New Oral Anticoagulants for Atrial Fibrillation

Are They Worth the Risk?

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ABSTRACT

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the U.S. Anticoagulation is recommended for stroke prevention in AF patients with intermediate-to-high stroke risk (i.e., patients with a $CHADS_2$ score of 1 or greater). Warfarin was previously the only option for oral anticoagulation in these patients, but three new oral anticoagulants have become available as alternatives for warfarin in patients with nonvalvular AF. The advantages of the newer agents include a rapid onset, predictable pharmacokinetics, and no need for routine anticoagulation monitoring.

Dabigatran (Pradaxa) and apixaban (Eliquis) have demonstrated improved efficacy compared with warfarin. Rivaroxaban (Xarelto) was non-inferior to warfarin for stroke prevention in AF. Apixaban demonstrated a reduced incidence of major bleeding compared with warfarin and a reduction in all-cause mortality.

Limitations to the use of the new oral anticoagulants include the lack of a reversal agent; an inability to use the therapies in specific patient populations (such as those with severe renal or hepatic impairment); limited experience with drug–drug and drug–disease interactions; and a lack of available coagulation tests to quantify their effects. Although the newer agents have higher acquisition costs, the benefits of cost savings may be derived from the potential for decreasing the incidence of hemorrhagic stroke and intracranial bleeding and reducing the need for anticoagulation monitoring. Benefits and risks should be carefully weighed before these agents are prescribed for patients presenting with new-onset AF.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia in U.S.[1] The incidence and prevalence of AF increase with age.[2] The number of people affected by AF is projected to exceed 12 million by 2050.[3] The lifetime risk of AF in patients 40 years of age and older is estimated at 25%.[3,4] Stroke is a major complication associated with AF, which contributes to the morbidity and mortality associated with the disease. Patients with AF have a four-fold to five-fold increased risk of stroke. This risk varies among patient populations, according to age, sex, and the presence of comorbid disease states (e.g., diabetes, hypertension, congestive heart failure, and vascular disease).[3,5,6]

Anticoagulation is recommended for stroke prevention for intermediate-risk and high-risk patients (i.e., those with a $CHADS_2$ score of 1 or higher (Congestive Heart failure, Age over 75, Diabetes, and Stroke).[5,7–11] The presence of additional risk factors (female sex, age 65–74 years, and vascular disease) should be considered when health care professionals are determining whether patients in the intermediate-risk category should receive anticoagulation.[7–11] Previously, warfarin was the only option for oral anticoagulation in these patients.

Currently, three oral anticoagulants are approved by the FDA as alternatives to warfarin in patients with AF. Dabigatran (Pradaxa, Boehringer Ingelheim) was the first new oral anticoagulant approved for stroke prevention in AF, followed by the oral anti–factor Xa inhibitors rivaroxaban (Xarelto, Janssen) and apixaban (Eliquis, Bristol-Myers Squibb/Pfizer). Rivaroxaban is also approved for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), along with prevention of DVT/PE in patients undergoing knee or hip replacement surgeries.[12] Apixaban, the newest anti-Xa inhibitor, was approved for stroke prevention in December 2012.[13]

None of the new agents are approved for use in patients with AF secondary to valvular heart disease or mechanical heart valves. The labeling for anti-Xa inhibitors does not include any specific wording regarding their use in patients with bioprosthetic heart valves; however, dabigatran is specifically contraindicated in patients with mechanical bioprosthetic heart valves.[14] Results were published for a phase 2 dose–validation study comparing dabigatran with warfarin in 252 patients with mechanical heart values. The study was prematurely terminated because of an increased incidence of thromboembolic and bleeding events with dabigatran.[15]

A summary of FDA-approved indications and doses of these oral agents is provided in Table 1.[12–14]

COMPARISON OF WARFARIN AND THE NEW ORAL ANTICOAGULANTS

An ideal oral anticoagulant has a rapid onset and predictable pharmacokinetics with easily quantifiable and reversible therapeutic effects. Above all, the medication should be efficacious. When compared with warfarin, the new oral anticoagulants have a faster onset and predicable pharmacokinetics (Table 2).[12–14] In addition, routine anticoagulation monitoring is not required, and these agents are at least as efficacious as warfarin.

Warfarin exerts its anticoagulation effect by inhibiting the synthesis of vitamin K–dependent coagulation factors II, VII, IX, and X. The primary pharmacological effect of warfarin results from the inhibition of factor II or thrombin.[16] More frequent monitoring of the International Normalized Ratio (INR) may be required at the initiation of therapy in order to determine the patient's individual steady-state dose.

