Chapter 2

Overview of anticoagulants

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Historically anticoagulation involved the use of heparin and its derivatives or warfarin. However, the past few years have seen the introduction of a number of novel direct oral anticoagulants. These drugs are of interest as they require no laboratory monitoring, are relatively easy to use as they have a fixed dose and have demonstrated equivalence and in some cases superiority to warfarin, in the prevention of cardioembolic stroke in individuals with non-valvular atrial fibrillation, in deep vein thrombosis (DVT) prevention in patients undergoing hip and knee replacement surgery and in the treatment of DVT and pulmonary embolism (PE).

This chapter provides an overview of the currently available anticoagulant drugs, their licensed indications, their effects upon the standard laboratory tests and in addition provides guidelines on the management of patients undergoing invasive procedures.

Warfarin

Warfarin is a vitamin K antagonist [VKA] that inhibits γ-carboxylation of Factors II, VII, IX, and X [+ Proteins C, S and Z]. Warfarin has a half-life of 35–45 hours. The other common vitamin K antagonists (VKAs) include:

- Acenocoumarol with a half-life of 8–24 hours; and
- Phenprocoumon with a half-life of 5–6 days.
- Tecarfarin is a novel oral VKA that has been engineered so that it is not metabolized through the Cytochrome P450 [CYP]

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pathway. Tecarfarin is metabolized by esterases (mainly human carboxylesterase 2) to a single major metabolite, in rats, dogs, and humans. Tecarfarin is not significantly metabolized by CYP450 enzymes and for these reasons it has a decreased potential to interact with drugs that inhibit CYP450 enzymes. This drug may be of value for the treatment of patients with mechanical and prosthetic heart valves, as well as those with renal dysfunction.

- Phenindione is an inandione derivative but is now rarely used due to a high incidence of adverse events including skin rashes and abnormal liver function tests. Phenindione has a half-life of 5–10 hours.

The use of VKAs is complicated by a narrow therapeutic index and an unpredictable dose-response relationship, giving rise to bleeding complications or insufficient anticoagulation. The inter-individual variability observed with an individual's response to a VKA is in part due to the genetic variability arising from mutations in the *CYP2C9* and *VKORC1* genes. Mutations in *CYP2C9* have been linked to decreasing activity in metabolising VKA leading to a prolonged half-life and over-anticoagulation [1]. Conversely, mutations in the *VKORC1* gene have been linked to a decrease in requirements for warfarin [1]. An algorithm has been proposed to prevent over- or under-anticoagulation taking into account these two genes [2].

The *VKORC1* gene encodes the VKORC1 enzyme – a small transmembrane unit of the endoplasmic reticulum – and is primarily transcribed in the liver. Various polymorphisms and mutations within the *VKORC1* gene have been reported. The polymorphisms are associated with a reduction in the levels of VKORC1 and therefore a reduction in the amounts of warfarin that an individual requires to achieve a stable international normalized ratio (INR). Mutations within the *VKORC1* gene have been associated with a reduction in the levels of all the vitamin K-dependent clotting factors and are a rare cause of an inherited bleeding disorder [3].

Heparin

Several forms of heparin are available for therapeutic use.

Unfractionated heparin

Unfractionated heparin (UFH) is a sulphated polysaccharide with a molecular weight range of 3000–30,000 Da. It binds to the plasma serine protease inhibitor (SERPIN) antithrombin (AT) causing a conformational change in its structure and an acceleration of its inhibitory activity. UFH has both anti-IIa (thrombin) and anti-Xa activity.

Heparin binds to AT through a high affinity pentasaccharide binding site, which is present in ~one-third of heparin molecules. Maximal anti-IIa activity is dependent upon the binding of heparin to both thrombin and heparin. Heparin molecules <18 saccharide units lack the necessary chain length to form a bridge between the two molecules and so short chain heparin molecules have primarily anti-Xa inhibitory activity.

UFH binds to a number of plasma proteins, which accounts for the variable intra-individual anticoagulant response. While historically UFH was used for thromboprophylaxis, it is rarely used for this indication today. It is used primarily for patients who are at high risk of bleeding but in whom efficient anticoagulation is required. UFH has a short half-life and in addition can be efficiently reversed with the use of protamine sulphate. UFH is also used as an anticoagulant for patients on cardio-pulmonary bypass. UFH is commonly monitored by means of the activated partial thromboplastin time (APTT) test and occasionally by the anti-Xa assay.

