Old Versus New Oral Anticoagulants: Focus on Pharmacology

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Annu. Rev. Pharmacol. Toxicol. 2012. 52:79–99

First published online as a Review in Advance on August 5, 2011

The *Annual Review of Pharmacology and Toxicology* is online at pharmtox.annualreviews.org

This article's doi: 10.1146/annurev-pharmtox-010611-134633

0362-1642/12/0210-0079$20.00

Keywords

vitamin K antagonists, factor Xa inhibitors, factor IIa inhibitors, direct thrombin inhibitors

Abstract

Since the discovery of heparin nearly a century ago, there have been large gaps in the development of anticoagulants. The discovery of warfarin was the first step toward using oral anticoagulants, but warfarin use has been associated with its own challenges from the perspectives of the prescribing physician and the patient. Warfarin, along with other coumarins, has a narrow therapeutic index, requires frequent monitoring, exhibits interindividual response variations, and is associated with several adverse effects. Frequent drug and food interactions contribute to potential safety and efficacy compromise. The indications for use of oral anticoagulants have increased, as these drugs are used not only for thrombosis management but also for cardiovascular indications, producing more challenges for oral anticoagulant use. Factor Xa and thrombin targeting has provided a rational approach to develop new oral anticoagulants with improvements over warfarin. In this review, the pharmacology of warfarin and the pharmacology of the newly developed oral anti-Xa and antithrombin agents are discussed.

INTRODUCTION

VKA: vitamin K antagonist

Oral anticoagulant therapy is in the midst of a transition: Investigators are introducing substitutes for warfarin, which has been used clinically for almost 50 years. Newer anticoagulants inhibit a single target (factor Xa and factor IIa) within the coagulation cascade and may offer distinct advantages over vitamin K antagonists (VKAs) such as warfarin. The specific targeting of factor Xa and thrombin by newer anticoagulant drugs provides a more predictable and consistent pharmacokinetic and pharmacodynamic response. On the basis of these factors, the newer anticoagulants do not require follow-up monitoring and can be dosed once or twice a day. These newer anticoagulants are claimed to not require dosage adjustments for the majority of patients. There have been many unsuccessful attempts throughout the years to discover anticoagulants that can be administered orally, including the development of an oral heparin, sodium *N*-(8-(2-hydroxybenzoyl)amino)caprylate: SNAC heparin. The first specific direct oral thrombin inhibitor, ximelagatran, was withdrawn from development and clinical use because of hepatic toxicity.

In recent years, numerous new oral anticoagulants have been able to provide superior efficacy and safety in comparison with warfarin. Among these, dabigatran (factor IIa inhibitor) was approved recently in the United States for prevention of stroke in patients with atrial fibrillation. Rivaroxaban and apixaban (both factor Xa inhibitors) have been approved in several countries outside the United States for the prevention of thrombosis after total knee and hip surgery. Rivaroxaban and apixaban are nearing the completion and reporting of several additional clinical trials. Other Xa inhibitors such as edoxaban and betrixaban are currently under clinical development. In this review, the pharmacology of established and new oral anticoagulants is discussed, with reference to their mechanisms of action and anticoagulant effects.

THE HEMOSTATIC SYSTEM

Hemostasis is the fundamental mechanism that leads to the arrest of localized bleeding at the site of injury. This is achieved through multiple mechanisms working in harmony to form a barrier against ongoing blood loss. Primary hemostasis is achieved by platelet–vessel wall interaction. Secondary hemostasis results from the conversion of soluble fibrinogen to insoluble fibrin. Interwoven with the hemostatic process is the fibrinolytic system that works to maintain vascular patency. All three mechanisms are activated simultaneously during normal hemostasis as well as pathological thrombosis. The endothelium regulates the extent of reactions within a specified domain (of injury) to prevent bleeding and pathological extension of the hemostatic and fibrinolytic processes (1).

The coagulation cascade is a series of reactions in which each product of a reaction converts an inactive plasma-protein zymogenic precursor to an active serine protease product (**Figure 1**) (2). Factor Xa and thrombin play central roles in the coagulation cascade, and their inhibition by direct or indirect means results in anticoagulation. Several other coagulation factors have been targeted in the development of newer anticoagulants, including factors XIIIa, XIIa, XIa, IXa, and VIIa. Antibodies to some of the coagulation proteins such as factor VIII also are being developed.

VITAMIN K ANTAGONISTS

Warfarin

For many decades, warfarin has been the standard of care for a wide variety of indications. Warfarin is a VKA and is one of the many hydroxycoumarins that were synthesized from dicoumarol, a naturally occurring anticoagulant isolated from fermented clover. The name warfarin was coined by Karl Paul Link, who named it for the foundation that funded his work, Wisconsin Alumni

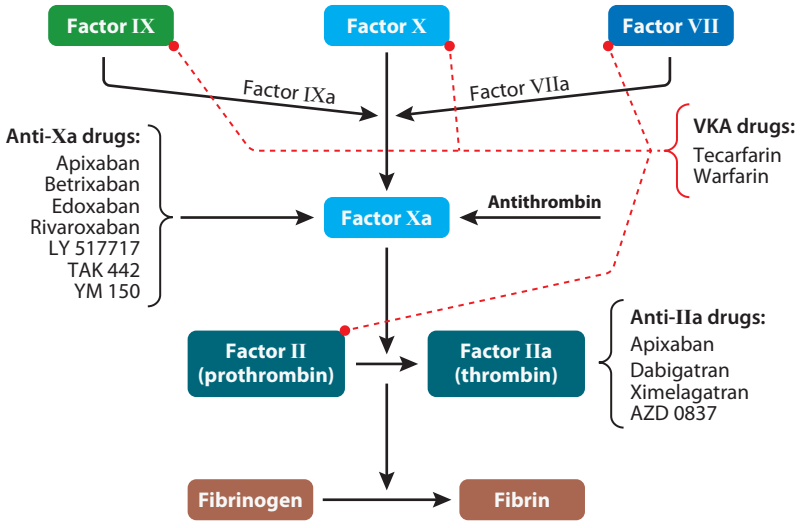

Figure 1

Oral anticoagulants: target sites. Abbreviation: VKA, vitamin K antagonist.

