated without other causes for elevation, but a normal PT does not rule out drug on board.

Table 17.8 Dosing of direct oral anticoagulants (DOACs) for stroke prevention in atrial fibrillation and treatment of acute and extended VTE

	Atrial fibrillation		Treatment of acute VTE		Extended VTE treatment	Joint replacement
Drug	Standard dosing	Modified dosing	Standard dosing	Modified dosing	Standard dosing	Standard dosing
Dabigatran	150 mg twice daily 110 mg twice daily (CrCl >30 ml/min)[a]	75 mg twice daily (CrCl 15–30 ml/min) (in the United States only)	150 mg twice daily (after 5–10 day heparin lead-in) (CrCl >30 ml/min)	None	150 mg twice daily CrCl <50 ml/min avoid use of concomitant P-gp inhibitor	110 mg for first day, then 220 mg once daily (CrCl >30 ml/min)
Rivaroxaban	20 mg once daily (CrCl >50 ml/min) with evening meal	15 mg once daily (CrCl 15–50 ml/min) with evening meal	15 mg twice daily for first 21 days and then 20 mg once daily with food	None (no renal dose adjustment)	20 mg once daily with food	Hip: 10 mg once daily for 35 days Knee: 10 mg once daily for 12 days
Apixaban	5 mg twice daily	2.5 mg twice daily with any two of following: age ≥80y; weight <60 kg; ser Cr ≥1.5 mg/dL	10 mg twice daily for 7 days and then 5 mg twice daily	None (no renal dose adjustment)	2.5 mg once daily after >6 months treatment of acute VTE	Hip: 2.5 mg twice daily, 12–24 h after surgery for 35 days Knee: 2.5 mg twice daily, 12–24 h after surgery for 12 days
Edoxaban	60 mg once daily	Half dose if CrCl 30–50 ml/min; wt <60 kg or with potent P-gp inhib; not used CrCl >95	60 mg once daily (after 5-day heparin lead-in)	30 mg once daily with a CrCl 30–50 ml/min or weight <60 kg or with potent P-gp inhib	None	None

[a]110 mg dosing not FDA approved in the United States

Table 17.9 Assays to measure effect of DOACs

Clinical objective					
	Determine if clinically relevant below on-therapy drug levels are present		Estimate drug levels within on-therapy range	Determine if above on-therapy drug levels are present	
Drug	Suggested test	Interpretation	Suggested test	Suggested test	Interpretation
Dabigatran	TT	Normal TT likely excludes clinically relevant drug levels	Dilute TT, ECA, ECT	aPTT, dilute TT, ECA, ECT	Normal aPTT likely excludes excess drug levels; only dilute TT, ECA, and ECT are suitable for quantitation
Rivaroxaban	Anti-Xa	Normal anti-Xa activity likely excludes clinically relevant drug levels	Anti-Xa	Anti-Xa, PT	Normal PT likely excludes excess drug levels; only anti-Xa is suitable for quantitation
Apixaban	Anti-Xa	Normal anti-Xa activity likely excludes clinically relevant drug levels	Anti-Xa	Anti-Xa	
Edoxaban	Anti-Xa	Normal anti-Xa activity likely excludes clinically relevant drug levels	Anti-Xa	Anti-Xa, PT	Normal PT likely excludes excess drug levels; only anti-Xa is suitable for quantitation

Abbreviations: *aPTT* activated partial thromboplastin time, *ECA* ecarin chromogenic assay, *ECT* ecarin clotting time, *PT* prothrombin time, *TT* thrombin time

Managing Invasive Procedures

With the rapid onset and offset of action of the DOACs, the management of patients requiring invasive procedures during therapy is greatly simplified compared to the VKAs. Analyses of interruptions of therapy in the major AF clinical trials of DOACs show that outcomes with the DOACs are no different than outcomes with warfarin, whether bridging is used or not. When a procedure is associated with little or no bleeding, there is no reason to interrupt DOAC therapy. If mild to moderate bleeding from the procedure is a potential, then skipping doses equivalent to 2–3 half-lives is recommended. For procedures that might incur major bleeding, one should skip 4–5 or more half-lives of the DOAC. In this calculation, it is important to be aware of renal function,

which, if impaired, may significantly prolong the half-lives of the DOACs, especially dabigatran. Restarting the drug post-procedure should be done when there is hemostatic stability, usually within 12–24 h depending on the procedure. It is important to remember that re-anticoagulation occurs almost immediately with the DOACs compared to the several days it takes with reinitiation of warfarin therapy.

