Management of Warfarin Therapy

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Warfarin, a vitamin K antagonist, has been approved for use as an anticoagulant for nearly 60 years. It is not only the most commonly used oral anticoagulant in the United States, but it also ranks among the top 40 most commonly used medications in nonhospitalized adult patients. Although warfarin is prescribed frequently, it is not viewed favorably due to its complicated management.

In fact, a recent study showed that more than 10% of patients treated with warfarin discontinued therapy within 3 months and nearly 20% were not monitored during therapy. This is alarming, considering that inappropriate use or insufficient monitoring of warfarin can result in serious thromboembolic or hemorrhagic events. The Institute for Safe Medication Practices has deemed warfarin a high-alert medication as a result of its risk for causing patient harm when used in error.

This review discusses the complicated nature of warfarin therapy, including its extensive monitoring requirements and significant adverse events (AEs), as well as emerging alternatives to this therapy.

Pharmacology and Pharmacokinetics
Warfarin inhibits the γ-carboxylation of the vitamin K-dependent coagulation factors II, VII, IX, and X, as well as the anticoagulant proteins C and S. Although warfarin is absorbed rapidly after oral administration, its therapeutic effect is delayed for a week or more due to the long half-lives of factors II, IX, and X. Compared with other vitamin K-dependent coagulation factors, such as factor II, which has a 50-hour half-life, factor VII has a much shorter half-life (approximately 6 hours), which results in elevation of the prothrombin time (PT) shortly after administration. Clinicians must use caution because this early elevation does not reflect a full
Anticoagulant effect. Additionally, protein C has a half-life of 8 hours; thus, hypercoagulability may result.

Unfortunately, a number of pharmacokinetic drug interactions occur with warfarin because it is highly bound to plasma proteins and metabolized via the cytochrome P450 (CYP) enzyme system. Different CYP enzymes are responsible for the metabolism of the 2 warfarin enantiomers. The more potent S-enantiomer is metabolized by CYP2C9 and the R-enantiomer by CYP1A2, CYP2C19, and CYP3A4.

**Indications**

The anticoagulant properties of warfarin are useful in multiple clinical situations, including primary and secondary prophylaxis of venous thromboembolism (VTE), prevention of systemic embolism and stroke in patients with prosthetic heart valves or atrial fibrillation (AF), and, in some patients, secondary myocardial infarction (MI) prophylaxis. The American College of Chest Physicians (ACCP) 2012 Practice Guidelines on antithrombotic and thrombolytic therapy provide an in-depth review of these indications as well as chapters on the management of warfarin and other oral anticoagulants.

**Primary VTE Prevention**

Primary prevention of VTE is most commonly required for hospitalized patients, especially those with prolonged immobilization, cancer, thrombophilia, or a history of VTE. Typically, heparin, a low-molecular-weight heparin (LMWH), or the injectable factor Xa inhibitor fondaparinux (Arixtra, GlaxoSmithKline) is recommended for nonsurgical patients. However, warfarin is a potential option for patients undergoing orthopedic surgery, according to the most recent ACCP guidelines.

Warfarin may be continued up to 35 days after such surgery. Low-dose (sometimes referred to as mini-dose) warfarin has been used to prevent clotting of central catheters in patients with cancer, but this is no longer recommended.

**Secondary VTE Prevention**

Warfarin commonly is used for secondary prevention of VTE in patients who have a deep vein thrombosis (DVT) or pulmonary embolism (PE). The purpose of anticoagulation in this situation is 2-fold: minimizing expansion of the current embolus and reducing the risk for recurrent events. Warfarin should be initiated at the time of diagnosis and continued for a minimum of 3 months. Patients with VTE initially should receive heparin, LMWH, or fondaparinux with warfarin due to the delayed anticoagulant properties of warfarin. These agents should be overlapped for at least 5 days and until the international normalized ratio (INR) is at least 2.0 for 24 hours. Patients who have a reversible risk factor for VTE (eg, an extended period of immobilization) may discontinue therapy after 3 months (provided the risk factor has been eliminated), whereas patients without a known risk factor should be considered for a longer treatment duration.

