# Changing Practice of Anticoagulation: Will Target-Specific Anticoagulants Replace Warfarin?

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## Keywords

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## Abstract

The target-specific oral anticoagulants are a class of agents that inhibit factor Xa or thrombin. They are effective and safe compared to warfarin for the prevention of stroke and systemic embolism in patients with atrial fibrillation and for the treatment of venous thromboembolism, and they are comparable to low-molecular-weight heparin for thromboprophylaxis after hip or knee arthroplasty. For other indications, however, such as the prevention of stroke in patients with mechanical heart valves, initial studies have been unfavorable for the newer agents, leaving warfarin the anticoagulant of choice. Further studies are needed before the target-specific anticoagulants can be recommended for patients with cancer-associated thrombosis or heparin-induced thrombocytopenia. Concerns also persist about difficulties with the laboratory assessment of anticoagulant effect and the lack of a specific reversal agent. For these reasons, we anticipate that the vitamin K antagonists will continue to be important anticoagulants for years to come.

## INTRODUCTION

**AF:** atrial fibrillation

**INR:** international normalized ratio

**PCC:** prothrombin complex concentrate

The vitamin K antagonists (VKAs), such as warfarin, dicumarol, and similar agents, were the only oral anticoagulants available for more than half a century, until recently. In 2010, dabigatran, a thrombin-specific inhibitor, received approval by the US Food and Drug Administration (FDA) for the prevention of thromboembolic complications in patients with atrial fibrillation (AF). Rivaroxaban and apixaban, two factor Xa–specific inhibitors, followed soon after, with FDA approvals for AF in 2011 and 2012, respectively. Subsequently, rivaroxaban and dabigatran received approval for the treatment of venous thromboembolic disease, and rivaroxaban and apixaban received approval for thromboprophylaxis following major orthopedic surgery.

As a class, the VKAs exhibit a narrow therapeutic index, and regular laboratory monitoring is necessary to achieve optimal efficacy (prevention of thromboembolism) and safety (avoidance of hemorrhagic complications). Diet and the use of other medications, including many complementary or alternative medications, can dramatically influence the response to warfarin. As a result of the difficulties surrounding laboratory management and the bleeding risk associated with the VKAs, many patients who had an appropriate indication for anticoagulation were treated with antiplatelet therapy or simply not at all. These limitations of the VKAs, combined with the market recognition that the number of patients who would benefit from chronic anticoagulant therapy is substantial, have driven the search for safe, effective alternative therapies.

The introduction of these new agents has fueled considerable speculation that "the king [warfarin] is dead" (1). However, for a variety of reasons, the target-specific anticoagulants are unlikely to completely replace the use of the VKAs, and broad substitution of target-specific anticoagulants for warfarin in unselected groups of patients has resulted in adverse outcomes. We anticipate that although the target-specific anticoagulants will ultimately become the primary choice for most clinical indications, many patients will continue to be best served with an inexpensive, multi-target anticoagulant such as warfarin.

## TARGET-SPECIFIC ORAL ANTICOAGULANTS

The VKAs exert their anticoagulant effect by interfering with the vitamin K–dependent post-translational γ-carboxylation of coagulation factors VII, IX, X, and II (**Figure 1**). This results in dysfunctional proteins that are unable to localize through calcium ions to negatively charged membrane surfaces. As the functional zymogen levels drop, there is a gradual prolongation of the prothrombin time. When converted to the international normalized ratio (INR) to correct for reagent differences, this test is used to monitor the anticoagulant effect of the VKAs. An excess of warfarin results in an elevated INR and an increased risk for hemorrhage. The incidence of major bleeding into gastrointestinal, genitourinary, or soft tissue sites is estimated at 6.5% per year, whereas the incidence of fatal bleeding is ~1% per year (2). Reversal strategies for warfarin therapy include oral or intravenous vitamin K, which exerts its effect over a 24-h time period (3), or prothrombin complex concentrates (PCCs), which provide rapid reversal over a 15- to 30-min time period through replacement of deficient proteins. Efficacy of vitamin K for reversal of warfarin coagulopathy is highly variable, depending on the dose (1–10 mg) and route of administration (intravenous or oral), whereas efficacy of PCCs has been shown to be more complete and predictable in clinical trials (76–85%) (4).