Low molecular weight heparin

The LMWHs are primarily inhibitors of factor Xa but they also have some anti-IIa activity. The anti-Xa:IIa ratio varies from LMWH to LMWH preparation. LMWHs (of which there are a number) are prepared from UFH and are enriched for short-chain heparin molecules and so have primarily anti-Xa activity. LMWHs have a molecular weight range of 1000–10,000 Da with a mean range of 4500–5000 Da.

LMWHs have more predictable pharmacokinetics than UFH due to reduced binding to plasma proteins and so can be given once daily without (in the majority of individuals) any need for laboratory monitoring.

LMWHs are excreted through the kidneys and so may accumulate in patients with impaired renal function. The LMWHs may be monitored, if necessary, by means of an anti-Xa assay.

Synthetic pentasaccharide: fondaparinux and idraparinux

Fondaparinux is a synthetic pentasaccharide Xa-specific inhibitor identical to that found in LMWH and UFH. It is given subcutaneously and has a half-life of 17–21 hours. Fondaparinux is renally excreted and so may accumulate in patients with impaired renal function. Fondaparinux may be monitored, if necessary, by means of an anti-Xa assay.

Idraparinux, a specific Xa inhibitor, is a hypermethylated derivative of fondaparinux and binds to antithrombin with a strong affinity that accounts for its long half-life of 80–130 hours, which means the drug only requires weekly administration. However, although the drug is effective it may be associated with an increased risk of bleeding. Idrabiotaparinux is similar to idraparinux but contains a biotin group, which allows its anticoagulant activity to be rapidly reversed with avidin.

Danaparoid

Danaparoid is a mixture of heparan sulphate, chondroitin sulphate, and dermatan sulphate. Danaparoid has an anti-Xa elimination half-life of ~25 hours but the thrombin generation-inhibiting activity is eliminated with a half-life of ~7 hours. Danaparoid is excreted through the kidneys and so may accumulate in patients with impaired renal function. Danaparoid has an anti-Xa:anti-IIa activity ratio of 20 compared with ~2.5 for the LMWHs and 1 for UFH.

Danaparoid is not widely used and is usually reserved for individuals with heparin-induced thrombocytopenia (HIT) but in whom anticoagulation is required or in patients who develop other allergic reactions to LMWHs eg, skin rashes.

Direct IIa (thrombin) inhibitors

Bivalirudin

Bivalirudin is a 20 amino acid synthetic peptide that is a potent, reversible, direct inhibitor of thrombin. Bivalirudin binds to the catalytic site and the anion binding exosite of both circulating and clot-bound thrombin. This reaction is reversible as thrombin slowly cleaves the bivalirudin. It has a half-life of ~25 minutes if renal function is normal.

Dabigatran

Dabigatran is an oral, direct thrombin inhibitor with a high affinity (but reversible binding) for thrombin (factor IIa). Dabigatran also inhibits thrombin-induced platelet aggregation. Dabigatran etexilate is a prodrug that is converted into the active metabolite dabigatran with a low bioavailability. The intestinal absorption of dabigatran etexilate is pH sensitive and therefore its absorption is reduced in individuals receiving proton pump inhibitors.

Licensed indications

Dabigatran is licensed for thromboprophylaxis in patients undergoing hip and knee replacement surgery, for the treatment of DVT and PE and for the prevention of cardio-embolic stroke in patients with non-valvular atrial fibrillation. The dosing regimes for dabigatran are in Table 2.1 [4].

Direct oral Xa inhibitors

Currently two oral factor Xa (FXa) inhibitors are in common use – rivaroxaban [5] and apixaban [6]. A third oral FXa inhibitor, edoxaban, was recently approved. In the US, edoxaban is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (patients with creatinine clearance ≤95 mL/min), and for the treatment of DVT and PE following 5 to 10 days of initial therapy with a parenteral anticoagulant. In the EU, edoxaban was approved in June 2015 for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more risk factors (such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack). In addition, it received approval for the treatment of DVT and PE, and prevention of recurrent DVT and PE in adults following initial use of parenteral anticoagulant for at least 5 days. The recommended dose of edoxaban is 60 mg taken orally once daily (30 mg once daily in patients with creatinine clearance 15 to 50 mL/min, patients who weigh less than or equal to 60 kg, or patients who are taking certain concomitant P-gp inhibitor medications).