Inhibition of multiple vitamin K–dependent coagulation

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Table 1 Indications and Doses for FDA-Approved Oral Anticoagulants

	Atrial Fibrillation	VTE Prevention	VTE Treatment
Dabigatran (Pradaxa)[14]	150 mg b.i.d; 75 mg b.i.d.[a]	—	—
Rivaroxaban (Xarelto)[12]	20 mg daily; 15 mg daily[b]	10 mg daily[d,e]	15 mg b.i.d. x 21 days, then 20 mg daily[e]
Apixaban (Eliquis)[13]	5 mg daily; 2.5 mg daily[c]	—	—

[a]For patients with a CrCl of 15 to 30 mL/minute or a CrCl of 30 to 50 mL/minute and concomitantly receiving a strong P-glycoprotein inhibitor.
[b]For patients with a CrCl of 15 to 50 mL/minute.
[c]If the patient is taking a strong dual inhibitor of CYP3A4 and a permeability glycoprotein (P-gp) inhibitor, or has two or more of these characteristics: 80 years of age or older, body weight 60 kg or less, or serum creatinine 1.5 mg/dL or greater.
[d]Postoperative thromboprophylaxis following hip or knee replacement surgery.
[e]Avoid use in patients with a CrCl of 30 mL/minute or lower.
b.i.d. = twice daily; CrCl = creatinine clearance; CYP = cytochrome P450; VTE = venous thromboembolism.
Data from prescribing information for rivaroxaban,[12] apixaban,[13] and dabigatran.[14]

factors and genetic variations of the VKORC1 and cytochrome P450 (CYP) 2C9 enzymes contribute to the variation in dosing required for therapeutic anticoagulation.[17–20] The amount of dietary vitamin K consumed can also affect the dosing requirements of warfarin; therefore, dietary intake should remain consistent. Subtherapeutic anticoagulation may result in thrombosis, yet overanticoagulation can lead to bleeding complications.

Warfarin also inhibits natural anticoagulant proteins C and S, resulting in an increased risk of thrombosis at the initiation of therapy.[21,22] Patients at a high risk of thrombosis (who have a high risk for AF and acute thrombosis or who have a mechanical heart valve) may need bridge therapy with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) until a steady-state concentration is achieved.

A slow onset of action, a narrow therapeutic index, numerous drug–food interactions, variable pharmacokinetics, and the need for monitoring for therapeutic INR are major limitations to the use of warfarin in patients with AF. The newer anticoagulants exert their therapeutic effects by directly inhibiting a single factor in the coagulation cascade; dabigatran targets factor IIa, and rivaroxaban and apixaban bind to factor Xa. These new agents also have a more reliable pharmacodynamic profile and provide a less complicated dosing regimen (see Table 2).[12–14] However, limitations to their use include a higher acquisition cost, the contraindication for patients with severe renal impairment, a lack of an antidote for reversal, and an inability to quantify their effects in routine coagulation testing and limited experience with drug–drug and drug–disease interactions.

DIRECT THROMBIN INHIBITORS

Three parenteral direct thrombin inhibitors (DTIs) have been approved by the FDA: argatroban (GlaxoSmithKline), bivalirudin (Angiomax, The Medicines Company), and desirudin (Iprivask, Canyon). Dabigatran etexilate is the only available oral DTI. In October 2010, it was approved by the FDA for stroke prevention in patients with nonvalvular AF.[14]

The 9th edition of Chest Guidelines suggests dabigatran over warfarin as a first-line agent for anticoagulation for stroke prevention in AF.[7] The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines recommend dabigatran as an alternative to warfarin, whereas the European Society of Cardiology's guidelines recommend considering dabigatran, rivaroxaban, or apixaban instead of warfarin for anticoagulation in most patients with AF when the drug is administered, as studied in the clinical trials performed so far.[8–10]

Dabigatran

Dabigatran etexilate (Pradaxa), a competitive and reversible inhibitor of free and clot-bound thrombin, prevents soluble fibrinogen from converting to fibrin.[14,23] It is a prodrug that is converted to its active form via esterase catalyzed hydrolysis.[14,24] Dabigatran is formulated as encapsulated pellets with a tartaric acid core to enhance its oral absorption and to ensure consistent and pharmacologically desirable concentrations.[25] Crushing or breaking the capsules and administration via a nasogastric (NG) tube should be avoided, because pellet administration outside of the capsule can increase bioavailability by up to 75%.[14,25]