**Atrial Fibrillation**

Patients with AF are at risk for systemic embolism and stroke. The risk for stroke in a patient with AF commonly is determined using the Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke (doubled) (CHADS2) score. This risk stratification tool assigns 2 points to patients with prior stroke or transient ischemic attack (TIA) and 1 point for each of the following: heart failure, hypertension, diabetes, and age 75 years or older.

The 2006 American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC) guidelines for AF recommend that patients with 1 moderate-risk factor receive either aspirin or warfarin and those with a high-risk factor or those with more than 1 moderate-risk factor receive warfarin (risk factors, Table 1). The ACCP guidelines recommend an oral anticoagulant (warfarin or dabigatran [Pradaxa, Boehringer Ingelheim]) for patients with a CHADS2 score of 1 or more. Lifelong therapy is recommended unless the patient develops contraindications.

**Myocardial Infarction**

Antiplatelet therapy is typically recommended over warfarin therapy for most patients who have had an MI; however, some patients may benefit from warfarin in combination with antiplatelet agents. The ACCP guidelines recommend that patients with an anterior MI and left ventricular thrombus (or those at high risk for thrombus) be given antiplatelet agents with warfarin.

**Prosthetic Heart Valves**

Anticoagulant therapy initially is recommended for most patients with prosthetic heart valves; however, patients with an aortic bioprosthetic valve may be managed with aspirin. In patients with newly placed mechanical valves, heparin or LMWH may be given with warfarin until the warfarin reaches a therapeutic level. Anticoagulation with warfarin also is recommended for some patients with mitral valve disease.

**Dosing and Monitoring**

**Initiation of Therapy**

Several factors complicate the initiation of warfarin therapy. First, consideration must be given to the fact that vitamin K-dependent clotting factors are not immediately depleted. Therefore, when an immediate anticoagulant effect is desired, therapy with heparin, LMWH, or fondaparinux must be overlapped with warfarin. Additional consideration must be given to the fact that there is great interpatient and intrapatient variability in response to warfarin. Thus, no clear-cut initial dose is suitable for every patient.

Much research effort has been directed at predicting dosing requirements for individual patients. Factors such as age, gender, body size, vitamin K intake, and concomitant medications or disease states affect warfarin requirements, and these should be taken into consideration.
when choosing an initial dose.\(^{33}\) Recently, pharmacogenomic studies have revealed that variant alleles of the genes for CYP2C9, which is responsible for the metabolism of the S-isomer of warfarin, and vitamin K epoxide reductase (VKOR), a target site for warfarin’s action, both lower warfarin dose requirements.\(^{20,21}\)

Multiple studies have compared a 5-mg initial warfarin dose with a variety of other regimens, including a 2.5- or 10-mg initial dose or a dose calculated on patient-specific parameters, such as age. A 2003 publication by Kovacs et al concluded that a 10-mg initial dose resulted in more rapid achievement of a therapeutic INR compared with a 5-mg dose.\(^{22}\) However, 2 early studies comparing 5- and 10-mg doses concluded that a 5-mg dose of warfarin more effectively achieved therapeutic INRs than a 10-mg dose,\(^{23,24}\) and a recent systematic review concluded that an initial dose of 10 mg has no benefit over 5 mg.\(^{17}\) The ACCP guidelines suggest initial warfarin doses between 5 and 10 mg are appropriate, but lower initial doses can be considered in elderly individuals and in patients with heart failure, liver disease, poor nutritional status, and in those at high risk for bleeding.\(^{3}\) For healthy outpatients, a 10-mg dose for 2 days is recommended.\(^{25}\) One cohort study revealed that older women require the lowest warfarin doses and that a 5-mg dose of warfarin will result in excessive anticoagulation in more than 80% of this population; thus, a lower initial dose should be chosen for patients in this group.\(^{26}\) Concomitant medications that may alter sensitivity to warfarin or increase the risk for bleeding also should be considered when choosing an initial dose.\(^{3}\) Wittkowski et al found that more than 80% of patients prescribed warfarin were receiving concomitant therapy with a potentially interacting drug.\(^{27}\) This study was conducted with data from a pharmacy claims database and may underestimate the true potential for drug interactions because nonprescription medications, including herbal products and supplements, were not identified. Thus, a thorough medication history must be collected at therapy initiation.