Research Foundation. It was used initially as rodenticide but came to be used clinically after an incident involving an army recruit: The recruit attempted suicide by taking a large quantity of this rodenticide but was treated successfully with a blood transfusion and vitamin K (3). Warfarin is the VKA of choice for most countries. Phenprocoumon and acenocoumarol also are used in some European countries.

Warfarin pharmacology: 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one sodium salt. Warfarin is a racemic mixture of two enantiomers (*S*-warfarin and *R*-warfarin) in equal proportions and is generally administered as a sodium salt (**Figure 2**). The *S*-enantiomer is three times more potent than the *R*-enantiomer. Although warfarin exhibits near 100% bioavailability, it is highly (99%) bound to plasma albumin, which may explain its small volume of distribution and its long half-life (4) (**Table 1**). Warfarin is administered once daily, but the dosage is variable and is based on factors such as genetic polymorphisms and diet. To achieve effective anticoagulation, warfarin levels need to be monitored using prothrombin time and international normalized ratio (INR). Like *S*-warfarin, *S*-acenocoumarol is more potent than *R*-acenocoumarol (5). Similarly, the *S*-enantiomer of phenprocoumon is largely responsible for the anticoagulant effect of phenprocoumon (6).

Mechanism of action and pharmacogenomics. Warfarin (and other coumarins) blocks the gamma carboxylation of several glutamate residues in coagulation factors II, VII, IX, and X as well as endogenous anticoagulant proteins C and S. The blockade results in biologically inactive coagulation factors. The protein carboxylation reaction is coupled to the oxidation of vitamin K, leading to oxidized vitamin K production (vitamin K 2,3-epoxide). The vitamin K epoxide then must be reduced in order to be reactivated. Warfarin inhibits vitamin K epoxide reductase (VKOR), preventing the formation of vitamin K hydroquinone (active form) from vitamin K 2,3-epoxide (inactive form) in the vitamin K cycle. Single-nucleotide polymorphisms in the gene encoding VKOR, termed *VKORC1*, have been linked to reduced efficacy of vitamin K recycling. The resulting lower VKOR activity requires higher dosing of warfarin (8).

INR: international normalized ratio

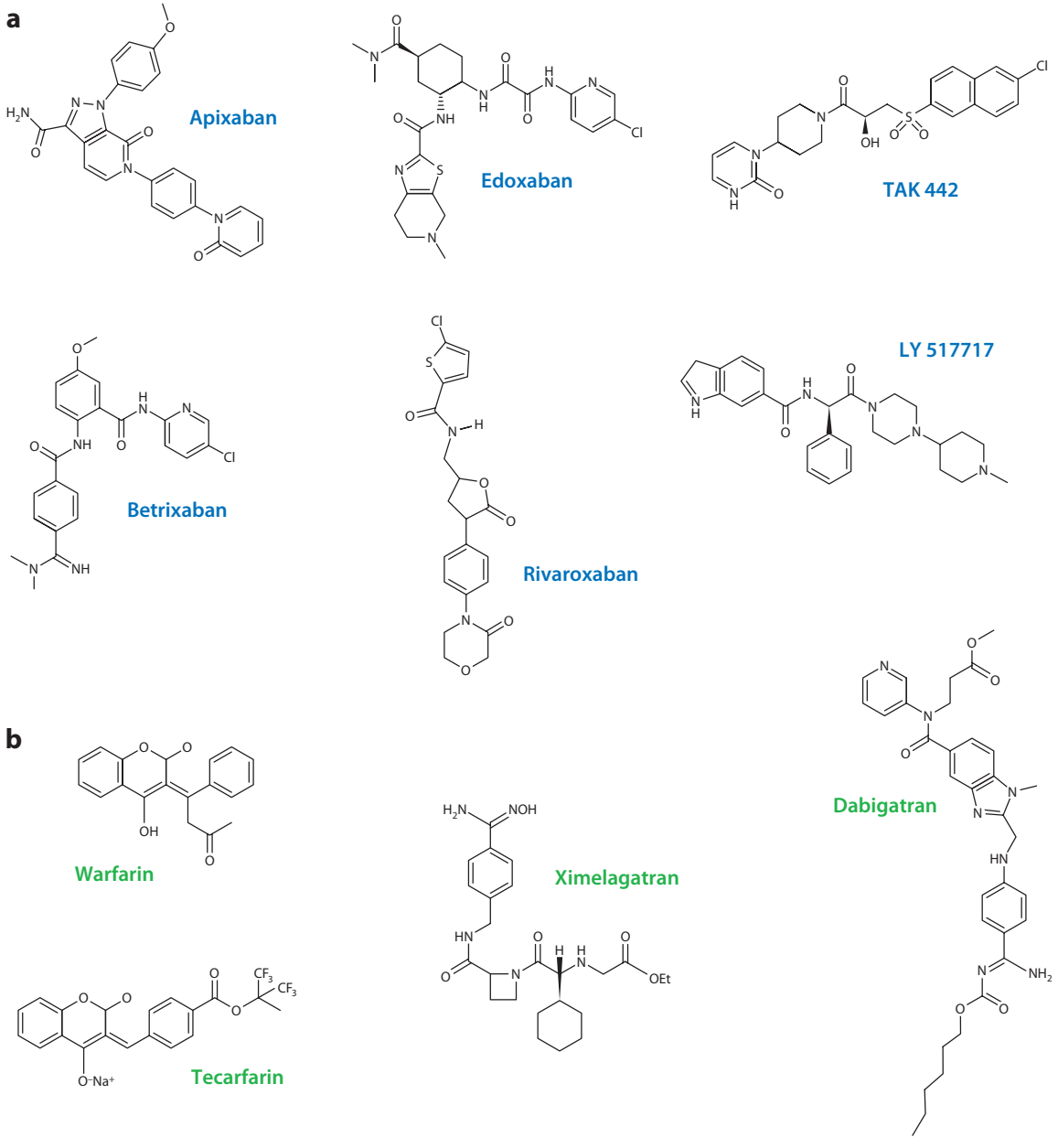

Figure 2

(*a*) Chemical structure of various oral anti-Xa agents. (*b*) Chemical structure of various oral anti-IIa agents and warfarin-related agents.