Table 2 Pharmacokinetic Properties of Recently Approved Oral Anticoagulants

	Dabigatran (Pradaxa)[14]	Rivaroxaban (Xarelto)[12]	Apixaban (Eliquis)[13]
Mechanism of action	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Oral bioavailability	6%	60%–80%	50%
Volume of distribution	50–70 L	50 L	21 L
Half-life	12–17 hours	5–13 hours	9–14 hours
Metabolism/elimination	80% renal	33% renal; 66% hepatic	25% renal; 75% fecal
Protein binding	35%	> 90%	87%

Data from prescribing information for rivaroxaban,[12] apixaban,[13] and dabigatran.[14]

In patients with AF, dabigatran 150 mg is taken twice daily with or without food. A reduced dose of 75 mg is recommended if the patient's creatinine clearance (CrCl) is 15 to 30 mL/minute, as calculated with the Cockcroft–Gault formula using actual body weight (see Table 1). Clearance is primarily renal, and the drug is a substrate of permeability glycoprotein (P-gp). The use of dabigatran with P-gp inducers (such as rifampin) should be avoided. The combination of renal impairment and P-gp inhibition has a greater tendency to achieve undesirable concentrations when compared with each factor separately.[12–14,26]

For patients with moderate renal impairment (a CrCl of 30–50 mL/minute) who are concomitantly taking P-gp inhibitors such as dronedarone (Multaq, Sanofi) or systemic ketoconazole, a reduced dose of 75 mg is recommended. Approval of the 75-mg dose was based on pharmacokinetic modeling data.[14,26] The clinical efficacy of the reduced dose regimen has not been studied.[7,10–14] Significant adverse effects occurring with dabigatran at a rate exceeding 15% include dyspepsia and gastritis-like symptoms.[14]

Routine monitoring of anticoagulation activity is not necessary if dabigatran is administered according to the manufacturer's recommendations. Dabigatran prolongs thrombin clotting time (TCT), prothrombin time (PT), activated partial thromboplastin time (aPTT), and ecarin clotting time (ECT). TCT, aPTT, and ECT can be used to estimate the drug's serum concentration. However, the degree of aPTT elevation is not linearly correlated with the dabigatran concentration, and it is particularly inaccurate at higher concentrations of the drug.[14,17]

A boxed warning cautions against interruptions in dabigatran therapy to avoid an increased risk of stroke resulting from the drug's short half-life. Therefore, withholding dabigatran for bleeding or invasive surgery should be minimized when possible.[14] Dabigatran should be withheld for 1 to 2 days before an invasive procedure in patients with normal renal function and for 3 to 5 days in patients if the CrCl is 50 mL/minute or below.[14] TCT and aPTT can be used to determine the residual anticoagulation activity of dabigatran before the procedure.[17,27]

There is no known reversal agent for dabigatran. Symptomatic management is the primary approach for bleeding because of dabigatran's relatively short half-life. Recombinant factor VIIa (rFVIIa), prothrombin complex concentrates (PCCs), or hemodialysis can be considered for reversing life-threatening bleeding.[27–30]

Clinical Trials and Efficacy

In the Randomized Evaluation of Long-Term Anticoagulation Therapy trial (RE-LY), patients older than 65 years of age with AF received blinded doses of dabigatran 110 mg or 150 mg twice daily to establish non-inferiority versus unblinded, dose-adjusted warfarin. Study participants (n = 18,133) were observed for up to 2 years (Table 3).[31–35] Two independent investigators who were blinded to treatment assignments confirmed the detection of events from hospital records to minimize potential reporting bias from unblinded INR monitoring. The mean $CHADS_2$ score was 2.1 (see Table 3).[32]

The incidence of stroke and systemic embolism was similar between dabigatran 110 mg and warfarin (1.54% vs. 1.71% per year, respectively). The relative risk (RR) was 0.9 with a 95% confidence interval (CI) of 0.74 to 1.1 ($P < 0.001$ for non-inferiority).

The higher dose of dabigatran (150 mg twice daily) was associated with a significant reduction in stroke and systemic embolism compared with warfarin (1.11% per year; RR, 0.65%; 95% CI, 0.52–0.81; $P < 0.001$ for non-inferiority and superiority). Dabigatran 150 mg was associated with a lower incidence of both ischemic stroke (hazard ratio [HR], 0.75; 95% CI, 0.58–0.97) and hemorrhagic stroke (HR, 0.26; 95% CI, 0.14–0.49).