Surgery	Dabigatran dosing	Comments
Elective knee replacement surgery	Age >18 yrs <75 yrs. Commence dabigatran 110mg 1–4 hrs following surgery followed by 220 mg once daily 12–24 hours later for 9 days. Patients >75 yrs OR patients receiving amiodarone or verapamil. The dabigatran dose is reduced to 75 mg 1–4 hrs following surgery followed by 150mg once daily 12–24 hours later for 9 days	1. PPI inhibitors: Dabigatran requires an acidic environment for absorption and therefore, its absorption is reduced in individuals receiving PPIs. 2. Drugs affecting the P-gp pathway: i. Dabigatran etexilate is a substrate for P-gp although dabigatran is not and as a result its absorption can be altered by P-gp inducers or inhibitors during its passage through the gut enterocyte. Once dabigatran etexilate is absorbed and converted from the prodrug to the active drug, it is no longer susceptible to P-gp inhibitors. P-gp inhibitors such as amiodarone, verapamil, itraconazole, ketoconazole, diltiazem, ritonavir and tacrolimus will increase the plasma concentrations of dabigatran. ii. P-gp inducers such as rifampicin will decrease plasma dabigatran levels. St John's Wort and carbamazepine are similarly likely to affect plasma dabigatran levels. 3. Dabigatran has a T1/2 of 12–17 hrs with ~80% of the drug excreted renally. Therefore: a. CrCL <30 mL/min: dabigatran should be avoided. b. CrCL >50– ≤80 mL/min: no dose adjustment is necessary c. CrCL 30–50 mL/min: the recommended dose of dabigatran is 300 mg taken as one 150 mg capsule twice daily. However, for patients with high risk of bleeding, a dose reduction of dabigatran to 220 mg taken as one 110 mg capsule twice daily may be considered.
Elective hip replacement surgery	Age >18 yrs <75 yrs. Commence dabigatran 110 mg 1–4 hrs following surgery followed by 220 mg once daily 12–24 hours later for 27–34 days. Patients >75 yrs OR patients receiving amiodarone or verapamil – the dose of dabigatran is reduced to 75 mg 1–4 hrs following surgery and then 150mg once daily 12–24 hours later for 27–34 days	
Treatment of DVT or PE and prophylaxis of recurrent DVT and/or PE	Age >18 yrs <80 yrs. Dabigatran 150 mg twice daily following at least 5 days' treatment with a parenteral anticoagulant. Age >80 years OR receiving treatment with verapamil – dabigatran 110 mg twice daily following at least 5 days' treatment with a parenteral anticoagulant. The lower dose of dabigatran 110 mg twice daily may be considered in patients aged 75-80 yrs with moderate renal impairment [CrCL >30–<50 mL/min] or at increased risk of bleeding.	
Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation	Age >18 yrs <80 yrs dabigatran 150 mg twice daily. Age >80 yrs OR receiving treatment with verapamil – dabigatran 110 mg twice daily. The lower dose of dabigatran 110 mg twice daily may be considered in patients aged 75-80 yrs with moderate renal impairment [CrCL >30–<50 mL/min] or at increased risk of bleeding.	

Table 2.1 Dosing regimens for dabigatran. For additional information consult the dabigatran summary of product characteristics. CrCL, creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism. P-gp, P-glycoprotein; PPI, proton pump inhibitor; T1/2, half-life.

Rivaroxaban

Rivaroxaban is an oral, direct factor Xa inhibitor that inhibits prothrombinase-bound factor Xa, free factor Xa and clot-bound factor Xa. The majority of rivaroxaban [90–95%] is protein bound. Rivaroxaban is cleared from the plasma by the kidneys and in the feces:

- One-third of rivaroxaban is excreted unchanged by the kidneys
- One-third is metabolized by the liver [via CYP3A4-dependent and CYP3A4-independent pathways] and excreted into the feces
- One-third is metabolized to inactive metabolites which are then excreted by the kidneys.