CYP: cytochrome P450

Warfarin is subject to cytochrome P450 (CYP) metabolism, and the presence of variant alleles of CYP2C9—including CYP2C9*2 and CYP2C9*3—results in impaired metabolism. This impaired metabolism requires reduction in dosages to avoid increased bleeding complications (9). Mutations in numerous other genes also have been associated with causing distorted warfarin metabolism and a resultant variable pharmacologic response: CYP1A2, CYP3A4 and CYP4F2, apolipoprotein E,

Table 1 A comparison of pharmacologic properties of various oral anticoagulants

Oral anticoagulant	Agent	Time to peak plasma concentration (h)	Half-life (h)	Bioavailability (%)	Dosing frequency	Drug interaction(s)
Vitamin K antagonist	Warfarin	72–96	20–60	100	od	CYP2C9, CYP1A2, CYP3A4 (7)
	Tecarfarin (ATI 5923)					
Xa inhibitor (activated factor Xa inhibitor)	Rivaroxaban	2.5–4	5–9 (9–13 in elderly)	80	od/bid	CYP3A4 inhibitors and P-gp inhibitors[a]
	Apixaban	3	8–13	~66	bid	CYP3A4 inhibitors and P-gp inhibitors
	Betrixaban		20	47	od/bid	
	Edoxaban (DU-176b)	1.5	9–11	50[b]	od	P-gp inhibitors
	TAK 442	1–2	9–13		od/bid	
	YM 150	2	18–20		od	
	LY 517717	0.5–4	~25	~25–82	od[c]	
Direct thrombin inhibitor	Dabigatran	2–3	14–17	6.5	od/bid	P-gp inhibitors
	AZD 0837	9–14	2–3	~22–55	od	CYP3A4 inhibitors
	Ximelagatran (melagatran)	1.6–1.9	4–5	~20	bid	
Oral heparin	SNAC heparin					

[a]Potent inhibitors of CYP3A4 and P-gp include "-azole" antifungals (e.g., ketoconazole, voriconazole) and protease inhibitors (ritonavir).
[b]Determined from animal models.
[c]Based on a Phase II study.
Abbreviations: bid, twice daily; CYP, cytochrome P450; od, once daily; P-gp, P-glycoprotein; SNAC, sodium *N*-(8-(2-hydroxybenzoyl)amino)caprylate.

and gamma-glutamyl carboxylase (9, 10). Phenprocoumon may be preferable in poor metabolizers of coumarin anticoagulants (11, 12).

Warfarin's onset of action occurs 8–12 h following the initiation of therapy. As the anticoagulant effect of warfarin is dependent on the inhibition of synthesis as well as the degradation of factors II, VII, IX, and X, the half-lives of these factors affect the anticoagulation response. Factor II has the longest half-life, at 60 h, whereas factors VII, IX, and X have half-lives of 6, 24, and 40 h, respectively. Warfarin's anticoagulant response is hastened by doses of up to 0.75 mg kg^{-1}; no further shortening of the time of onset is achieved with higher doses (4). Warfarin treatment requires close monitoring of its anticoagulant effect through use of the prothrombin time (PT) assay. The therapeutic range for oral anticoagulation is defined in terms of INR. INR is the PT ratio (patient's PT/mean of normal PT for Lab)^{ISI}, where ISI refers to the International Sensitivity Index of the thromboplastin reagent used. The current recommended INR range for prophylaxis and treatment is 2–3 for most thrombotic disorders. A higher range (2.5–3.5) is recommended for high-risk groups, including patients with prosthetic heart valves (13).

PT: prothrombin time

Drug and food interaction and toxicity. Warfarin is subject to a wide array of drug interactions that can be caused by enzyme induction, enzyme inhibition, or decreased plasma-protein

binding. Various antibiotics are associated with the aforementioned interaction, including but not limited to metronidazole, cephalosporins, and fluconazole (4). Other interactions arise from an altered physiologic control loop for vitamin K, competitive antagonism, and reduced clotting factor synthesis, as seen in hepatic diseases. Warfarin treatment also requires significant dietary restrictions because foods rich in vitamin K—such as spinach, mustard greens, collards, and beets—alter warfarin's therapeutic levels. Patients are often instructed to watch their diet closely to maintain therapeutic levels of warfarin.

aPTT: activated partial thromboplastin time

LMWH: low-molecular-weight heparin

Warfarin can cross the placental barrier, and it may cause serious birth defects in the fetus, including abnormal fetal bone formation and hemorrhagic disorder; therefore, it is contraindicated during pregnancy. By inducing the depression of protein C synthesis, warfarin may cause side effects (although rarely) that range from skin necrosis to frank infarction of breast, intestine, and extremities (4).

Reversal of warfarin. Vitamin K administered orally or subcutaneously is the preferred way to achieve warfarin reversal. Intravenous (IV) administration is effective but is associated with adverse effects, such as anaphylaxis, and hypersensitivity reactions, such as facial flushing, diaphoresis, chest pain, hypotension, and dyspnea (14). Therefore, the IV route is to be used only when other routes are not feasible and the risk is justified (15). Rapid reversal in the setting of bleeding may be achieved through administration of vitamin K along with fresh frozen plasma or prothrombin complex concentrates and recombinant factor VIIa (16).