Managing Drug Interactions

Drug-drug interactions with the DOACs occur either by induction or inhibition of the P-glycoprotein (P-gp) drug transporter (for dabigatran, rivaroxaban, apixaban, and edoxaban) or by induction or inhibition of the CYP450 3A4 metabolic enzyme (only Xa inhibitors with rivaroxaban being most sensitive, apixaban less sensitive, and edoxaban essentially not sensitive). There are many fewer important drug interactions with DOACs compared to those with VKAs, but when a potential or known interaction is present, the management difficulty lies in not knowing how much the interaction impacts DOAC drug concentration and inhibition of coagulation because there is no simple assay to accurately measure this effect. Generally, strong P-gp inhibitors and inducers should be avoided with dabigatran, especially in the setting of renal impairment. For the Xa inhibitors, it is recommended to avoid combined P-gp and strong CYP 3A4 inducers or inhibitors. The package inserts for each drug contain prescribing information for drug interactions. For some of the DOACs, dose reduction is suggested (e.g., dabigatran and apixaban) in the setting of certain drug-drug interactions, and for others (rivaroxaban and edoxaban) avoidance is suggested.

Adverse Events: Managing Bleeding and Reversal of Therapy

Besides maintaining hemodynamic balance with fluids and red cell transfusions and identifying the site of bleeding and treating it directly, if possible, managing bleeding in patients on DOACs also requires knowledge of which DOAC the patient is taking and when the last dose was taken, assessing renal function and trying to assess the degree to which the coagulation system is impaired [63, 65]. Lastly, for major bleeding, especially life-threatening bleeding, reversal of DOAC activity should be implemented. Although major bleeding with the DOACs still occurs at a rate of 1–3%, the DOACs are associated with less major bleeding, especially intracranial bleeding, compared to traditional therapy. Most minor or even moderate bleeding episodes are easily managed with a wait-and-see strategy allowing the drug effect to wear off. Knowledge of renal function impairment is particularly important for patients on dabigatran and to a somewhat lesser extent for edoxaban, the two DOACs with the highest rate of renal excretion. Assessing residual drug effect by the PT or aPTT assays (or TT for dabigatran) may be helpful, but, as previously discussed, normal assays do not fully exclude the presence of drug. For major life-threatening bleeding such as intracranial bleeding, bleeding into a vital organ, or hemodynamically unstable GI bleeding, reversal of the anticoagulant effect (if any remaining) should be attempted.

Idarucizumab is a specific reversal agent for dabigatran [66]. Andexanet alfa is a specific reversal agent for the factor Xa inhibitors [67]. A third reversal agent, ciraparantag, is currently under development [68]. The off-label use of PCCs as a prothrombotic agent to counter the anticoagulant activity of the factor Xa inhibitor is an alternative to andexanet alfa. This use is recommended only in life-threatening bleeding.

Idarucizumab (Praxbind®, Boehringer Ingelheim) is a murine monoclonal antibody that reverses the anticoagulant activity of dabigatran in patients with major bleeding or needing urgent surgery, as demonstrated in a recent clinical trial. Idarucizumab was able to normalize clotting times (dilute thrombin time or ecarin clotting time) in almost all patients within minutes of infusion which remained normal for the subsequent 24 h [66]. Ninety-three percent of patients who required emergent surgery experienced normal hemostasis during surgery as reported by their surgeon. The dose of idarucizumab is 5 gm given as sequential 2.5 gm intravenous injections.

Andexanet alfa (Portola Pharmaceuticals) is a unique recombinant human factor Xa that is modified so as to have no procoagulant effect but still retain binding specificity for the Xa inhibitors. It was recently approved by the FDA for clinical use to reverse anticoagulation in patients with major or life-threatening bleeding related to anticoagulation with rivaroxaban or apixaban. It needs to be given as a continuous infusion (given over 2 h in clinical trials) to maintain normal coagulation since its effect dissipates rapidly and anticoagulation will return based on the residual level of the DOAC. In two clinical trials, andexanet alfa was shown to rapidly reverse the anticoagulant effect of apixaban and rivaroxaban in healthy elderly volunteers and to restore adequate hemostasis within 12 h of administration in approximately 80% of patients who present with major bleeding [67].