The concept of a target-specific anticoagulant was first demonstrated with the development of the parenteral direct thrombin inhibitors lepirudin and argatroban. These agents have no effect on the synthesis of the specific factors but specifically block coagulant activity once the inactive zymogen (prothrombin) is converted to the active proteinase (thrombin). Though effective as

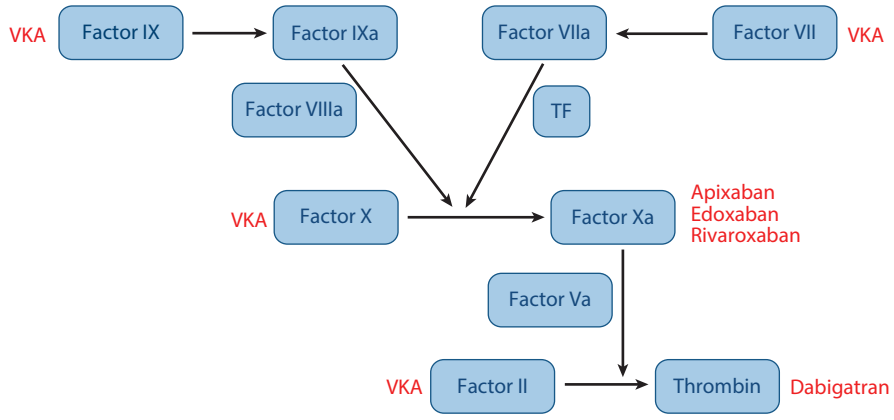


**Figure 1**

Therapeutic targets of oral anticoagulants. Vitamin K antagonists decrease the circulating levels of the zymogens factor VII, factor IX, factor X, and factor II. These agents have no inhibitory effect on the activated factors. In contrast, the factor Xa–specific inhibitors (apixaban, edoxaban, and rivaroxaban) inhibit the serine proteinase factor Xa, and the direct thrombin inhibitor (dabigatran) inhibits the serine proteinase thrombin. These target-specific anticoagulants have no known effect on circulating levels of the zymogens. Abbreviations: VKA, vitamin K antagonist; TF, tissue factor.

anticoagulants, the parenteral direct thrombin inhibitors are primarily used in patients with heparin-induced thrombocytopenia (HIT). The subsequent development of fondaparinux demonstrated that targeted inhibition of factor Xa could also provide an anticoagulant effect for the prevention and treatment of arterial thrombosis. Conceptually, inhibiting at the level of factor Xa has been attractive; this strategy would prevent thrombin formation by targeting the "gatekeeper" of coagulation (5).

The oral target-specific anticoagulants were developed based on the knowledge of the crystal structures of thrombin and factor Xa (6), as well as the sequence specificity of the substrate cleavage sites. Dabigatran targets the active site of thrombin, whereas rivaroxaban, apixaban, and edoxaban target the active site of factor Xa (**Table 1**). In contrast to therapy with warfarin or other VKAs, laboratory monitoring is typically not required for the target-specific anticoagulants. However, if bleeding should occur, there are currently no agents available that can actively reverse the anticoagulant effect of these agents. This issue of reversibility is discussed further below.

The following sections discuss the clinical areas where the target-specific oral anticoagulants have been approved for use, followed by a discussion of those indications where these agents may have limited efficacy or utility. We then review special situations (selected indications, monitoring, reversal, and cost) where warfarin therapy retains some potential clinical advantages.