In 2007, the FDA recommended incorporation of pharmacogenetic information in the warfarin labeling.\(^{28}\) The prescribing information was updated again in 2010 with more specific dosing information for VKORC1 and CYP2C9 genotypes.\(^{29}\) However, pharmacogenetic testing is not required, and studies on the utility of pharmacogenetic dosing algorithms have been conflicting.\(^{30,31}\) One recent study compared 2 pharmacogenetic warfarin dosing algorithms with standard care and found improved time in therapeutic range and a reduction in serious AEs with the pharmacogenetic algorithms.\(^{32}\) Pharmacogenetic testing is not used frequently in clinical practice today, and is not routinely recommended in the ACCP guidelines. However, programs are being developed. For example, the University of Illinois Hospital and Health Sciences System developed a coordinated, genotype-guided dosing and management approach for patients newly initiating warfarin to potentially improve warfarin dosing and safety.

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ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; ESC, European Society of Cardiology; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack

Based on reference 12.

Ongoing research in this area will better define the role of pharmacogenetic testing in patients receiving warfarin therapy.\(^{25}\)

**Monitoring and Dosage Adjustment**

Monitoring of PT is used to determine the appropriate maintenance dose of warfarin for a specific patient.\(^{33}\) The PT level is a marker of the reduction in factors II, VII, and X. Because PT is not standardized, it is converted to a standard measure and reported as the INR. Typically, an INR of 2.0 to 3.0 is considered appropriate for most indications. A higher INR goal of 2.5 to 3.5 is recommended for some patients with prosthetic heart valves.\(^{25}\)

Monitoring should be initiated within the first few days of therapy (in hospitalized patients, the INR often is obtained daily after the second or third dose), and subsequent doses should be adjusted as needed.\(^{3}\) A 2008 consensus statement from The Anticoagulation Forum recommended monitoring 2 or 3 times weekly for the first 7 to 10 days or until a stable INR and dose are reached.\(^{34}\) Algorithms and computer programs are available to assist in adjusting maintenance doses to sustain an INR in the therapeutic range. Illness, medication changes, and alterations in diet may affect warfarin requirements, and clinicians should remain vigilant for circumstances necessitating more frequent monitoring or dosage adjustments. Patient adherence to the medication regimen also must be closely monitored. Individuals who achieve a stable INR are generally monitored every 4 weeks, but the 2012 ACCP guidelines suggest this interval can be extended to every 12 weeks in patients who have consistently stable INRs.\(^{25}\)

Generally, the weekly warfarin dose may be adjusted to correct INR measurements outside of the therapeutic range. In some cases in which the INR is minimally outside of the desired range or a causative factor for the alteration is identified, it may be appropriate to merely increase the frequency of monitoring, with the assumption that the INR will return to the therapeutic range without a dosage adjustment.\(^{25,33}\) Options other than dosage adjustment for patients with supratherapeutic

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**Table 1. ACC/AHA/ESC Stroke Risk Factors for Patients With AF**

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ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; ESC, European Society of Cardiology; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack

Based on reference 12.
INRs include holding a dose or doses of warfarin or administering vitamin K. A recent randomized trial comparing 1.25 mg of vitamin K with placebo for non-bleeding patients with supratherapeutic INRs of 4.5 to 10 found no differences in bleeding or thromboembolism between groups. This study supports the recommendation that vitamin K often is unnecessary for patients with mild to moderate supratherapeutic INRs. The ACCP guidelines do not routinely recommend vitamin K administration for patients with INRs of 10 or less but suggest that vitamin K be administered orally to patients with INRs greater than 10, even if there is no evidence of bleeding.

Patients with an isolated subtherapeutic INR have a low risk for thromboembolism and administration of a rapid-acting anticoagulant rarely is necessary.

Warfarin monitoring can be conducted by the prescriber in his or her individual practice; however, evidence suggests that patients who receive warfarin monitoring at an anticoagulation clinic or through a designated anticoagulation monitoring service have better outcomes. A 2006 systematic review showed that patients managed in community practice spent 8.3% less time in therapeutic range than patients managed in an anticoagulation clinic. Pharmacist-managed anticoagulation clinics also have been shown to improve outcomes. One study found that patients managed by a pharmacist-run anticoagulation clinic not only spent more time in therapeutic range than patients managed by their physician but also had fewer thromboembolic events and less bleeding.