Lastly, ciraparantag (Perosphere Inc.) is a small synthetic compound that binds to and neutralizes apixaban, rivaroxaban, and edoxaban as well as dabigatran and the indirect Xa inhibitor, enoxaparin [68]. Early studies indicate that a single intravenous injection can reverse anticoagulation induced by the abovementioned DOACs and enoxaparin with reversal persisting for up to 24 h. Ciraparantag is in the early stages of development and phase three trials have not yet been initiated.

Finally, other actions that might be suitable for select situations include activated charcoal lavage for patients who have recently ingested a DOAC (within 2–3 h) and, in the

case of dabigatran, hemodialysis. Dialysis is not suitable for the highly protein-bound Xa inhibitors.

Managing Transitions of Care

Care transitions, such as transferring from one medical institution to another or to home, are critical points in time where lack of a well-defined, organized, and efficient transition plan can result in adverse outcomes, loss of therapeutic effectiveness, and patient harm. Because DOACs have been promoted as drugs that do not need monitoring compared to the VKAs, there is the concern that patients will be left on their own with no oversight. For long-term outpatient follow-up, essential considerations include education about the drug and its potential side effects, the importance of drug adherence, dose reductions when applicable for the treatment of VTE, and periodic assessment of renal function, especially in those whose renal function is already impaired or who have concomitant illnesses that may accelerate decline.

Advantages/Disadvantages Compared with Warfarin

The DOACs have proven themselves to be as effective as traditional therapy for the major indications of stroke prevention in AF and the treatment of acute and chronic VTE. Perhaps more importantly, they have shown themselves to be safer than traditional therapy, especially for the incidence of intracranial hemorrhage. Because warfarin therapy has numerous drawbacks related to fluctuations in therapeutic range that require experienced and often labor intensive dose management, the DOACs are also attractive alternatives. With a wide therapeutic window, predictable dose response, and minimal influence by diet or other medications, they do not require routine monitoring. Their rapid onset of action eliminates the need for initial heparin therapy in many circumstances, and managing intervening invasive procedures is less complex. Table 17.10 summarizes the advantages of the DOACs. At the present time, the DOACs are rapidly gaining market share over the VKAs, although the latter will not totally go away. Meta-analysis data indicate that DOACs are as effective as warfarin in atrial fibrillation, deep venous thrombosis, and pulmonary embolism, but in all categories they have less bleeding [69]. However, there are certain indications for which the VKAs are still the mainstay of therapy, and in some circumstances, having a monitored, easily adjustable drug will have advantages for select patients.

Table 17.10 Characteristics of the direct oral anticoagulants (DOAC) versus warfarin

Characteristic	Warfarin	DOAC
Onset of anticoagulant effect	Slow	Rapid
Half-life	Long	Short (with normal renal function)
Dosing	Variable	Fixed (some variability)
Food effect	Yes	No
Drug interactions	Many	Few
Monitoring of anticoagulant effect	Yes	No
Antidote	Yes	Yes

Treatment of VTE

VTE treatment is divided into three phases: acute (first 5–10 days), long-term (first 3 months), and extended (>3 months). In the acute phase, the risk for adverse events such as deep vein thrombosis (DVT) extension, VTE recurrence, bleeding, and death is extremely high. Rapid attainment of therapeutic levels of anticoagulation is imperative to minimize short- and long-term morbidity and mortality.

Because of warfarin's slow onset, dosing strategies involving use of rapid-acting parenteral anticoagulants overlapped with warfarin evolved over time and have been shown to be extremely effective. With the advent of the direct oral anticoagulants (DOAC), approaches to VTE management have appreciably changed (Fig. 17.8). Based on their equal efficacy and improved safety compared to conventional approaches, DOACs are now preferred for treatment of VTE [24, 70]. It is important to emphasize that not all patients are DOAC candidates due to presence of contraindications or lack of evidence in certain populations. Thus, thoughtful patient selection is imperative for optimizing outcomes (Table 17.7).

When deciding on initial anticoagulation, the severity of presentation, potential need for invasive procedures, eligibility for outpatient treatment, and the patient's clinical characteristics, as well as their preferences, must all be considered (Fig. 17.9). Due to better safety and efficacy, the ACCP guidelines (9th ed. 2012) suggest either LMWH or fondaparinux (overlapped with warfarin) over UFH for initial management of VTE when a conventional approach is chosen. In general, unfractionated heparin should be reserved for use in specific clinical situations, such as patients with potential need for invasive procedures, potential for thrombolysis, or with increased bleeding risk, given its short half-life and complete reversibility with protamine sulfate. For VTE patients with severe renal impairment, UFH is preferred, as it is less reliant on renal elimination as compared to LMWHs, fondaparinux, and the DOACs. For all VTE patients who meet the criteria listed in Table 17.7, DOACs should be considered first-line therapy for treatment of VTE.