The maximum inhibition of FXa occurs 1–4 hours after ingestion. Rivaroxaban has a half-life of 7–11 hours.

Licensed indications

See Table 2.2 for licensed indications.

Apixaban

Apixaban is an oral factor Xa inhibitor that inhibits prothrombinase-bound factor Xa, free factor Xa and clot-bound factor Xa. The majority of apixaban [87–93%] is protein bound with a half-life of 8–15 hours. The renal clearance is approximately 27%.

Licensed indications

See Table 2.3 for licensed indications.

Laboratory tests in patients on direct oral anticoagulant agents

The effects of the direct oral anticoagulant agents (DOACs) on routine hemostatic laboratory tests are summarized below. In general, the routine measurement of dabigatran, rivaroxaban, or apixaban levels is not indicated although assays for these drugs are available (Table 2.4). The data are also summarized in Table 2.5.

Surgery	Rivaroxaban dosing	Comments
Elective knee replacement surgery	Age >18 yrs Commence rivaroxaban 10 mg once daily 6–10 hrs after surgery and continue for 14 days.	1. No dose adjustment is needed for the elderly. 2. Rivaroxaban has a T½ of 7–11 hrs and one-third is excreted by the kidneys. Therefore: a. CrCL <15 mL/min: rivaroxaban is contraindicated b. 15–29 mL/min: i. Use with caution in patients undergoing hip and knee replacement surgery. ii. In patients with DVT or PE reduce the dose of rivaroxaban to 15 mg twice daily for 21 days and then1 5 mg once daily. iii. In the prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation the dose of Rivaroxaban should be reduced to 15 mg once daily. c. 30–49 mL/minute – no dose adjustment necessary. d. 50–80 mL/minute – no dose adjustment necessary. 3. Drug interactions: potent inhibitors of the CYP3A4 pathway and inhibitors of the P-gp pathway eg, ketoconazole [and related preparations] or ritonavir – can lead to an increase in the plasma concentration of rivaroxaban and therefore, to an increased risk of bleeding. Rivaroxaban is not advised in such cases. 4. Potent inducers of CYP3A4 such as rifampicin can lead to a decrease in mean rivaroxaban levels and to a decreased efficacy. Similarly other inducers of CYP3A4 such as phenytoin, carbamazepine and St John's Wort may also lead to reduced rivaroxaban levels and rivaroxaban should be avoided in such cases.
Elective hip replacement surgery	Age >18 yrs Commence rivaroxaban 10 mg once daily 6–10 hrs after surgery and continue for 35 days.	
Treatment of DVT or PE and prophylaxis of recurrent DVT and/or PE	Age >18 yrs Commence treatment with rivaroxaban 15 mg twice daily for 21 days then reduce the dose to 10 mg twice daily.	
Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation	Age >18 yrs Commence rivaroxaban 20 mg once daily.	

Table 2.2 Licensing indications for rivaroxaban. For additional information consult the summary of product characteristics. CrCL, creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism; P-gp, P-glycoprotein; T1/2, half-life.

Surgery	Apixaban dosing	Comments
Elective knee replacement surgery	Age >18 yrs Commence apixaban 2.5 mg once daily 12–24 hrs after surgery and continue for 10–14 days.	1. No dose adjustment is needed for the elderly although increasing age may increase the hemorrhagic risk. 2. Renal impairment: a. CrCL <15 mL/min: apixaban is contraindicated b. 15–29 mL/min: i. Use with caution in patients undergoing hip and knee replacement surgery. ii. Use with caution in patients with DVT or PE iii. In the prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation and age >80 yrs or weight <60 kg – the dose of apixaban is reduced to 2.5 mg twice daily. 3. Drug Interactions: i. Strong inhibitors of CYP3A4 and P-gp. Apixaban is not recommended in patients receiving concomitant systemic treatment with itraconazole, voriconazole and posaconazole, and HIV protease inhibitors (eg, ritonavir). These drugs may increase apixaban exposure by twofold. ii. Apixaban is not recommended for the treatment of DVT and PE in patients receiving strong CYP3A4 and P-gp inducers (eg, rifampicin, phenytoin, carbamazepine, St John's Wort) as these may lead to a reduction in apixaban levels and potentially, therefore, a reduction in efficacy.
Elective hip replacement surgery	Age >18 yrs Commence apixaban 2.5 mg once daily 12–24 hrs after surgery and continue for 32–38 days.	
Treatment of DVT or PE and prophylaxis of recurrent DVT and/or PE	Age >18 yrs i. Commence apixaban 10 mg orally twice daily for the first 7 days followed by 5 mg orally twice daily. ii. For the prevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE, the dose of apixaban is 2.5 mg twice daily.	
Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation	i. Age >18 yrs apixaban 5 mg taken orally twice daily ii. Age > 80 yrs or weight <60 kg – the dose of apixaban is reduced to 2.5 mg twice daily.	