The primary safety outcome (major bleeding) for dabigatran 150 mg and 110 mg was 3.32% ($P = 0.32$) and 2.87% ($P = 0.003$) per year, respectively, compared with 3.57% per year with warfarin. The incidence of gastrointestinal bleeding was higher in the dabigatran 150-mg treatment arm compared with the warfarin arm, (1.5% vs. 1.02% annually respectively; RR, 1.5; 95% CI, 1.19–1.89; $P < 0.05$). Outcomes in the RE-LY trial are summarized in Table 4.[32–35]

The percentage of time in the therapeutic INR range (TTR) of 2 to 3 in patients receiving warfarin was approximately 64%, which is similar to the 66.4% TTR reported in a meta-regression analysis of warfarin trials published in 2006 and 2010.[36,37] Available INR home-monitoring systems may produce higher rates of TTR than conventional INR monitoring in ambulatory settings.[35] An indirect comparison of home monitoring of vitamin K antagonist (VKA) treatment with dabigatran found no

Table 3 Characteristics of Study Patients in Clinical Trials of New Oral Anticoagulants

	Dabigatran (RE-LY)[32,33]	Rivaroxaban (ROCKET-AF)[35]	Apixaban (ARISTOLE)[34]
Study design	Randomized, open-label	Randomized, double-blind	Randomized, double-blind
Follow-up period, median	2 years	1.9 years	1.8 years
Age, mean	71.5 years	73 years*	70 years
Male sex	63.6%	61.3%	64.5%
$CHADS_2$ score, mean ± SD[32–35]	2.1 ± 1.1	3.48 ± 0.94	2.1 ± 1.1
Prior stroke (%)	20.3	54.9	19.2
Prior vitamin K antagonist therapy (%)	50.2	62.3	57.1
Mean TTR (%)	64	55	62

*Median.
TTR = time in therapeutic range (for warfarin therapy).
Data from Connelly et al.,[31–33] Granger et al.,[34] and Patel et al.[35]

significant differences in the incidence of thrombosis, bleeding, and death between groups. Patients in the home-monitoring group included those taking warfarin for reasons other than AF. The TTR for home monitoring was 61.9%, which was slightly lower than TTR values in RE-LY.[38]

A secondary (facility-level) analysis of the RE-LY trial compared the efficacy of dabigatran versus warfarin. Study centers were stratified based on mean TTR quartiles (<57.1%, 57.1% to 65.5%, 65.5% to 72.6%, and >72.6%). Dabigatran 150 mg twice daily demonstrated a lower risk of stroke or systemic embolism across all quartiles of TTR. Meanwhile, rates of stroke or systemic embolism increased with lower-center TTR in the warfarin group. Fewer hemorrhagic strokes were noted in both dabigatran arms.[37]

Seven studies reported an estimated cost benefit of dabigatran over warfarin. Two studies from the United Kingdom, published in 2011, and one Danish study, published in 2012, demonstrated a beneficial incremental cost-effectiveness ratio (ICER) of dabigatran over warfarin with data from the RE-LY trial.[39–41] The ICER describes the additional cost of using dabigatran over warfarin in order to see an improvement in one quality-adjusted life year (QALY), which is the easiest approach for estimating quality-of-life benefits. A wide range of ICERs have been reported for dabigatran, compared with warfarin, in European studies: $7,350 in patients younger than age 80; $12,300 for patients 80 years of age or older; and $35,800 for patients with $CHADS_2$ scores of 3 or higher.[39,40]

A retrospective Canadian study also reported a beneficial ICER of dabigatran as $10,440/QALY versus warfarin and $3,962/QALY versus "real-world" prescribing. This analysis incorporated a lower time in the therapeutic range (59%) and more warfarin-eligible patients taking aspirin (11%) or no treatment at all (6%).[42,43]

A U.S. analysis of the RE-LY data found an ICER of $25,000/QALY, based on a dabigatran cost of $6.75 per day ($210/month).[14,44] In this analysis, the ICER continued to show more benefit with decreasing TTR on warfarin therapy. Cost-effectiveness was most sensitive to monthly costs of recurrent stroke , intracerebral hemorrhage (ICH), or both; the initial age of the cohort; the relative risk of stroke; the cost of dabigatran; and the TTR. Based on a willingness-to-pay threshold of $50,000 per QALY, dabigatran 150 mg was deemed to be cost-effective in the target population of patients 70 years of age and older with nonvalvular AF, prior stroke, or transient ischemic attack, and with no contraindications to anticoagulation. Notable exceptions in which no cost–benefit was seen applied to patients 81 years of age and older, a TTR with warfarin greater than 73%, and monthly costs of dabigatran exceeding $320.