## APPROVED CLINICAL INDICATIONS

### Atrial Fibrillation

**HIT:** heparin-induced thrombocytopenia

Atrial fibrillation is the most common sustained cardiac arrhythmia; an estimated one-fourth of individuals aged 40 years or older develop AF during their lifetime (7). In the absence of thromboprophylaxis, the risk of ischemic stroke in patients with nonrheumatic AF has been estimated to be approximately 5% per year. Until recently, the primary antithrombotic strategy for patients with

**Table 1 Oral anticoagulant agents (adapted from References 5, 50, 68)**

| | Warfarin | Dabigatran etexilate | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|---|
| **Target** | VKOR | Thrombin | Factor Xa | Factor Xa | Factor Xa |
| **Bioavailability** | >95% | 6.5% | 80% | 66% | 50% |
| **Time to peak effect** | 4–5 days | 2 h | 2–3 h | 1–2 h | 1–2 h |
| **Half-life** | 40 h | 12–14 h | 7–13 h | 8–13 h | 5–11 h |
| **Laboratory monitoring** | Required | No | No | No | No |
| **Elimination** | Hepatic | 80% renal, 20% hepatobiliary | 67% renal (30% inactive), 33% hepatobiliary | 25% renal, 75% hepatobiliary | 35% renal, 65% hepatobiliary |
| **Interactions** | CYP 2C9, 3A4, and 1A2 | Potent P-gp inhibitors and inducers | Strong dual CYP 3A4 and P-gp inhibitors/ inducers | Strong dual CYP 3A4 and P-gp inhibitors/ inducers | P-gp |
| **Antidote** | Yes | No | No | No | No |
| **Approved clinical indications:** | | | | | |
| **Atrial fibrillation** | Yes | Yes | Yes | Yes | Phase III studies |
| **VTE prophylaxis** | Yes | Phase III studies | Yes | Phase III studies | Phase III studies |
| **VTE treatment** | Yes | Yes | Yes | Phase III studies | Phase III studies |

Abbreviations: VKOR, vitamin K epoxide reductase; VTE, venous thromboembolism; P-gp, P-glycoprotein.

AF has been the use of VKAs, which has been shown to decrease the risk of death by one-fourth and the risk of nonfatal stroke by two-thirds (7).

All of the target-specific anticoagulants have been studied in patients with AF (**Table 1**) (8–11). The target population included patients with a $CHADS_2$ score of 2 or above, indicating an increased risk for stroke in the absence of anticoagulant therapy. In each study, the target-specific anticoagulant was noninferior to warfarin in the prevention of stroke and systemic embolism. Although the quality of warfarin management, as judged by the time in therapeutic range with the INR, varied between the studies (e.g., 55% to 64.9%), subsequent analyses showed that the antithrombotic efficacy of the target-specific agents was comparable to the best-managed patients on a VKA (e.g., centers with an average time in therapeutic range of >72.6%) (12).

**$CHADS_2$:** A scoring system for predicting thromboembolic risk in patients with atrial fibrillation, giving points for congestive heart failure (1), hypertension (1), age >75 years (1), diabetes mellitus (1), and prior stroke or transient ischemic attack (2). The higher the $CHADS_2$ score, the greater the risk for thromboembolic events

Hemorrhagic complications were either similar or decreased in comparison to warfarin, and all of the target-specific agents exhibited a decreased risk for intracranial hemorrhage. In contrast, gastrointestinal hemorrhage was increased for patients treated with dabigatran (11) or rivaroxaban (8) as compared to warfarin. Patients with renal insufficiency (typically, a creatinine clearance of <25–30 ml per minute), concomitant dual antiplatelet therapy, and hemodynamically significant mitral stenosis were excluded from these studies. The 2014 AHA/ACC/HRS Guideline recommends oral anticoagulant therapy for patients with nonvalvular AF and prior stroke, transient ischemic attack, or a $CHA_2DS_2$-VASc score of 2 or greater, with therapeutic options including warfarin (target INR 2–3), dabigatran, rivaroxaban, or apixaban (13).