Table 2.3 Licensing indications for apixaban. For additional information consult the summary of product characteristics for apixaban. CrCL, creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism; P-gp, P-glycoprotein.

	Direct IIa inhibitor
	Dabigatran
PT	The PT is relatively insensitive to dabigatran. Although the PT will prolong with increasing concentrations of dabigatran, at trough dabigatran levels it can be normal. A normal PT, therefore, does not exclude the presence of dabigatran. The PT is less sensitive to dabigatran than the APTT. Factor assays based upon the PT will underestimate the factor level in the presence of dabigatran.
APTT	The APTT response curve flattens as the concentration of dabigatran increases above 200 ng/mL and the APTT is, therefore, relatively insensitive to the plasma concentrations of dabigatran that are likely to be encountered in clinical practice. The APTT can be used with most reagents for urgent determination of the relative intensity of anticoagulation due to dabigatran but it cannot be used to determine the drug level. Factor assays based upon the APTT will underestimate the factor level in the presence of dabigatran.
TT	The thrombin time is very sensitive to the effects of dabigatran and displays a linear dose-response curve over therapeutic levels but at high concentrations the actual clotting time may exceed the time that many instruments allow. A normal thrombin time excludes the presence of dabigatran.
Fibrinogen (Clauss)	Dabigatran may interfere with the Clauss fibrinogen assay and at high concentrations, fibrinogen levels may be underestimated. The effect is dependent upon the tests used in the assay.
ACT	The ACT shows a linear relationship with dabigatran with concentrations up to 250 ng/mL but is not specific for dabigatran.
ECT	Directly assesses the activity of thrombin in a plasma sample and displays a linear dose-response to therapeutic concentrations of dabigatran. However, the ECT is hampered by lack of standardization, different lots of ecarin, and limited availability.
Anti-Xa assays	Not applicable.

Table 2.4 The effects of the direct oral anticoagulant agents on routine hemostatic laboratory tests (continues overleaf).

Direct Xa inhibitors	
Rivaroxaban	**Apixaban**
i. The PT in patients receiving rivaroxaban varies significantly with differing thromboplastins and therefore individual labs need to determine the sensitivity of their PT for rivaroxaban. ii. INR: Conventional INR for monitoring patients on VKAs is not suitable for monitoring patients. Rivaroxaban INR: The possibility of developing a PT-based assay for rivaroxaban similar to the INR has been explored. Rivaroxaban has been assigned an ISI [$ISI^{Rivaroxaban}$] and the rivaroxaban 'INR' derived using a similar formula to that of the INR. The scheme is very similar to that proposed for the ISI^{Liver}. Factor assays based on the PT will underestimate the factor level in the presence of rivaroxaban .	The PT appears less sensitive to apixaban than rivaroxaban. A normal PT does not exclude significant levels of apixaban. Factor assays based upon the PT will underestimate the factor level in the presence of apixaban.
The APTT is sensitive to the anticoagulant effects of rivaroxaban and can lead to a prolonged APTT. With appropriate reagents, the APTT can be used for the urgent determination of the relative intensity of anticoagulation due to rivaroxaban (although the PT is usually more sensitive) but it cannot be used to determine the drug level. Factor assays based upon the APTT will underestimate the factor level in the presence of rivaroxaban.	The APTT is prolonged by the apixaban but less so than with rivaroxaban. There may be significant levels of apixaban in the plasma but only minimal prolongation of the APTT. Factor assays based upon the APTT will underestimate the factor level in the presence of apixaban.
No effect.	No effect.
Rivaroxaban appears to have minimal effect upon Clauss fibrinogen assays but at high rivaroxaban concentrations, may lead to a 10% reduction in fibrinogen levels.	No effect.
Supratherapeutic levels of rivaroxaban will prolong the ACT.	Supratherapeutic levels of apixaban will prolong the ACT.
No effect .	No effect.
Current data indicate that an anti-Xa assay appropriately calibrated correlates with apixaban.	Current data indicate that an anti-Xa assay appropriately calibrated correlates with apixaban concentrations.