**Perioperative Management**

Warfarin often is discontinued before a major surgical procedure to minimize the risk for bleeding. Unfortunately, it must be discontinued several days in advance of any surgical procedure to allow regeneration of coagulation factors. The ACCP guidelines recommend that warfarin be discontinued 5 days prior to surgical intervention. Therapy may be resumed 12 to 24 hours after the procedure. Patients with elevated INRs at the time of the procedure may require vitamin K administration.

Heparin or LMWH often is used to provide perioperative anticoagulation while warfarin therapy is held (a process called bridging). Bridging is recommended for patients with a history of VTE, AF, or mechanical valves, unless they are at low risk for thromboembolism. Low-risk patients are defined in Table 2.

**Adverse Effects**

**Bleeding Complications**

Bleeding is the primary AE associated with warfarin therapy. In clinical trials, the risk for major bleeding has been reported to increase by 0.3% to 0.5% per year in patients treated with warfarin compared with those not receiving anticoagulation therapy. Risk factors for bleeding include use of concomitant medications affecting coagulation, patient characteristics (eg, age, concomitant disease states), and the intensity and duration of anticoagulation therapy. IV vitamin K (5-10 mg) should be administered to all patients with clinically significant bleeding. The subcutaneous route is not recommended because of variable absorption, and the intramuscular route should be avoided because it is associated with hematoma at the administration site. Vitamin K alone is insufficient for patients with serious or life-threatening bleeding. Options for additional therapy include fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), or recombinant factor VIIa. FFP contains clotting factors that are necessary to replete those inhibited by warfarin; however, disadvantages of FFP treatment include a long infusion time and risk for fluid overload. The use of PCCs may be advantageous for some patients. PCCs are derived from plasma and contain varying concentrations of factors II, VII, IX, and X. Individualized dosing of PCCs based on INR and body weight is recommended.

The PCCs available in the United States (Bebulin VH, Baxter; Profilnine SD, Grifols) lack factor VII activity; however, CSL Behring is seeking FDA approval for a 4-factor product. The updated ACCP guidelines recommend the use of a 4-factor PCC in patients with warfarin-related bleeding. Recombinant factor VIIa (NovoSeven, NovoSeven RT, NovoNordisk) was a recommended option in the 2008 ACCP guidelines; however, a 2008 review of the literature recommended against use of this agent because of a lack of quality evidence in favor of its use. A more recent retrospective study showed an improved time to therapeutic INR with the use of factor VIIa in patients receiving warfarin with a traumatic intracranial hemorrhage but did not show improved survival.

**Other Adverse Events**

Warfarin is associated with AEs other than hemorrhage, the most significant of which are thrombotic complications that typically occur early after therapy initiation. Skin necrosis may occur as a result of hypercoagulability caused by a rapid decline in protein C levels. Patients typically present with thrombosis of capillaries and venules in subcutaneous tissue. If this situation develops, an alternative anticoagulant may be required; however, some patients may receive another trial of warfarin initiated at a very low dose.

**Warfarin Alternatives**

Only recently have viable oral alternatives to warfarin emerged. These agents are direct inhibitors of either thrombin or factor Xa. They do not require INR monitoring and offer a faster onset and more predictable response than warfarin.

**Dabigatran Etexilate**

Dabigatran etexilate is a prodrug of dabigatran, which directly inhibits thrombin (factor IIa). It is FDA-approved to reduce the risk for stroke in patients with AF. Parenteral direct thrombin inhibitors such as...
bivalirudin (Angiomax, The Medicines Company) and argatroban (GlaxoSmithKline) have been available for some time, but dabigatran is the first oral agent available in the United States. (Ximelagatran did not reach the US market due to hepatotoxicity associated with its use.)