In another U.S. analysis, dabigatran was generally considered to be cost-effective as an alternative to warfarin, but it appeared to be less cost-effective when daily dabigatran costs exceeded $13.70 for the high dose (150 mg) in patients 65 years of age and older.[45]

Medicare Part D currently provides coverage for dabigatran. The wholesale cost of dabigatran 150 mg twice daily, according to *Red Book*, is $10 per day, which may support warfarin as a more economical option, especially for patients paying out of pocket.[46] The cost-effectiveness analysis comparing dabigatran with the other new oral anticoagulants is discussed on page 62.[47]

FACTOR Xa INHIBITORS

Factor Xa enables the conversion of prothrombin to thrombin, which is involved in the formation of clots. Rivaroxaban and apixaban work by binding to the active site of factor Xa to inhibit clot formation independent of cofactor anti-thrombin III. This mechanism differs from that of parenteral factor Xa inhibitors, such as fondaparinux (e.g., Arixtra, GlaxoSmithKline).[25]

Rivaroxaban

Rivaroxaban (Xarelto) was the first oral reversible factor Xa inhibitor approved by the FDA for stroke prevention in nonvalvular AF in November 2011. It is also approved for treatment

Table 4 Outcomes in Clinical Trials of New Oral Anticoagulants

	Dabigatran (RE-LY)[32,33]	Rivaroxaban (ROCKET-AF)[35]	Apixaban (ARISTOLE)[34]
Stroke/systemic embolism	1.71% warfarin 1.54% dabigatran 110 mg 1.11% dabigatran 150 mg[a,b]	2.4% warfarin 2.1% rivaroxaban	1.6% warfarin 1.27% apixaban[a,b]
Safety			
Major bleeding	3.57% warfarin 2.87% dabigatran 110 mg[a] 3.32% dabigatran 150 mg	3.4% warfarin 3.6% rivaroxaban	3.09% warfarin 2.13% apixaban[a]
Intracranial hemorrhage (%/year)	0.74% warfarin 0.23% dabigatran 110 mg[a] 0.3% dabigatran 150 mg[a]	0.7% warfarin 0.5% rivaroxaban[a]	0.8% warfarin 0.33% apixaban
Myocardial Infarction	0.64% warfarin 0.82% dabigatran 110 mg 0.81% dabigatran 150 mg	1.1% warfarin 0.9% rivaroxaban	0.61% warfarin 0.53% apixaban

[a] $P < 0.05$.
[b] Superiority.
Data from Connelly et al., Granger et al., and Patel et al.[32–35]

of VTE and PE and VTE prophylaxis in patients undergoing knee or hip replacement.[10] For patients with AF, rivaroxaban 20 mg once daily should be taken with food. Because of the drug's partial renal elimination, the dose should be reduced to 15 mg once daily in patients with a CrCl of 15 to 50 mL/minute (calculated with the Cockcroft–Gault equation using actual body weight). Rivaroxaban dosing is presented in Table 1.[12–14]

Rivaroxaban, also a P-gp substrate, is metabolized by CYP3A4 pathways. The concomitant use with a P-gp and a strong CYP3A4 inhibitor (e.g., a protease inhibitor, ketoconazole, or itraconazole) can lead to increased rivaroxaban exposure by 30% to 160%, resulting in increased bleeding risk and, therefore, should be avoided. Clinicians should weigh the risks and benefits in patients with renal impairment who are receiving concomitant P-gp and weak-to-moderate CYP3A4 inhibitors such as amiodarone (Cordarone, Pfizer), diltiazem (Cardizem), verapamil (e.g., Calan), quinidine, erythromycin, and azithromycin (Zithromax). Conversely, rivaroxaban concentrations can be reduced by 50% with dual P-gp and strong CYP3A4 inducers such as rifampin, phenytoin (Dilantin), carbamazepine (Carbatrol), and St. John's wort; concomitant administration should be avoided.[12]

The use of rivaroxaban in patients with hepatic impairment (a Child–Pugh class of B or C) is not recommended. Additional warnings include an increased risk of thrombotic events with the cessation of rivaroxaban therapy. The drug's half-life is 5 to 9 hours in young, healthy patients (20–45 years of age); its half-life is 11 to 13 hours in elderly people. The peak effect occurs 2 to 4 hours after administration. Rivaroxaban can also be given by nasogastric tube or a gastric feeding tube.[12]