Tecarfarin (AT 5923)

Tecarfarin (AT 5923) is a selective inhibitor of the VKOR enzyme and is referred to as a VKOR inhibitor. Tecarfarin is metabolized through the esterase pathway rather than through CYP450 and thus does not exhibit drug-drug interactions. The drug is identical to warfarin with regard to pharmacokinetics but not to pharmacodynamics. Tecarfarin's effectiveness is measured the same way that warfarin's is measured: through the use of INR. A Phase II/III trial [EmbraceAC (CLN-505)] failed to prove tecarfarin superiority over warfarin as measured by time in the therapeutic range (17). This drug is not approved for clinical use.

ORAL HEPARINS

Heparin produces its anticoagulant effect indirectly by binding with antithrombin and forming a protease inhibitory complex. The effectiveness of orally administered heparin has been limited by its lack of oral bioavailability. Heparin's high negative ionic charge creates repulsion with the negatively charged epithelial tissue and thus interferes with its absorption (18). This was overcome through the use of a SNAC delivery system. SNAC is a synthetic amino acid that aids in heparin absorption after oral administration. This carrier dissociates from heparin in circulation, allowing for its anticoagulant effect (19). Studies performed on healthy individuals demonstrated that activated partial thromboplastin time (aPTT) elevation could be achieved with oral heparin dosing (18). However, a large follow-up study (PROTECT) did not demonstrate superiority of oral heparin over subcutaneous enoxaparin in reducing the deep-vein thrombosis (DVT) rate as detected by bilateral ascending contrast venography at day 27–30. This result likely resulted from a suboptimal dosage form and a poor-tasting liquid formulation. This study provided proof of concept that heparin delivered by the oral route had potent antithrombotic activity (20). Delivery systems also have been developed for low-molecular-weight heparins (LMWHs). *N*-(8-{2-hydroxybenzoyl}amino) decanoate has been studied to facilitate absorption of LMWHs from

the gastrointestinal tract. Deoxycholic acid conjugated with LMWH has been studied in rats (21, 22).

Concerns regarding side effects, including heparin-induced thrombocytopenia, remain with the oral formulations of heparin. No oral heparin formulations are currently available for clinical use.

VTE: venous thromboembolism

FACTOR Xa AND FACTOR IIa INHIBITORS

Following the success of heparin and warfarin, multiple parenterally administered anticoagulants were approved for various indications; some of these (argatroban, bivalirudin, and lepirudin) were to replace heparin in heparin-compromised patients such as those with heparin-induced thrombocytopenia and congenital deficiency of antithrombin. Oral formulations of direct factor Xa and thrombin inhibitors are being developed. These drugs offer significant improvement over VKAs by having a more predictable anticoagulant response and by not requiring monitoring to measure effective anticoagulation. They have a relatively faster onset of action, and there is no need for overlap with a parenteral agent when initiating treatment or thromboprophylaxis. Most of these agents have short half-lives, and it has been hypothesized that there is no need for an antidote (**Table 1**). Another advantage of these newer oral anticoagulants is the absence of rebound thrombin generation, which can occur following withdrawal of unfractionated heparin, LMWH, and VKAs. Rebound thrombin generation may give rise to thrombin levels that are significantly greater than before and during treatment, leading to exaggerated reactivation of the coagulation system (23, 24). This may lead to a hypercoagulable state and, consequently, thrombus formation.

At this time, several factor Xa and factor IIa inhibitors are being tested in clinical trials. The three drugs that are the most advanced, from a clinical development standpoint, are dabigatran and rivaroxaban (approved in the EU and the United States) and apixaban (approved in the EU). One such agent that has already been withdrawn from the market is ximelagatran (**Figure 2**).

DIRECT THROMBIN INHIBITORS

Ximelagatran

Ximelagatran (Exanta™, AstraZeneca)—ethyl 2-[[(1R)-1-cyclohexyl-2-[(2S)-2-[[4-[(Z)-N′-hydroxycarbamimidoyl]phenyl]methylcarbamoyl]azetidin-1-yl]-2-oxoethyl]amino]acetate—was the first of the oral direct thrombin inhibitor drugs to be used clinically. It has a dipeptidomimetic domain mimicking the region of fibrinopeptide A that interacts with the active site of thrombin and blocks the enzyme's interaction with its substrates. Melagatran had poor bioavailability, so ximelagatran was designed with an ester and a hydroxyl group attached to melagatran. This design made ximelagatran lipophilic and improved its absorption in the intestine, giving it a bioavailability of ~20%. Through the use of a CYP-independent liver enzyme system, ximelagatran is converted to its active form melagatran. Melagatran has a half-life of approximately 4–5 h (25). It required twice-daily dosing and did not require anticoagulant monitoring or dose adjustment.

Ximelagatran was studied in a Phase III program for venous thromboembolism (VTE) prevention and treatment and was found to be superior or equivalent to warfarin in terms of efficacy (26, 27). Ximelagatran did not receive approval by the FDA but was approved in other countries for short-term post orthopedic thromboprophylaxis. Long-term data with ximelagatran revealed liver enzyme elevations of approximately 6%. Rebound hypercoagulability after withdrawal of ximelagatran also was reported (23). In February 2006, ximelagatran was withdrawn from the market.

Dabigatran

K_i: inhibition constant

IC_{50}: concentration necessary to inhibit 50% of generated thrombin

ECT: ecarin clotting time

AUC: area under the curve

Dabigatran etexilate (Pradaxa®, Boehringer Ingelheim)—β-alanine N-[[2-[[[4-[[[(hexyloxy)carbonyl]amino]iminomethyl]phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-, ethyl ester, methanesulfonate)—is the double prodrug for the active form of dabigatran, i.e., beta-alanine N-[[2-[[[4-(aminoiminomethyl)phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl. Dabigatran etexilate is a reversible, competitive, direct thrombin inhibitor that has been approved recently in the United States for stroke prevention in atrial fibrillation. The approved dosage is 150 mg given orally twice daily for patients with CrCl > 30 ml min^{-1} and 75 mg given orally twice daily for patients with CrCl between 15 and 30 ml min^{-1} (28).