A Phase III open-label noninferiority trial known as RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) compared dabigatran at a dose of either 110 or 150 mg twice daily with warfarin adjusted to maintain an INR of 2.0 to 3.0 in patients with AF who were at risk for stroke.50 The primary efficacy outcome was occurrence of stroke or systemic embolism; major hemorrhage was the primary safety outcome. The rate of stroke or systemic embolism was 1.69% per year with warfarin compared with 1.53% and 1.11% per year with dabigatran 110 and 150 mg, respectively. Dabigatran was deemed noninferior to warfarin. Major bleeding was lower in patients receiving dabigatran 110 mg (2.71% per year), but the rates of major bleeding were similar for the 150-mg dose (3.11% per year) and warfarin (3.36% per year). Dyspepsia was the most common AE reported with dabigatran.

The ACCP guidelines for anticoagulation prefer dabigatran to warfarin when anticoagulation is indicated in patients with AF.51 In February 2011, the ACC/AHA/Heart Rhythm Society (HRS) released an update to the AF guidelines, recommending dabigatran as a warfarin alternative.51 The recommendation is specific to patients with paroxysmal or permanent AF who have additional risk factors for stroke but do not have a prosthetic valve or hemodynamically unstable valve disease. Patients with severe renal or liver disease are not candidates for dabigatran, and the guideline cautions that patients who are well controlled on warfarin will receive little benefit from a switch to dabigatran therapy.

The recommended dose of dabigatran for patients with AF and normal renal function is 150 mg twice daily.49 The dose must be reduced in patients with renal dysfunction; the recommended dose is 75 mg twice daily in patients with a creatinine clearance of 15 to 30 mL per minute. The prescribing information for dabigatran provides detailed information on how to change from or to warfarin and from or to parenteral anticoagulants.

Dabigatran etexilate is a substrate for P-glycoprotein.49 Therefore, concomitant administration with drugs known to induce this enzyme may result in lower serum concentrations of dabigatran and generally should be avoided. P-glycoprotein inhibitors may cause increased dabigatran serum concentrations; however, pharmacokinetic studies with ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin revealed that no dose adjustments are necessary when dabigatran is used with these agents.

Dabigatran also has been studied for the prevention and treatment of VTE, but it is not approved for these indications.52-56 Post-marketing safety concerns with dabigatran include bleeding and MI. Data from the RE-LY trial indicated that the annual rate of MI was higher in the dabigatran groups (0.72% for the 110-mg group [P=0.07] and 0.74% for the 150-mg group [P=0.048]) compared with warfarin (0.53%).50 A meta-analysis that examined the risk for MI in clinical data from RE-LY as well as trials investigating dabigatran for other indications also was published recently.57 Overall, 30,514 patients in 7 trials were included. Dabigatran was associated with a significantly higher risk for MI and acute coronary syndrome (ACS) (1.19% with dabigatran vs 0.79% with control; odds ratio, 1.33; 95% confidence interval, 1.03-1.71; P=0.03). The authors of this analysis concluded that dabigatran was associated with an increased risk for MI or ACS compared with agents such as warfarin, enoxaparin, and placebo. However, this meta-analysis is not without limitations. The trials included in the meta-analysis involved a variety of dabigatran doses, both lower and higher than the FDA-approved dosage. Also, the patients included in this analysis had indications for treatment other than AF, which could present different inherent risk factors for MI and ACS when compared with AF patients.

RE-LY demonstrated similar bleeding rates with warfarin and dabigatran, with the exception of an increased incidence of major gastrointestinal bleeds in dabigatran-treated patients and an increased risk for intracranial bleeding in warfarin-treated patients.50 In December 2011, the FDA announced that it would be evaluating post-marketing reports of serious bleeding events in patients taking dabigatran.56 The aim of this evaluation is to determine whether dabigatran-related bleeding is occurring at rates higher than that observed in the RE-LY trial. Until further information is available, the FDA states that dabigatran may be safely used according to the package labeling.