The most common adverse events with rivaroxaban were related to bleeding and occurred at rates similar to those of warfarin in clinical trials. Nonhemorrhagic adverse drug events reported at a rate of 5% or more included peripheral edema, dizziness, nasopharyngitis, cardiac failure, bronchitis, dyspnea, and diarrhea, which occurred at rates similar to those receiving warfarin.[12]

Rivaroxaban causes concentration-dependent prolongation of PT and aPTT. Neither the manufacturer nor any organization recommends routine anticoagulation monitoring during rivaroxaban therapy. Factor Xa inhibitors (rivaroxaban and apixaban) have a more pronounced effect on PT than on aPTT. Abnormalities in coagulation tests can be observed with therapeutic doses.[48] Chromogenic anti-factor Xa assays calibrated specifically for rivaroxaban can be used to estimate the extent of anticoagulation. These tests are currently being used in Canada and Europe.[48–50]

Interruption of therapy should be minimized to reduce the risk of thrombosis. Anticoagulation activity may be prolonged in patients with renal dysfunction because of partial renal clearance (see Table 2).[12–14] Rivaroxaban should be withheld for at least 1 day before an invasive procedure for patients with normal renal function and longer for patients with renal dysfunction (2 days if the CrCl is 60–90 mL/minute, 3 days if the CrCl is 30 to 59 mL/minute, and 4 days if the CrCl 15 is 29 mL/minute).[27,51]

There is no specific antidote for rivaroxaban. It is not dialyzable, because its protein binding is nearly 95%. Limited data suggest that four-factor prothrombin complex concentrates (PCCs) and recombinant factor VIIa can be used in cases of life-threatening bleeding.[30,52,53]

Clinical Trials and Efficacy

The ROCKET-AF study (Rivaroxaban Once daily, oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) was conducted to compare rivaroxaban with dose-adjusted warfarin. A total of 14,264 patients with a $CHADS_2$ score of 2 or higher (mean score, 3.5) participated in an international, randomized, double-blind non-inferiority trial.[35]

The rates of stroke and systemic embolism were 2.1% in the rivaroxaban group and 2.4% in the warfarin group (HR, 0.88; 95% CI, 0.74–1.03; $P < 0.001$ for non-inferiority; $P = 0.12$ for superiority) in the intention-to-treat (ITT) analysis. Rivaroxaban was found to be at least as effective as warfarin; however, it did not prove to be superior in preventing stroke or systemic embolism in AF.

The risk of major bleeding was similar between rivaroxaban and warfarin, although the incidence of intracranial and fatal bleeding was higher in the warfarin arm. Rates of major and non-major clinically relevant bleeding were 14.9% per year with rivaroxaban and 14.5% per year with warfarin (HR, 1.03; 95% CI, 0.96–1.11; $P = 0.44$). The rate of hemorrhagic stroke was significantly lower in the rivaroxaban group (HR, 0.59; 95% CI, 0.37–0.93; $P = 0.024$), as was the rate of intracranial bleeding episodes (0.5% vs. 0.7% per year; HR, 0.67; 95% CI, 0.47–0.94; $P = 0.019$). The study proved the non-inferiority (but not the superiority) of rivaroxaban to warfarin. Outcomes of ROCKET-AF are summarized in Table 4.[32–35]

The cost-effectiveness of rivaroxaban, compared with warfarin, for stroke prevention in AF was evaluated in a base-case analysis study. The investigators developed a Markov model using a U.S. payer/Medicare perspective and measured the cost in 2011 U.S. dollars. They found that patients treated with rivaroxaban lived for an average of 10.03 QALYs at a lifetime treatment cost of $94,456, whereas patients receiving warfarin lived for an average of 9.81 QALYs and incurred a cost of $88,544. The incremental cost-effectiveness ratio was $27,498 per QALY. Rivaroxaban is a cost-effective alternative to warfarin, using the aforementioned willingness-to-pay threshold of $50,000.[54] An indirect comparison of the three new oral anticoagulants is discussed on pages 59 and 62.

Apixaban

Apixaban (Eliquis) is the second oral selective inhibitor of free and clot-bound factor Xa. In patients with AF, apixaban 5 mg twice daily is recommended. A reduced dose of 2.5 mg twice daily is recommended in patients with two or more of the following: age 80 years or older, body weight 60 kg or less, and a serum Cr level of 1.5 mg/dL or higher (see Table 1).