Pharmacokinetics and pharmacodynamics. Dabigatran is a peptidomimetic thrombin inhibitor. It is strongly basic and permanently charged at physiologic pH and therefore very hydrophilic (29). Consequently, it has poor intestinal absorption after oral dosing and a bioavailability of approximately 6%. The double prodrug requires ester cleavage to be transformed into its active form, resulting in a reduced number of drug-drug interactions and interindividual differences as esterases have high catalytic capacity and low substrate specificity (29). CYP enzymes or other oxidoreductases are not involved in the proteolytic reactions that convert dabigatran etexilate to dabigatran. Dabigatran etexilate's inhibition constant (K_i) is 4.5 nmol $liter^{-1}$, and the concentration necessary to inhibit 50% of generated thrombin (IC_{50}) is 0.56 μmol $liter^{-1}$ (30). Peak plasma concentrations are reached within 2 h of oral administration, and the half-life is approximately 8 h after a single dose, ranging from 12–17 h after multiple doses in healthy volunteers and patients undergoing total hip replacement surgery (31, 32). Steady-state concentration is achieved after approximately 3 days with multiple doses (33). The percentage of dabigatran bound to plasma proteins is approximately 35%, and the extent of protein binding does not depend on dabigatran plasma concentration (29). Because dabigatran follows first-order distribution kinetics, the distribution volume, plasma clearance, and elimination half-life are independent of administered dosage (34).

Renal excretion is the predominant elimination pathway of dabigatran; more than 80% of systemically available dabigatran is eliminated unchanged, and a small fraction undergoes biotransformation into glucuronide conjugates. This may be of significance as renal function declines with age and may be associated with prolonged elimination (29). The plasma concentration of the drug declines in a biexponential manner, incorporating a slow terminal elimination and maintaining therapeutic concentrations for 24-h periods (33).

Monitoring. Validated methods for monitoring dabigatran are not available currently. Increases in ecarin clotting time (ECT) and INR are linearly related to dabigatran concentration. ECT is considered a better measure to evaluate anticoagulant response (34, 35). This may become clinically relevant in cases of hemorrhage or therapeutic failure. Other global anticoagulant assays such as aPTT are not used for monitoring dabigatran etexilate.

Drug and food interaction. Because dabigatran is not metabolized by CYP, it has a better profile regarding drug interaction in comparison with VKAs. However, dabigatran is a substrate of efflux transporter P-glycoprotein that is involved in the transport of many drugs (28, 36). The exposure to dabigatran is reduced in the presence of drugs such as rifampicin that use this transporter (**Table 1**). Coadministration with atorvastatin reduces the area under the curve (AUC) of dabigatran by 18%, but this has been found to be of no clinical relevance (37). Coadministration with

other blood thinners such as clopidogrel, ticlopidine, glycoprotein IIb/IIIa inhibitors, and nonsteroidal anti-inflammatory drugs increases the risk of bleeding (28). The time to peak circulating concentration of dabigatran is delayed by a high-fat, high-caloric diet, but no difference in the extent of absorption has been noted in comparison with a fasting state. The maximum plasma concentration and AUC remain unchanged (37).

Adverse effects and reversal. The most common side effects noted in the pivotal RE-LY study were bleeding and gastrointestinal effects such as dyspepsia, nausea, upper abdominal pain, gastrointestinal hemorrhage, and diarrhea. In the RE-LY study, the overall risk for major bleeding was similar with dabigatran and warfarin treatment. A trend toward a higher incidence of bleeding with dabigatran (hazard ratio 1.2, 95% confidence interval: 1.0 to 1.4) for patients ≥75 years of age was observed. There also was a higher incidence of gastrointestinal adverse reactions (35% versus 24% on warfarin) in older patients treated with dabigatran (28). Hypersensitivity also may occur in some cases.

There are currently no available antidotes for dabigatran overdose or complications leading to hemorrhage. Blood products (fresh frozen plasma) remain the mainstay of treatment in case of bleeding associated with dabigatran. Maintaining adequate diuresis is necessary, and dialysis may be attempted because dabigatran does not have significant protein binding. The data for this approach are limited. Measurement of aPTT and ECT may be recommended in such situations (28).

AZD 0837

AZD 0837 (AstraZeneca) is an oral anticoagulant that is rapidly absorbed and metabolized from its prodrug form into its active form AR-H067637, which is a selective and reversible direct thrombin inhibitor. An intermediate metabolite AR-H69927 is formed in its bioconversion through a two-step process. The terminal elimination half-lives of AZD 0837 and AR-H69927 are approximately 2–3 h. The K_i of AZD 0837 is 2–4 nM, and the IC_{50} is 0.6 μM (38). This drug currently is being investigated in Phase II clinical trials.

FACTOR Xa INHIBITORS

Rivaroxaban

Rivaroxaban (Xarelto®, Bayer/Johnson & Johnson) (5-chloro-N-(((5S)-2-oxo-3-(4-(3-oxomorpholin-4-yl)phenyl)-1,3-oxazolidin-5-yl)methyl)thiophene-2-carboxamide) is an oral, direct, competitive inhibitor of factor Xa. It is approved in the United States, Canada, and Europe for VTE prophylaxis after orthopedic surgery. The dosage is 10 mg to be administered 6–10 h after surgery provided hemostasis has been established. It is to be used with caution in patients with CrCl in the range of 15–30 ml min^{-1} owing to an increased risk of bleeding. It is contraindicated in patients with CrCl < 15 ml min^{-1}, in patients with hepatic disease associated with coagulopathy, and in patients below 18 years of age due to lack of data (39).