## Venous Thromboembolism: Prophylaxis

Total hip and total knee arthroplasties are being performed with increasing frequency, with almost 200,000 hip replacement procedures each year (14). The risk for venous thromboembolism (VTE) with these procedures is among the highest for all surgical subspecialties, but multiple studies have

shown that this risk can be effectively and safely decreased with a variety of thromboprophylactic approaches. Until recently, the primary agent for these patients was low-molecular-weight heparin (LMWH), although VKAs, aspirin, and nonpharmacologic strategies have also been endorsed by some in the field.

Each of the target-specific oral anticoagulants shown in **Table 1** has been studied for thromboprophylaxis in patients undergoing total hip or knee replacement surgery (15–19). All were effective in preventing VTE postoperatively, with similar risks of major bleeding. Currently, rivaroxaban is the only target-specific oral anticoagulant approved in the United States for the prevention of VTE after hip arthroplasty and total knee arthroplasty. Because of a small increase in the risk of bleeding associated with the use of rivaroxaban, the American College of Chest Physicians recommended LMWH as the preferred pharmacologic treatment for patients undergoing hip or knee arthroplasty (14).

Rivaroxaban and apixaban have also been studied as thromboprophylactic agents in acutely ill medical patients (20, 21). Both of these studies compared an extended course of the target-specific oral anticoagulant (~30 to 35 days) with a standard course of therapy with enoxaparin. During the standard course of therapy, VTE rates were similar for the target-specific anticoagulants and enoxaparin. During the extended course of therapy, however, patients who had completed the parenteral therapy arm had a higher rate of VTE than patients who continued on the oral agents, a difference that was significant for the rivaroxaban study (21). Both studies had an increased risk of bleeding in patients taking the target-specific anticoagulants compared to the patients taking enoxaparin. Presently, none of these agents have been approved in the United States for thromboprophylaxis of medically ill patients.

**$CHA_2DS_2$-VASc:** A scoring system for predicting thromboembolic risk in patients with atrial fibrillation, giving points for congestive heart failure (1), hypertension (1), age >75 years (2), diabetes mellitus (1), prior stroke or transient ischemic attack (2), vascular disease (1), age 65–75 years (1), and sex (1)

**VTE:** venous thromboembolism

**LMWH:** low-molecular-weight heparin

## Venous Thromboembolism: Treatment

Venous thromboembolism is the third leading cause of vascular death, with an annual incidence of nearly 1% in persons aged 80 years or older. The approach to treatment for several decades has involved bridging anticoagulation therapy from a parenteral anticoagulant—typically unfractionated heparin or LMWH, both of which have a rapid onset of action (minutes to hours, respectively)—to a VKA, which has a slower onset of action (days; **Table 1**). In addition, this transition, and ongoing therapy with the VKA, needs to be monitored by the INR. The target-specific oral anticoagulants, with their rapid onset of action and no requirement for laboratory monitoring, provide several opportunities to improve the treatment of VTE.

All four of the target-specific oral anticoagulants shown in **Table 1** have been compared to VKAs in the treatment of acute VTE (22–26). All of the studies were prospective randomized noninferiority trials. The studies with dabigatran (24), apixaban (25), and edoxaban (26) were double blind, whereas the studies with rivaroxaban (22, 23) were open label. The studies with dabigatran and edoxaban initiated the patient on parenteral anticoagulation (heparin or LMWH) and then switched to the respective target-specific anticoagulant after five days of therapy, whereas the studies with rivaroxaban and apixaban started the patient directly on the oral agent, with no required initial parenteral anticoagulation. All of the studies met the primary endpoint, achieving noninferiority when compared to standard therapy. Hemorrhagic complications, particularly intracranial hemorrhage, were less frequent with the target-specific anticoagulants, with the exception of gastrointestinal bleeding, which was most notably increased with dabigatran. Currently, dabigatran and rivaroxaban have been approved for the treatment of patients with VTE (**Table 1**) in the United States.