Special Populations/Considerations

Pregnancy and Breastfeeding

Warfarin is a known teratogen and the DOACs have not been studied in pregnant patients. Therefore, these agents should

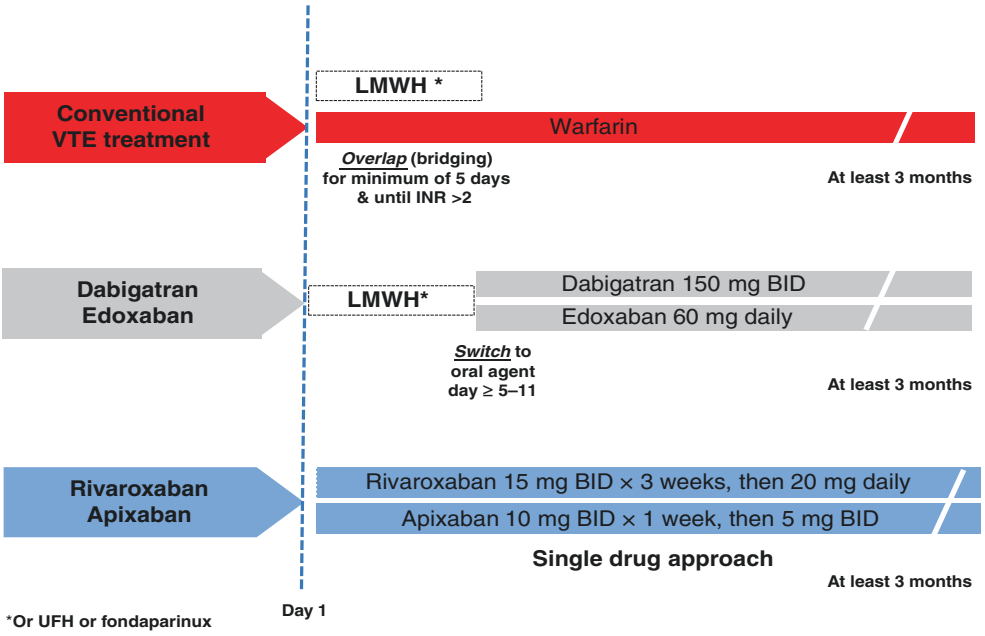

Fig. 17.8 Initiation of anticoagulation for acute VTE. BID twice daily, *INR* international normalized ratio, *LMWH* low-molecular-weight heparin, *UFH* unfractionated heparin, *VTE* venous thromboembolism

be avoided in pregnant patients with VTE. The exception to this is pregnant women with mechanical cardiac valves, in whom warfarin therapy may be considered during pregnancy. Fondaparinux is pregnancy category B and has been used successfully in pregnant patients with a contraindication to heparins. It may enter breast milk. However, due to its extensively proven safety and efficacy, the drug of choice for VTE in pregnancy is LMWH. If a pregnant patient has significant renal impairment, long-term SQ UFH therapy may be employed. There are no formal studies in humans evaluating the use of bivalirudin or argatroban during pregnancy, and use should be limited to situations that preclude the use of more conventional anticoagulants. They are relatively small molecules, and it is expected that they should cross the placenta. For breastfeeding, warfarin and LMWH are preferred therapies. The safety of parenteral DTIs, fondaparinux, or DOACs has not been established in breastfeeding women, and they should be avoided.

Cancer

Among patients with active malignancy and acute VTE, LMWH monotherapy for the first 3–6 months is preferred based on data from clinical trials showing superior efficacy and safety. Meta-analyses suggest DOACs are as efficacious as warfarin in preventing VTE recurrence; however, the number of patients with active cancer that were treated with DOACs in the clinical trials is small, and it is unknown if they are comparable to LMWH for this indication. Two prospective randomized clinical trials of ~1500 patients indicate that DOACs are equivalent to LMWH (dalteparin) in managing thrombosis in cancer patients [71, 72]. If a patient adamantly refuses long-term LMWH injections or warfarin plus frequent monitoring, use of DOACs may be considered (Fig. 17.9).