Pharmacokinetics and pharmacodynamics. Rivaroxaban inhibits factor Xa in a concentration-dependent manner (K_i, 0.4 nmol $liter^{-1}$), with rapid [kinetic association rate constant (k_{on}), 1.7×10^7 mol $liter^{-1}$ s^{-1}] and reversible [kinetic dissociation rate constant (k_{off}), 5×10^{-3} s^{-1}] binding (40, 41). Factor Xa is at the convergence of both the extrinsic and intrinsic pathways; therefore, rivaroxaban inhibits thrombin generation via both pathways (42). Rivaroxaban

competitively inhibits factor Xa by >10,000-fold selectivity compared with relevant serine proteases such as thrombin, trypsin, and activated protein C (40) and may have the ability to inhibit clot-bound factor Xa (43). The bioavailability of rivaroxaban is high (>80%), with the maximum concentration occurring 2–4 h after oral intake (44). It is extensively bound (~90%) to plasma proteins, and its maximum plasma concentration is dose dependent (44, 45). The half-life is 5–9 h (44), and the kidneys excrete 66% of the orally ingested drug (46). Other modes of excretion include fecal elimination and hepatic metabolism primarily via CYP isozyme 3A4 (47). These factors lead to an increased AUC in the elderly population (>75 years of age) as well as an increased half-life (**Table 1**).

Monitoring. Rivaroxaban was not monitored with any clotting assays in clinical trials, although it is known to affect aPTT, PT, and HEPTEST®. PT prolongation due to rivaroxaban correlates with the drug's plasma concentration and its inhibition of factor Xa activity (44). However, accuracy and validation of monitoring rivaroxaban by PT have not been established. No effect on ECT has been demonstrated (48).

Drug and food interactions. Rivaroxaban is metabolized by CYP3A4-, CYP2J2-, and CYP-independent mechanisms prior to elimination. Rivaroxaban also is a substrate for P-glycoprotein transporters. These properties subject it to a wide variety of drug interactions. It is contraindicated in patients receiving HIV-protease inhibitors and antimycotics ("-azole" drugs) owing to their strong inhibition of both CYP3A4 and P-glycoprotein. The antibiotic rifampicin is a strong inducer of P-glycoprotein and also CYP3A4. Thus coadministration of rifampicin (600 mg once daily) results in a shorter elimination half-life of rivaroxaban and 50% lower plasma AUC (39), and its concomitant use with rivaroxaban is therefore cautioned. The anticoagulant effect of rivaroxaban, measured by PT, was not influenced by clopidogrel or aspirin alone or in combination (49). No significant differences in plasma concentration profiles, PT prolongation, or inhibition of factor Xa activity were noted after coadministration with ranitidine (50). St. John's Wort, used for depression, is known to be an inducer of CYP3A4 and P-glycoprotein (51), and its concomitant use with rivaroxaban is cautioned.

Rivaroxaban may be taken with or without food (39); however, it has resulted in delayed time to maximum concentration and higher AUC in subjects who were fed compared with those who fasted (52). Maximum PT prolongation was smaller and delayed by 1.5 h, and the maximum inhibition of Factor Xa activity was slightly lower as well (43).

Adverse effects and reversal. The safety profile was assessed using three Phase III studies that involved 4,571 patients exposed to rivaroxaban for orthopedic surgeries. These studies revealed adverse events in 14% of the treated patients. Bleeding and anemia were expected side effects. Nausea, increased gamma-glutamyl transferase, and increased transaminases also were documented (39). Elevation of alanine aminotransferase to greater than 3 times the normal limit occurred in 1.9–4.3% of patients on rivaroxaban in comparison with 21.6% in the enoxaparin-warfarin group during the ODIXa-DVT study (53).

Other less common adverse events included tachycardia, syncope, pruritis, pain in extremities, and hypotension. Abnormality in hepatic function was reported in rare cases (39).

Only recombinant factor VIIa has been studied as a method of reversing rivaroxaban-induced anticoagulation. Anticoagulation is partially reversed as measured by bleeding time, PT prolongation, and other clotting assays, without affecting factor Xa inhibition (54, 55).

Apixaban

Apixaban (Pfizer/Bristol-Myers Squibb)—(1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide)—is a direct, reversible, competitive, selective inhibitor of factor Xa with >30,000-fold selectivity over other coagulation proteases (56, 57). It is a follow-on molecule to razaxaban (discontinued during development on the basis of pharmacologic properties) (58) with an improved pharmacokinetic profile (59). Apixaban is in various stages of clinical trials for different indications, including stroke prevention in atrial fibrillation (60) and VTE prevention in hip and knee replacement patients (61).

Pharmacokinetics and pharmacodynamics. In vitro experiments for apixaban using platelet-poor plasma from healthy volunteers demonstrate that it is a potent and highly selective inhibitor of free factor Xa ($K_i = 0.08$ nM) with minimal affinity ($K_i \sim 3$ μM) for thrombin, plasma kallikrein, and chymotrypsin. Negligible affinity for trypsin and other tested serine proteases was found (57). Apixaban's IC_{50} value is 329 nM (59), and the volume of distribution in animal models was small (30–50%). This is thought to arise from limited extravascular tissue distribution and not from extensive plasma-protein binding. The bound fraction is approximately 87% in humans (62).

Apixaban is well absorbed from the intestinal tract and achieves a peak plasma concentration in approximately 3 h. The effective half-life is 8–11 h when given twice daily and 12–15 h when given once daily (63). Steady-state concentration is achieved by day 3 with modest accumulation. The elimination of apixaban involves multiple pathways. It is metabolized mainly by O-demethylation, forming a phenol metabolite using the CYP3A4 system (62). Apixaban is subject to drug interactions with other drugs that induce or inhibit CYP3A4.

Monitoring. Apixaban shows a concentration-dependent effect in factor Xa–mediated assays. Dose-dependent mild prolongation in INR and aPTT is also seen. Apixaban has no effect on human platelet aggregation (63). Modest changes are seen in PT assays modified for more sensitivity to the effects of direct-acting factor Xa inhibitors; however, these assays are not useful for clinical monitoring of apixaban (64).