Current guidelines from the American College of Chest Physicians recommend that individuals with unprovoked VTE should be considered for a longer course of therapy than the standard

three months if they have a low or moderate bleeding risk (27). Dabigatran (28), rivaroxaban (22), and apixaban (29) have been studied for their ability to decrease the risk for recurrent VTE after completion of an initial course of anticoagulant therapy (e.g., three to six months). When administered at the standard therapeutic dose, all three effectively decrease the risk of recurrent VTE compared to placebo, but this is associated with an increased risk for hemorrhagic complications. Apixaban was also studied at a lower dose (2.5 mg twice daily) that was also effective at decreasing the risk of recurrent VTE and did not increase hemorrhage risk (29).

## ONE SIZE DOES NOT FIT ALL: LIMITATIONS OF TARGET-SPECIFIC AGENTS

The target-specific oral anticoagulants should, in principle, readily substitute for warfarin and LMWH in a wide variety of clinical indications. In certain clinical settings, however, emerging clinical and in vitro data suggest that selective or targeted inhibition of individual proteases may not be biologically comparable to inhibition of multiple proteases in coagulation. In the OASIS-5 clinical trial comparing enoxaparin to fondaparinux (30), it was noted that fondaparinux, a highly selective factor Xa inhibitor, was associated with higher rates of catheter-associated thrombosis than was enoxaparin, a LMWH with broader substrate specificity (31). Subsequent studies have shown that catheter-mediated thrombosis is caused by contact pathway activation, a pathway inhibited by heparin and dose-dependently by enoxaparin but not by fondaparinux (32).

To what extent the selective agents can be substituted for warfarin and/or LMWH in other special populations, such as those with mechanical valves, malignancy, HIT, renal disease, hepatic disease, and/or pregnancy, remains to be seen. Given the unique predisposition to thrombosis and/or bleeding risk in each of these various subpopulations, it is unlikely that large prospective studies of these agents will be conducted in the near future. This section reviews available data on the use of these target-specific agents in specialized patient populations.

### Mechanical Valves

The overall incidence of prosthetic valve thrombosis is estimated at ~0.4% without anticoagulation and 0.1% with warfarin therapy (33). The risk of valve thrombosis varies by anatomic site (mitral > aortic) and type of prosthesis (caged ball > tilting disc = bileaflet valves). The efficacy of target-specific agents for prevention of mechanical valve thrombosis was recently tested in a phase II clinical trial (RE-ALIGN) comparing dabigatran to warfarin. This trial was terminated prematurely because of increased thromboembolic and bleeding complications in patients treated with dabigatran. In this study of 252 patients treated with dabigatran (n = 168) or warfarin (n = 84), 9% of patients treated with dabigatran as compared to 5% of patients on warfarin experienced thromboembolic complications; the majority of thromboses occurred in the first 90 days after valve placement. Bleeding complications were also increased in the dabigatran group as compared to warfarin (27% versus 12%; HR 2.45, 95% CI 1.23–4.86, p = 0.01) (34). Although some elements of the clinical design of the trial could explain these adverse outcomes (35), the occurrence of transient ischemic attack or stroke in 12 of 15 patients despite high-dose dabigatran (220 or 300 mg twice daily) suggests an incomplete antithrombotic effect, perhaps owing to a single rather than a multi-targeted inhibitory effect of dabigatran.

### Cancer-Associated Thrombosis

Low-molecular-weight heparins are now the mainstay of therapy for the long-term management of cancer-associated thrombosis (36). However, LMWH use in cancer patients remains challenging.

Even with therapeutic dosing, VTE patients with cancer experience higher rates of recurrent thrombosis and bleeding complications than those without cancer (37). For many cancer patients, the daily parenteral administration and/or high treatment costs of LMWHs make these agents less appealing for long-term use.