Thrombophilias

The DOACS have not been specifically studied in inherited or acquired thrombophilia. It is likely that a number of patients with an undiagnosed thrombophilia were enrolled in the DOAC VTE trials, suggesting these agents may be a viable option in this population. There are anecdotal reports that patients with a strong thrombophilic condition such as antiphospholipid syndrome do not do well with the DOACS. Until more robust data is available, a conventional approach with LMWH plus warfarin titrated to an INR of 2–3 is recommended (Fig. 17.9).

Extremes of Weight

The DOAC VTE trial populations did not adequately represent patients at extremes of weight. For patients <40 kg or >120 kg, it is unknown if fixed-dose DOACs might lead to over- or undertreatment in these patients. A conventional approach with LMWH (without dose capping in obesity) or fondaparinux (without need for dose adjustment in obesity) overlapped with warfarin is currently recommended until more data and experience are available (Fig. 17.9).

Renal Impairment

The LMWHs, fondaparinux, and the DOACs are all renally eliminated to an appreciable degree and thus should be avoided in severe renal impairment (estimated CrCl <30 ml/min). Preferred therapies in this population include UFH for acute management, with transition to warfarin for longer-term therapy. Either argatroban or dose-adjusted

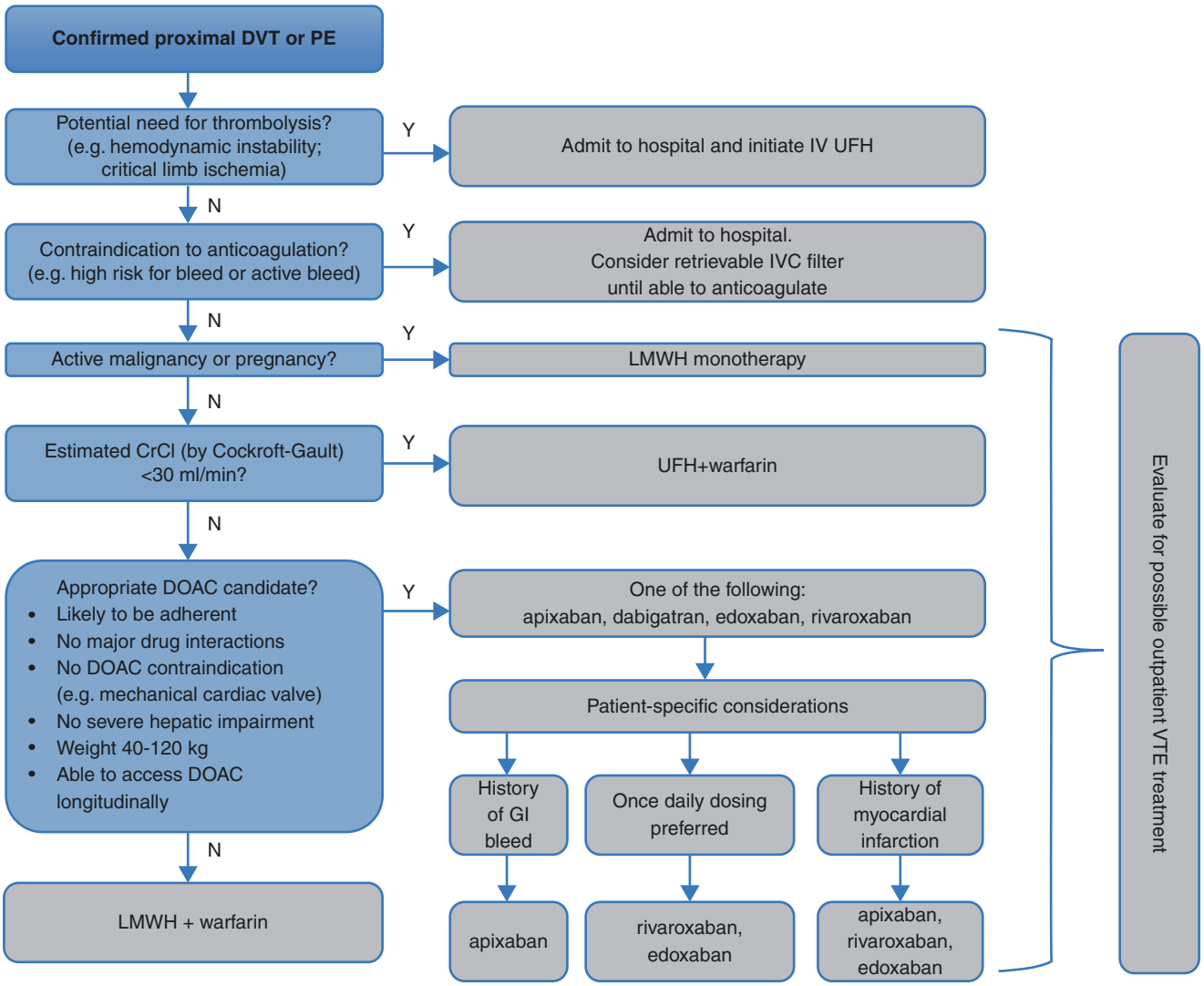

Fig. 17.9 Selection of anticoagulant for VTE treatment. *DOAC* direct oral anticoagulant, *DVT* deep vein thrombosis, *GI* gastrointestinal, *IVC* inferior vena cava, *LMWH* low-molecular-weight heparin, PE pulmonary embolism, *UFH* unfractionated heparin, *VTE* venous thromboembolism

bivalirudin may be used in patients with severe renal impairment requiring a parenteral DTI (Fig. 17.5).

Pediatrics

Warfarin, UFH, and LMWH have been used extensively in the pediatric population for a variety of indications. The evidence for use of fondaparinux, parenteral DTIs, and DOACs in pediatric patients is more limited and should be reserved for patients that are unable to receive warfarin, UFH, or LMWH.

In conclusion, clinicians now have several anticoagulants in the armamentarium of options for VTE treatment. Consideration of patient preferences and clinical characteristics, along with properties and dosing strategies of each of the agents, is imperative for optimal anticoagulation therapy.

IVC Filter Indications

In select patients who present with acute VTE, the risk of bleeding may be so high that the use of anticoagulation is contraindicated. In such patients, blocking or filtering blood flow from the inferior vena cava (IVC) to prevent pulmonary emboli is considered by inserting an IVC filter. Although this intervention developed over 100 years ago using ligation of the IVC, only in the last 50 years have practical mechanical devices been developed to achieve this with minimal intervention. Many different filters have been designed over the years, and today, retrievable IVC filters are mostly used. There is only one long-term randomized study assessing the efficacy and safety of these filters [73]. In patients with acute VTE randomized to an IVC filter plus anticoagulation compared with those with anticoagulation alone, the long-term