Table 2.4 The effects of the direct oral anticoagulant agents on routine hemostatic laboratory tests (continued). ACT, activated clotting time; APTT, activated partial thromboplastin time; ECT, ecarin clotting time; INR, international normalized ratio; PT, prothrombin time.

	Dabigatran	Rivaroxaban	Apixaban
PT (INR)	↑	↑↑↑	↑↑
APTT	↑↑↑		↑
Thrombin time	↑↑↑↑	–	–
Fibrinogen (Clauss)	↓	–	–
PT-based factor assays	↓↓	↓	↓
APTT-based factor assays	↓	↓↓	↓↓
ACT	↑	(↑)	(↑)

Table 2.5 Summary of the data on the effects of the direct oral anticoagulant agents on routine hemostatic laboratory tests. ACT, activated clotting time; APTT, activated partial thromboplastin time; ECT, ecarin clotting time; INR, international normalized ratio; PT, prothrombin time.

Perioperative management of patients on direct oral anticoagulant agents

The management of patients on DOACs undergoing invasive procedures is becoming increasingly important [7]. The advised times to discontinue DOACs are summarized in the tables below (Table 2.6, Table 2.7, and Table 2.8). For patients at high risk of thrombosis bridging with a LMWH may be required.

Direct oral anticoagulant agents: summary of pharmacokinetic properties

Table 2.9 below summarizes the pharmacokinetic (PK) properties of dabigatran, rivaroxaban, and apixaban.

		Dabigatran dose	
eGFR	**Estimated half-life**	**High risk of bleeding**	**Standard risk of bleeding**
>80mL/minute	~13 hours	Discontinue 2 days before	Discontinue 24 hours before
≥50–<80 mL/minute	~15 hours	Discontinue 2–3 days before	Discontinue 1–2 days before
≥30–<50 mL/minute	~18 hours	Discontinue 4 days before	Discontinue 2–3 days before [>48 hours]

Table 2.6 The advised times for discontinuing dabigatran.

	eGFR			
	Normal	**60–90 mL/min**	**30–59 mL/min**	**15–29 mL/min**
Discontinue rivaroxaban	1 day	2 days	3 days	4 days

Table 2.7 The advised times for discontinuing rivaroxaban.

	eGFR		
		50–59 mL/min	**30–49 mL/min**
Discontinue apixaban	1-2 days	3 days	5 days

Table 2.8 The advised times for discontinuing apixaban.

	Dabigatran	**Rivaroxaban**	**Apixaban**
Prodrug	Yes	No	No
Frequency of dosing	Twice daily	Once daily	Twice daily
Effect of food	Delays absorption	Delays absorption	None
Bioavailability	6.5%	10 mg dose: 60–100% 20 mg dose: 66%	50%
Time to maximum inhibitory effect	1–3 hrs	2–4 hrs	2–4 hrs
Protein binding	25%	90–95%	87–93%
Metabolism	Predominantly by the kidneys	Predominantly through the liver	Predominantly through the liver
Half-life	12–17 hrs	7–11 hrs but may be longer in the elderly	8–15 hrs
Potential drug interactions	CYP3A4 P-gp inhibitors	CYP3A4 P-gp inhibitors	CYP3A4 P-gp inhibitors

Table 2.9 The pharmacokinetic properties of dabigatran, rivaroxaban, and apixaban. P-gp, P-glycoprotein.

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