The newer agents are attractive for use in patients with cancer because they are orally administered and do not require monitoring. However, there are a number of concerns about the use of these agents in cancer patients. Patients with cancer suffer from a variety of gastrointestinal problems, including vomiting, mucositis, and diarrhea, which impact drug delivery and absorption. Cancer patients can also have deranged hepatic and/or renal function that may lead to altered drug metabolism and clearance. Finally, drug–drug interactions between the target-specific inhibitors and some commonly used chemotherapy and/or hormonal therapies can lead to unpredictable pharmacokinetics (36).

Only one small phase II study has examined the tolerability and safety of target-specific agents in patients with cancer. Levine et al. (38) conducted a randomized placebo-controlled pilot study in cancer patients without thrombosis using apixaban at three doses (5, 10, and 20 mg). All patients had advanced malignancy and were on active chemotherapy (chemotherapy was initiated within six weeks of starting anticoagulation). There were no fatal bleeding events, but major bleeding was slightly higher (6.3%) in the high-dose apixaban arm compared to patients treated with placebo (3.4%). There were 3 VTE events in placebo-treated patients as compared to 1 deep venous thrombosis in the 20-mg apixaban-treated cohort. There were no significant adverse events. Although the cohorts were small, this study suggests that apixaban is generally tolerable and not associated with significant complications.

To date, there have been no prospective trials on the efficacy of target-specific oral anticoagulants in cancer-associated VTE. A post hoc meta-analysis of cancer subpopulations enrolled in three randomized controlled trials in VTE and AF ($n = 550$) indicates similar outcomes among patients treated with these agents and LMWH/warfarin therapy. Bleeding risk could not be adequately addressed in this post hoc analysis owing to lack of study data (39).

Given the paucity of data on the safety and efficacy of target-specific oral anticoagulants in cancer-associated thrombosis, current guidelines by the American Society of Clinical Oncology (ASCO) (40) and the International Society of Thrombosis and Haemostasis (41) do not advise use of target-specific agents in the management of cancer-associated thrombosis.

## Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia is a transient, immune-mediated prothrombotic disorder caused by antibodies that recognize a platelet protein, platelet factor 4 (PF4), in complex with heparin or LMWH. The thrombotic manifestations of HIT are attributed to antibody-mediated platelet and cellular activation culminating in thrombin generation. Once HIT is diagnosed, current guidelines recommend treatment with parenteral nonheparin anticoagulants (danaparoid, bivalirudin, or argatroban) with overlap of warfarin therapy once platelet counts are in the normal range (42). In vitro studies have shown that dabigatran and rivaroxaban have no cross-reactivity with PF4/heparin antibodies and can theoretically be used for treatment of HIT (43). A prospective single-arm multi-center trial of rivaroxaban treatment of suspected or confirmed HIT is planned (43), but as yet, there are no published data on the safety or efficacy of the target-specific agents in HIT. Given the lack of published data and the significant morbidity associated with thrombotic disease (44), we would not recommend treatment with the target-specific oral anticoagulants in patients with acute or symptomatic HIT.