outcomes including death, recurrent VTE, or post-thrombotic syndrome were no different, although those with filters had more DVT compared to those without filters who had more PE. Unfortunately, the study subjects were not the typical patients most likely considered for filter placement, and most of the study patients continued on anticoagulation.

The indications for IVC filter placement, as proposed by professional societies, vary depending on the medical discipline. Examples include the following:

The American College of Chest Physicians advocates for the use of IVC filters as follows:

- *Vena cava filters for the initial treatment of DVT or PE:* For patients with acute proximal DVT or PE, if anticoagulant therapy is not possible because of the risk of bleeding, we recommend placement of an inferior vena cava (IVC) filter (Grade 1C).
- For patients with chronic thromboembolic pulmonary hypertension undergoing pulmonary thromboendarterectomy, we suggest the placement of a permanent vena cava filter before or at the time of the procedure (Grade 2C).

The Society of Interventional Radiology advocates for the uses of IVC filters as follows:

- *Absolute indications (proven VTE):* recurrent VTE (acute or chronic) despite adequate anticoagulation, contraindication to anticoagulation, complication of anticoagulation, and inability to achieve/maintain therapeutic anticoagulation
- *Relative indications (proven VTE):* iliocaval DVT; large, free-floating proximal DVT; difficulty establishing therapeutic anticoagulation; massive PE treated with thrombolysis/thrombectomy; chronic PE treated with thromboendarterectomy; thrombolysis for iliocaval DVT; VTE with limited cardiopulmonary reserve; recurrent PE with filter in place; poor compliance with anticoagulant medications; and high risk of complication of anticoagulation (e.g., ataxia, frequent falls)
- *Prophylactic indications* (no VTE, primary prophylaxis not feasible as a result of high bleeding risk, inability to monitor the patient for VTE, etc.): trauma patients with high risk of VTE, surgical procedure in patient at high risk of VTE, and medical condition with high risk of VTE

One thing that is certain is that filters have been progressively overused. Retrievable filters were developed so that they could be removed once the contraindication against anticoagulation is resolved, as is the case in many patients. Unfortunately, patients with retrievable filters are not always followed up, and in more than 50% patients, such filters are not removed. IVC filters are also associated with serious complications in 1–3% of individuals such as filter migration, filter fracture, perforation of the IVC, and others [74].