Drug and food interactions. Potent inhibitors of CYP3A4, such as ketoconazole, are recommended to be avoided or at least stopped 14 days prior to the use of apixaban because significant changes in pharmacokinetics have been demonstrated with concomitant use (64). Moderate inhibitors of CYP3A4, such as selective serotonin reuptake inhibitors, diltiazem, and cimetidine, are to be used with caution.

High-fat, high-calorie meals have no effect on the absorption of apixaban (65). Moreover, medications that alter gastric pH are not likely to affect its absorption on the basis of its physical-chemical properties (66).

Adverse effects and reversal. As expected with antithrombotic drugs, bleeding is the primary concern with apixaban. Coadministration with antiplatelet agents has led to a clear increase in major bleeding and clinically relevant nonmajor bleeding (67). Because reversal agents are not available, supportive treatment is suggested for bleeding. Blood products may be necessary to reverse acute hemorrhage under certain circumstances.

Other Factor Xa Inhibitors in Development

Numerous other oral factor Xa inhibitors are under various stages of investigation. Edoxaban (DU-176b, Daiichi Sankyo) is in the advanced stages of its clinical development. It is a competitive

inhibitor of factor Xa and displays 10,000-fold selectivity for factor Xa relative to inhibition of thrombin (68). Because of the high selectivity, it suppresses factor Xa bound to the prothrombinase complex (69). The time to maximum plasma concentration is 1–1.5 h with a plasma half-life of 8.6–10.7 h (70). Elimination is mainly renal, and bleeding is the main adverse event noted with administration.

TAK 442 (Takeda) is another factor Xa inhibitor that has been proven to have good oral bioavailability. It has a time to maximum plasma concentration of 1–2 h and an elimination half-life of 9–12 h after 6 days of dosing (71).

Betrixaban (Portola) is an oral, direct, competitive inhibitor of factor Xa, with a long half-life (20 h) and mostly biliary clearance (<5% renal clearance). It has been investigated in VTE prophylaxis in total knee replacement patients with favorable results (72).

YM 150 (Astellas Pharma) is an oral factor Xa inhibitor being tested for VTE prevention in orthopedic surgery patients (73). Another factor Xa inhibitor, LY 517717, has been tested in a Phase II study for VTE prevention in hip or knee replacement patients (74). Many other factor Xa inhibitors and combined factor Xa/thrombin inhibitors are in various stages of clinical development.

All the new factor Xa inhibitor drugs have differences regarding their pharmacokinetic and pharmacodynamic profiles. As such, they may become useful in different clinical indications or in special populations such as patients with renal or liver dysfunction.

DISCUSSION

The clinical development of new anticoagulant drugs has followed the conventional path of first usage in the postsurgical (orthopedic hip or knee replacement) prophylaxis of VTE. Initially, these drugs are compared with the heparins, including LMWHs, and conventional oral anticoagulants, such as warfarin, in the prevention of DVT after orthopedic surgery. Thereafter, these drugs are evaluated in medical indications, including treatment of VTE, treatment of acute coronary syndrome (ACS), and prevention of stroke in atrial fibrillation. Additional indications include cancer-associated thrombosis and management of heparin- and warfarin-compromised patients.

Table 2 provides a summary of the relevant clinical trials on apixaban, rivaroxaban, dabigatran, and edoxaban in the following areas: postsurgical prophylaxis of DVT, DVT treatment, ACS, and atrial fibrillation. On the basis of the DVT prophylaxis trials, dabigatran, rivaroxaban, and apixaban have been approved for the prophylaxis of DVT in orthopedic surgery patients in the European community. Dabigatran has been approved in the United States for stroke prevention in atrial fibrillation (75). Edoxaban has been approved in Japan for atrial fibrillation. The studies in ACS have been less successful; associated bleeding complications resulted in the premature termination of several trials. Although comparable at the optimized dosages for the prophylaxis of DVT, these drugs behave differently in different indications, as can be projected from the differences in their pharmacologic profiles (**Table 1**).

Similar to other new classes of drugs, the factor Xa and thrombin inhibitors are used cautiously in various clinical settings and watched closely for both effectiveness and side effects. The new oral anticoagulants add to the pharmacologic agents currently available. On the basis of methods of clearance, the indications for use in special populations, such as liver or kidney disease patients, may be addressed. This way of addressing the need for anticoagulation in case of hepatic or renal impairment, however, does not address the unmet need for anticoagulation in other special populations such as pregnant patients, children, and patients with prosthetic heart valves. With the approval of multiple oral anticoagulants targeting factor Xa and thrombin, the question becomes whether these new drugs are interchangeable with one another. Moreover, could substitution be

Table 2 A summary of completed and ongoing trials for various anticoagulants

Agent	Postsurgical prophylaxis of DVT	DVT treatment	Atrial fibrillation	ACS
Apixaban				
	APROPOS (78)	Botticelli DVT dose-ranging study (82)	A Phase IIb, randomized, partially blind (open-label warfarin), active-controlled (warfarin), multicenter study to evaluate the safety and efficacy in 2 doses of apixaban in comparison with warfarin, administered for 12 weeks in subjects with NVAF (unpublished) (85)	APPRAISE-1 (67)
	ADVANCE-1 (79)	AMPLIFY (ongoing) (83)	ARISTOTLE (unpublished; full results of the trial will be presented August 28 at the European Society of Cardiology Congress 2011) (86)	APPRAISE-2 (study terminated because of bleeding) (87)
	ADVANCE-2 (80)	AMPLIFY-EXT (ongoing) (84)	AVERROES (60)	APPRAISE Japan (study terminated) (88)
	ADVANCE-3 (81)			
Rivaroxaban[a]				
	ODIXa-KNEE (89)	EINSTEIN-DVT (95)	ROCKET-AF (98)	ATLAS ACS-TIMI 46 (100)
	ODIXa-HIP (90)	EINSTEIN-EXT (96)	ROCKET-J (completed) (99)	ATLAS ACS-TIMI 51 (completed) (101)
	RECORD-1 (91)	EINSTEIN-PE (ongoing) (97)		
	RECORD-2 (92)			
	RECORD-3 (93)			
	RECORD-4 (94)			
Dabigatran[b]				
	RE-MODEL (102)	RE-COVER (106)	RE-LY (109)	RE-DEEM (unpublished) (110)
	RE-MOBILIZE (103)	RE-MEDY (ongoing) (107)		
	RE-NOVATE (104)	RE-SONATE (unpublished) (108)		
	RE-NOVATE 2 (unpublished) (105)			