## Renal Disease

**eGFR:** estimated glomerular filtration rate

The target-specific oral anticoagulants are contraindicated for use in patients with renal failure. Renal excretion is the predominant route of clearance for dabigatran and contributes variably to clearance of the factor Xa inhibitors (see **Table 1**). Although patients with severe renal impairment were excluded from clinical trials, significant numbers of patients with moderate (eGFR 30–49 ml/min) and mild (eGFR 50–79 ml/min) renal insufficiency were enrolled in the AF and VTE trials. A meta-analysis of ~40,000 patients with mild or moderate renal insufficiency enrolled in 10 clinical trials was recently reported (45). Of ~22,000 patients treated with one of the target-specific oral agents (dabigatran, rivaroxaban, and apixaban), 16,000 had mild and ~6,000 had moderate renal insufficiency. Surprisingly, patients treated with target-specific anticoagulants had lower rates of major or clinically relevant nonmajor bleeding as compared to patients on conventional agents, whether they had mild renal insufficiency (4.8% versus 5.5%, OR 0.81, 95% CI 0.72–0.90) or moderate renal insufficiency (6.8% versus 7.6%, OR 0.82, 95% CI 0.59–1.14). No significant differences in bleeding rates were observed among the three target-specific anticoagulants studied. As well, treatment with target-specific anticoagulants in both renal groups was associated with reduced thromboembolic complications. Although this post hoc analysis of trial data in renal patients is reassuring, clinicians are advised to use these agents judiciously in patients with renal disease until guidelines for monitoring and reversal agents become available.

## Pregnancy and Breast Feeding

There are currently no data in humans on the safe use of target-specific agents in pregnancy. An ex vivo perfusion study using human placenta showed significant transplacental passage of rivaroxaban but not dabigatran (46). Animal studies reported by the manufacturers of dabigatran and rivaroxaban have shown that both agents cause increased fetal loss and maternal hemorrhage; both are therefore listed as category C in pregnancy (no human data; adverse outcomes in animal studies) (47, 48). Rodent studies of apixaban, however, showed no significant maternal or fetal complications with increased maternal bleeding (49). For this reason, apixaban is given a category B indication in pregnancy. In humans, it is not known if the target-specific agents are excreted into milk; in rats, both apixaban and rivaroxaban can be detected in milk.

## Hepatic Disease

Known significant liver disease was an exclusionary criterion for participation in most of the large phase III clinical trials. In general, the target-specific oral anticoagulants should not be used in patients with severe hepatic insufficiency, particularly in patients with hepatic disease associated with coagulopathy (50).

## Pediatric Patients

With the exception of case reports (51), studies on the use of the target-specific oral anticoagulants in pediatric patient populations have not been reported.

# SPECIAL ISSUES WITH THE TARGET-SPECIFIC ANTICOAGULANTS

## Laboratory Monitoring

Warfarin and the other VKAs are narrow-therapeutic-index drugs, and clinical laboratory monitoring is essential for their effective and safe use. Although the target-specific oral anticoagulants do not require laboratory monitoring, there are clinical situations when a validated laboratory

assessment of anticoagulant effect would be valuable. The prothrombin time and activated partial thromboplastin time are variably affected by these agents, however, limiting their utility in assessing anticoagulant effect. Dabigatran is best detected by the thrombin time, which is quite sensitive to the presence of this agent. A dilute thrombin time or an ecarin clotting time can be used to measure dabigatran over a broad range of concentrations (52). For the factor Xa inhibitors, anti-factor Xa chromogenic assays with appropriate calibrators provide sensitive and specific assays for measuring drug concentrations (53, 54). For all of the target-specific anticoagulants, laboratory measurements need to be interpreted in relation to timing of drug administration and its pharmacokinetics. As noted in **Table 1**, the time to peak effect is 1–3 h, followed by a relatively rapid decline in activity.

Recently, the RE-LY investigators evaluated the effect of dabigatran plasma concentrations on the frequency of ischemic stroke and major bleeding in patients with AF (55). They found that these outcomes were correlated with dabigatran concentrations, with age being the most important covariate. These results suggest that the ability to quantitatively assess drug levels in individual patients, in addition to considering selected patient characteristics, may improve clinical outcomes.

## Anticoagulant Reversal

Presently, there are no effective agents to reverse bleeding complications in patients treated with the target-specific anticoagulants. Difficulties with use of existing reversal agents include lack of substrate-containing replacement product, inability of current products to antagonize or inactivate target-specific drugs, and limited correlative data on the relationship between laboratory parameters, drug levels, and bleeding risk. The reader is referred to a recent comprehensive review on this topic (56).