Apixaban is metabolized primarily by the liver CYP enzyme 3A4 and is a substrate of P-gp. A reduced dose of 2.5 mg twice daily is also recommended when apixaban is used concomitantly with a strong dual inhibitor of CYP3A4 and P-gp (i.e., ketoconazole, itraconazole, ritonavir, or clarithromycin). Manufacturers also advise against the concomitant use of apixaban with strong inducers of P-gp and CYP3A4 if the recommended dose for the patient is 2.5 mg (based upon age, body weight, and renal function). Apixaban is not recommended for patients

with severe hepatic impairment.

The drug's biological half-life is 12 hours *in vivo*.[13] Adverse events with its use were related primarily to bleeding.[13,31,34]

Apixaban produces dose-dependent elevations in aPTT, PT and chromogenic anti–factor Xa assay. Abnormalities in coagulation tests (PT and aPTT) can be observed with therapeutic doses. Anticoagulation monitoring with routine tests is not recommended because of the high degree of variation; however, drug-specific chromogenic anti–factor Xa assay can be used to estimate the extent of anticoagulation.[55] Renal and hepatic impairment may result in an extended biological half-life.

Apixaban should be withheld 1 to 2 days before an invasive procedure in patients with normal renal function (see Table 1) and longer for patients with renal impairment (3 days if the CrCl is 50 to 59 mL/minute and for 4 to 5 days if the CrCl ranges from 30 to 49 mL/minute).[27]

No antidote is currently available for apixaban; however, PCCs can be considered for reversal of a life-threatening bleeding episode. *In vitro* data supporting its use are lacking.[27,30,56]

Clinical Trials and Efficacy

ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) was a randomized clinical trial that compared the efficacy of apixaban with warfarin in 18,201 patients with AF and a $CHADS_2$ score of 1 or higher. Patients received apixaban 5 or 2.5 mg twice daily, with the dose adjusted for selected patients, or warfarin in a blinded fashion for a median of 1.8 years.

The primary outcome was stroke (ischemic or hemorrhagic) or systemic embolism. Major bleeding was the primary safety outcome. The study was designed as a non-inferiority trial with secondary objectives to test for superiority of primary outcomes and all-cause mortality. The mean $CHADS_2$ score for study patients was 2.1 (see Table 3).

Rates of stroke occurrence were 1.27% per year with apixaban and 1.6% per year with warfarin ($P < 0.01$ for superiority). Rates of major bleeding were also lower with apixaban than with warfarin (2.13% vs. 3.09% per year, respectively; $P < 0.001$). The rate of hemorrhagic stroke in patients treated with apixaban was 0.24% per year versus 0.47% per year in patients receiving warfarin ($P < 0.001$). Apixaban demonstrated comparable efficacy for ischemic stroke prevention (0.97% for apixaban vs. 1.05% per year for warfarin; $P = 0.42$). The superior efficacy of apixaban was driven by the reduction in hemorrhagic stroke.

Apixaban was also associated with reduced mortality rates from any cause (3.52% vs. 3.94% per year for warfarin; $P < 0.05$).[34] In a *post hoc* analysis evaluating patients based on treatment center average TTR, treatment effects and bleeding rates did not vary.[57] A summary of ARISTOTLE outcomes is presented in Table 4.[32–35]

Apixaban is also the only new oral anticoagulant that was compared with aspirin in patients deemed unsuitable for warfarin therapy by the prescribing physician. AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who have Failed or are Unsuitable for Vitamin K Antagonist Treatment) was a double-blind, double dummy superiority trial that compared apixaban 5 mg or 2.5 mg twice daily with aspirin.[31] Adjustments were made for age, body weight, and serum creatinine level. The study included 599 patients with AF and $CHADS_2$ scores of 1 or higher. An inability to monitor the INR was the most commonly documented reason for considering patients to be unsuitable for warfarin therapy.

The primary efficacy outcome was the occurrence of stroke or systemic embolism. Because the trial was halted early, patients were observed for a mean of only 1.1 years. Patients in the apixaban arm had a significantly lower incidence of stroke compared with those receiving aspirin (1.6 % vs. 3.7% per year, respectively; $P < 0.001$).