### Rivaroxaban

Rivaroxaban (Xarelto, Janssen) is an oral factor Xa inhibitor that is FDA-approved for the prevention of DVT in patients who are undergoing knee or hip replacement surgery, the prevention of stroke in patients with
nonvalvular AF, and the treatment of acute DVT and PE and prevention of their recurrence.59 Four Phase III trials (RECORD 1, 2, 3, and 4) compared rivaroxaban 10-mg once daily to enoxaparin in patients undergoing hip or knee replacement surgery and found a reduced risk for a composite primary end point that included death, DVT, or PE.60-63 No statistically significant difference in major bleeding rates was seen between the enoxaparin- and rivaroxaban-treated patients. Rivaroxaban should be initiated 6 to 10 hours postoperatively and continued for 12 days in patients who have undergone knee replacement surgery or for 35 days in patients who have received hip replacement surgery.59 The ROCKET AF (Randomized, Double-Blind Study Comparing Once Daily Oral Rivaroxaban With Adjusted-Dose Oral Warfarin for the Prevention of Stroke in Subjects With Non-Valvular Atrial Fibrillation) trial revealed a reduction in the composite end point of stroke or systemic embolism in patients with nonvalvular AF who were treated with 20 mg of rivaroxaban compared with warfarin.64

Rivaroxaban also has been studied for secondary prevention of ACS and treatment of VTE in Phase III clinical trials. Rivaroxaban was added to standard medical therapy in the ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction) trial.65 The composite end point of death from cardiovascular causes, MI, or stroke was reduced with rivaroxaban 2.5 or 5 mg twice daily; however, rivaroxaban increased the rates of major bleeding including intracranial hemorrhage. The FDA has delayed approval of rivaroxaban for this indication pending additional data from the manufacturer.66

Trials have evaluated the efficacy of rivaroxaban compared with standard treatment in VTE prevention in patients with a previous DVT or PE.67 The EINSTEIN—DVT trial demonstrated noninferiority for rivaroxaban when compared with enoxaparin and a vitamin K antagonist, but it was not shown to be superior. Rates of major bleeding were similar between groups. Similarly, in patients with a PE the EINSTEIN—PE study showed rivaroxaban to be noninferior to enoxaparin and a vitamin K antagonist.68 Patients treated with rivaroxaban also had lower rates of major bleeding (1.1% vs 2.2%) in this study. The FDA-approved dose of rivaroxaban for patients with AF is 20 mg daily; this dose should be reduced to 15 mg daily in patients with a creatinine clearance between 15 and 50 mL per minute and the drug should be avoided in patients with more severe renal dysfunction.59 The prescribing information for rivaroxaban provides detailed information on how to change from or to warfarin and from or to parenteral anticoagulants in AF patients. The dose is 10 mg once daily when used for DVT prophylaxis after hip or knee replacement. The manufacturer recommends that rivaroxaban should not be used for DVT prophylaxis if the creatinine clearance is less than 30 mL per minute. Rivaroxaban should not be administered in conjunction with strong inhibitors of CYP3A4 and P-glycoprotein.

**Other Investigational Agents**

A number of other oral factor Xa inhibitors are in Phase II or III trials. Apixaban (Eliquis, Bristol-Myers Squibb/Pfizer) has been studied for VTE prevention and treatment as well as for stroke prevention in patients with AF.69 A Phase III trial with apixaban in patients with ACS was terminated early due to increased bleeding events without improved efficacy.70 The FDA has delayed approval of this agent for patients with AF pending additional information.71

**Safety Concerns With Warfarin Alternatives**

Since the approval of dabigatran and rivaroxaban, some experts have expressed concern with the lack of required monitoring.72,73 Although clinical practice guidelines recommend at least quarterly INR monitoring with warfarin, no such parameters exist for dabigatran and rivaroxaban because INR monitoring is unnecessary.25,72,73 Typically, warfarin monitoring sessions not only ensure therapeutic INR levels but also serve as opportunities to uncover potential drug interactions, as well as bleeding complications or symptoms of a thromboembolic event. Patients receiving dabigatran or other anticoagulants are still at risk for these complications; therefore, clinicians must provide appropriate follow-up and monitoring.

**Conclusion**

Warfarin has been the mainstay in oral anticoagulation for decades, but its complicated dosing and frequent monitoring requirements make therapeutic management cumbersome for clinicians and patients alike. The recent approval of dabigatran and rivaroxaban provide alternative options for patients with AF receiving warfarin. Additionally, rivaroxaban is an alternative for DVT treatment and prevention. Future studies of dabigatran, rivaroxaban, and other agents may result in a diminished role for warfarin in clinical practice.

**References**


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