Attempts to use conventional agents, such as fresh frozen plasma (FFP) or prothrombin complex concentrates (three- or four-factor PCCs), for reversal of target-specific agents are predicated on studies showing that higher levels of zymogen proteins contained in FFP or PCCs enhance thrombin generation in vitro. Although activated PCCs, which contain mostly activated factor VII, and recombinant activated factor VII have been shown to be more potent prothrombotic agents in certain clinical settings, the activity of both these agents is proximal to factor X inhibition and therefore theoretically no more advantageous than therapies such as PCCs. To date, animal studies using various conventional reversal strategies have shown that these agents exert variable effects on laboratory parameters, depending on the doses and animal models used, and do not uniformly reverse bleeding complications. Human studies of anticoagulant reversal have been largely limited to studies examining the impact of reversal agents on laboratory parameters (57) and case reports documenting both successful (58–60) and unsuccessful outcomes (60).

Specific antidotes for target-specific agents are currently under development and hold promise for the future. A humanized antibody fragment (Fab) against dabigatran (aDabi-Fab) with high affinity for dabigatran (~350 times greater than dabigatran affinity for thrombin) reverses the anticoagulant effects of dabigatran both in vitro (61) and in a rat tail bleeding model (62). Andexanet alpha (PRT064445) is a recombinant human factor Xa protein under development as a universal reversal agent for treatment of bleeding caused by both target-specific and indirect (antithrombin-dependent) factor Xa inhibitors. This recombinant human protein lacks catalytic activity and the membrane-binding $\gamma$-carboxyglutamic acid domain of native factor Xa, but it serves as a substrate decoy for factor Xa inhibitors. In preclinical studies, andexanet fully reversed bleeding complications due to enoxaparin and fondaparinux and restored hemostasis in rabbits with rivaroxaban-induced bleeding (63). In a recent phase II trial, andexanet showed dose-dependent,

partial reversal of rivaroxaban-induced anti-factor Xa activity and thrombin generation as well as global clotting assays (prothrombin time and activated clotting time) (64).

## Cost

In the United States, the average wholesale acquisition costs for a 30-day supply are $349.99 for dabigatran, $1,030.86 for rivaroxaban, and $349.99 for apixaban (**http://www.lexi.com/**). Although several analyses indicate that the target-specific agents may be cost-effective alternatives to warfarin therapy (65, 66), other studies suggest that cost comparisons are highly sensitive to patient characteristics (including age, duration of therapy, and comorbidities) and the center's average time in therapeutic range (67). Additional cost considerations that affect the choice of warfarin over the newer agents in the United States include variability in insurance coverage and high copayments. For some patients, VKAs will remain more cost effective than the newer therapies.

### SUMMARY POINTS

1. Target-specific oral anticoagulants have been developed as alternatives to the vitamin K antagonists (VKAs). These include agents that directly inhibit thrombin (dabigatran) and factor Xa (rivaroxaban, apixaban, and edoxaban).
2. The target-specific agents have been shown to be safe and effective in the treatment of patients with atrial fibrillation and venous thromboembolism, and in the prevention of venous thromboembolism in patients undergoing hip or knee arthroplasty.
3. Target-specific agents are contraindicated in patients with mechanical heart valves, based on findings of increased thromboembolic events and hemorrhagic complications in patients treated with dabigatran.
4. The target-specific anticoagulants have not been studied sufficiently in patients with cancer-associated thrombosis or acute heparin-induced thrombocytopenia to recommend their use in these clinical situations.
5. The target-specific anticoagulants should be used with caution in patients with renal insufficiency or severe liver disease.
6. Laboratory assessment of the anticoagulant effect of the target-specific anticoagulants can be useful in certain clinical settings (e.g., hemorrhagic complications, recurrent thromboembolic events).
7. Specific reversal agents are currently not available for the target-specific anticoagulants.

## DISCLOSURE STATEMENT

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