Duration of VTE Therapy

One of the more controversial and unsettled aspects of the treatment of VTE is the appropriate duration of treatment [75]. Recurrent VTE is a common problem and occurs in as many as 30% of selected patients over 10 years [76]. The decision to continue treatment requires a continuous benefit/risk analysis, i.e., does the benefit of continuing anticoagulant treatment and preventing recurrent VTE outweigh the risk of bleeding from anticoagulant therapy [77]? The decision is guided by understanding the risk factors for recurrent VTE following an initial episode. The major factors include the following:

- Was the initial episode provoked by a risk factor, such as surgery or trauma, or was it unprovoked (idiopathic)?
- If risk factors were present, were they transient (i.e., reversible) or persistent (such as obesity and cancer)?
- Is the episode a proximal (thigh) DVT or PE or a distal (calf) DVT?
- Are certain biomarkers (D-dimer) positive or negative after several months of therapy?
- Is the patient a male?

Abundant evidence indicates that the risk of recurrent VTE after a provoked VTE with transient risk factors is low enough that only 3 months of therapy is warranted. Patients with a VTE and persistent risk factors or with an idiopathic VTE require longer treatment, and therapy is often recommended to be indefinite with ongoing evaluations for the risk/benefit of such therapy. Patients with a calf vein DVT usually require only 3 months of therapy and, in some cases, only observation and monitoring, but careful surveillance is suggested to look for recurrence, especially if no risk factors are identified. Patients with evidence of residual vein occlusion or an elevated D-dimer after 3–6 months of therapy have a higher risk of recurrence. Persistent risk factors include such things as cancer, a major thrombophilia, or marked obesity. Additionally, males have a higher risk of recurrence than females. Table 17.11 identifies common risk factors and the relative risk for recurrence. Table 17.12 summarizes the recommended duration of therapy and the strength of the recommendation.

Table 17.11 Risk factors for VTE recurrence

Risk factor	Relative risk/hazard ratio (95% CI)
Unprovoked proximal DVT	2.3 (1.8–2.9)
Obesity	1.6 (1.1–2.4)
Male sex	2.8 (1.4–5.7)
Positive D-dimer	2.6 (1.9–3.5)
Residual thrombosis	1.5 (1.1–2.0)
Antiphospholipid antibody	2.4 (1.3–4.1)
Inflammatory bowel disease	2.5 (1.4–4.2)
Hereditary thrombophilia	1.5 (1.1–1.9)

Table 17.12 Duration of anticoagulation in patients with acute DVT of the leg

Type of VTE	Duration of treatment	Recommendation
Provoked isolated distal DVT	3 months	Grade 1B
Unprovoked distal DVT	3 months and then evaluation of risk/benefit ratio of extended therapy	Grade 1B
	For low or moderate bleeding risk → 3 months	Grade 2B
	For high bleeding risk → 3 months	Grade 1B
Provoked proximal DVT	3 months	Grade 1B
Unprovoked proximal DVT	At least 3 months and then evaluation of risk/benefit ratio of extended therapy	Grade 1B
	For low or moderate bleeding risk → extended anticoagulant therapy	Grade 2B
	For high bleeding risk → 3 months	Grade 1B
Second unprovoked DVT	For low bleeding risk → extended anticoagulant therapy	Grade 1B
	For moderate bleeding risk → extended anticoagulant therapy	Grade 2B
	For high bleeding risk → 3 months	Grade 2B
DVT and active cancer	For low or moderate bleeding risk → extended anticoagulant therapy	Grade 1B
	For high bleeding risk → extended anticoagulant therapy	Grade 2B

Notes: Initial and long-term therapy for PE is the same as for proximal DVT. Incidentally found asymptomatic DVT is suggested to be treated with initial and long-term anticoagulation as for comparable patients with symptomatic DVT (Grade 2B)
Abbreviations: *DVT* deep vein thrombosis, *PE* pulmonary embolism

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