(*Continued*)

Table 2 (*Continued*)

Agent	Postsurgical prophylaxis of DVT	DVT treatment	Atrial fibrillation	ACS
Edoxaban[c]				
	Oral direct factor Xa inhibition with edoxaban for thromboprophylaxis after elective total hip replacement: a randomized double-blind dose-response study (111)	The Edoxaban Hokusai-VTE Study (ongoing) (117)	Randomized, parallel-group, multicenter, multinational Phase II study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation (118)	
	STARS J-1 (112)		ENGAGE AF-TIMI 48 (119)	
	STARS J-2 (completed June 2009; unpublished) (113)		Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with NVAF (120)	
	STARS E-3 (completed Feb. 2010; unpublished) (114)			
	STARS J-4 (completed Feb. 2010; unpublished) (115)			
	STARS J-5 (completed March 2010; unpublished) (116)			

[a]Rivaroxaban is approved in the European community for the prophylaxis of DVT after orthopedic surgery.
[b]Dabigatran is approved in the United States for the management of atrial fibrillation.
[c]Edoxaban is approved by the Japanese authority for atrial fibrillation.
Abbreviations: ACS, acute coronary syndrome; DVT, deep-vein thrombosis; NVAF, nonvalvular atrial fibrillation; VTE, venous thromboembolism.

done within this class of medication, and how would bridging be established when changing the class of medication?

If given the option, is one of the new oral anticoagulants better than the other? There is some evidence to suggest that factor Xa inhibitors incompletely block thrombin generation and that small levels of existing thrombin can potentially maintain hemostasis (56) and activate the protein C system, augmenting the antithrombotic potential. In vitro assay analysis suggests that factor Xa is progressively inhibited over a much wider concentration range than thrombin and thereby may have a wider therapeutic window than a thrombin inhibitor (76). Moreover, in animal models, dabigatran (a direct thrombin inhibitor) was proven to have anti-inflammatory and antifibrotic effects (77). As with warfarin, these drugs may be subject to genetic variations among individuals, but at this time there is minimal information.

These new oral anticoagulants have been designed on a one-size-fits-all basis. Therefore, the need for monitoring has been neither suggested nor addressed. However, this is of prime concern with regard to safety and in clinical situations such as toxicity and therapeutic failure. Furthermore, there is a lack of reversal agents for these new anticoagulants. Supportive treatment with blood products is the only option currently available. Moreover, both factor Xa and thrombin mediate several regulatory functions in the vasculature, and sustained inhibition of these enzymes may result in physiologic compromise of these functions.

In conclusion, the new oral anticoagulants are the drugs that will shape the future of anticoagulation. The acceptance of these medications among physicians and patients is expected to rise as they become more versed with the indications, side effect profiles, drug and food interactions, and toxicities. The concerns regarding lack of monitoring and reversal agents will need to be addressed if the acceptance of these medications is to be increased. As the current clinical trials with the new oral anticoagulants do not compare these drugs with all the indications for warfarin use, warfarin use most likely will continue for some time to come.

SUMMARY POINTS

1. The introduction of new oral anticoagulants such as dabigatran, rivaroxaban, apixaban, and edoxaban provides a spectrum of alternate pharmacologic agents that can be used for the long-term outpatient management of thrombosis and related disorders.
2. As the indications for the new oral anticoagulants expand, the use of warfarin is expected to decrease because of its narrow therapeutic index and interindividual response variations and because it requires frequent monitoring.
3. These medications may help provide further understanding of the coagulation cascade and its interaction with other pathophysiologic processes such as inflammation and cell-mediated occlusive events.
4. The requirement of oral anticoagulants continues to pose challenges in special populations such as children, pregnant patients, cancer patients, and patients with prosthetic heart valves. Lack of reversal agents is also of significant concern.
5. At this time, only a limited amount of data is available on the pharmacodynamic interactions of these agents. Additional information on drug-drug interactions, population pharmacokinetic/pharmacodynamic responses, and prolonged outcome analysis in various indications can be obtained only after postmarketing surveillance.
6. The cost of these medications may be contributing to the slow rate of acceptance. However, the introduction of multiple oral anticoagulants and the increased usage may drive the cost down.
7. The future will reveal any challenges that these new drugs may pose as well as additional information about their pharmacologic effects and modulatory actions on thrombogenesis and vascular responses.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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NOTE ADDED IN PROOF

Since the completion of this manuscript, rivaroxaban has been approved by the FDA for DVT prophylaxis in postsurgical hip and knee replacement patients and for stroke prevention in atrial fibrillation patients. Two studies that focused on prophylaxis of DVT in acutely medically ill patients, namely ADOPT (apixaban) and MAGELLAN (rivaroxaban), have also been completed. In addition, there have been reports of safety issues related to dabigatran in special patient populations that are being reviewed by various regulatory agencies. The Japanese authorities issued an advisory regarding the bleeding risk with dabigatran in elderly patients. Finally, there are continuous discussions among health care professionals pertaining to the monitoring, neutralization, and food and drug interactions of the newer agents. There is a need for further pharmacologic and toxicologic information to optimize use in expanded indications.

Annual Review of Pharmacology and Toxicology

Volume 52, 2012

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Errata

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