There was no difference in the incidence of major bleeding (1.4% per year with apixaban vs. 1.2% per year with aspirin; $P = 0.57$). Annual rates of hemorrhagic stroke were also similar among the two treatment arms (0.2% with apixaban vs. 0.3% with aspirin; $P = 0.45$). Most patients in the aspirin group (91%) received 81 or 162 mg (81 mg was the most common dose). The exclusions in the AVERROES trial should be taken into consideration when clinicians must decide between apixaban or aspirin for these patients (Table 5).[32–35]

A Markov decision model revealed that apixaban use was associated with an incremental cost-effectiveness ratio of $11,400 per QALY. According to this analysis, apixaban remained cost-effective up to a cost of $350 per month. The cost-effectiveness from reduced adverse events was more prominent in patients younger than 87 years of age and with reduced comorbidities.[58] In two independently conducted Monte Carlo sensitivity analyses, apixaban was cost-effective at the threshold of $50,000 per QALY 62% to 98% of the time.[58,59]

DIFFERENCES AMONG THE THREE NEW ORAL ANTICOAGULANTS

Efficacy

A direct comparison of efficacy among the three new oral anticoagulants is lacking. The clinician must consider the limitations of an indirect comparison (i.e., differences in study cohorts and trial design) when comparing efficacy and cost-effectiveness of these agents. A $CHADS_2$ score of 1 or higher was required for enrollment in the RE-LY and ARISTOTLE trials, whereas in ROCKET-AF, a $CHADS_2$ score of 2 or higher was required for enrollment (see Table 5). Consequently, a higher-risk cohort was enrolled in ROCKET-AF (mean $CHADS_2 = 3.5$) compared with the RE-LY and ARISTOTLE cohorts (mean $CHADS_2 = 2.1$).

Dabigatran and apixaban demonstrated improved efficacy, but rivaroxaban was non-inferior compared with warfarin for the intent-to-treat analysis. The average TTR was also the lowest in ROCKET-AF at 55%, compared with 64% and 62% for RE-LY and ARISTOTLE, respectively (see Table 3).[32–35] Prior vitamin K antagonist therapy was more common in ROCKET-AF patients (62.3%) than in ARISTOTLE (57.1%) and RE-LY (49.8%) patients, which can be explained by the higher $CHADS_2$ requirement in the enrolled patients.[32,34,35] None of the new oral anticoagulants are approved for use in patients with severe renal insufficiency (a CrCl below 15 mL/minute), and no published evidence is available for their use in patients with a CrCl of less than 25 mL/minute.

An adjusted indirect comparison of the subgroup of patients with $CHADS_2$ scores of 3 or higher who were enrolled in RE-LY, ARISTOTLE, and ROCKET-AF demonstrated no statistically significant differences among the three agents for stroke pre-

vention. Apixaban was associated with the lowest risk of major hemorrhage compared with dabigatran and rivaroxaban.[60] In a Danish modeling analysis of patients with CHA_2DS_2–Vasc (**V**ascular disease, **A**ge 65–74 years, **S**ex [female gender]) scores of 2 or higher and with $CHADS_2$ scores of 1 or higher, the use of all three agents, compared with warfarin, also demonstrated positive net clinical benefit (i.e., preventing ischemic stroke minus harm from hemorrhagic stroke).[61]

Cost-Effectiveness

In a Canadian study, both doses of dabigatran (150 mg and 110 mg) were found to be economically superior to rivaroxaban at a willingness-to-pay threshold of $20,000 per QALY. The cost–benefit analysis was based on lower acute-care and long-term follow-up costs per patient ($52,314 for dabigatran vs. $53,638 for rivaroxaban) exceeding higher drug costs ($7,299 for dabigatran vs. $6,128 for rivaroxaban).[62]

In a Monte Carlo estimated cost-effectiveness analysis com-

Table 5 Inclusion and Exclusion Criteria for Patients in Clinical Trials of New Oral Anticoagulants

Dabigatran[32,33]	
Inclusion Criteria	**Exclusion Criteria**
RE-LY AF ≤ 6 months before randomization plus one additional risk factor: • Previous stroke, TIA, or systemic embolism • Ejection fraction less than 40% in the last 6 months • Symptomatic heart failure, NYHA class 2 or higher in the last 6 months • Age at least 75 years • Age at least 65 years and one of the following: ◦ DM on treatment ◦ Documented coronary artery disease (any of prior myocardial infarction, positive stress test, positive nuclear perfusion study, prior bypass surgery or PCI, angiogram showing at least 75% stenosis in a major coronary artery) ◦ HTN requiring medical treatment	• History of heart valve disorder (i.e., prosthetic valve or hemodynamically relevant valve disease) • Severe, disabling stroke within the previous 6 months, or any stroke within the previous 14 days • Conditions associated with an increased risk of bleeding: ◦ Major surgery within the previous month ◦ Planned surgery or intervention within the next 3 months ◦ History of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intra-articular bleeding ◦ Gastrointestinal hemorrhage within the previous year ◦ Symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days ◦ Hemorrhagic disorder or bleeding diathesis ◦ Need for anticoagulant treatment of disorders other than AF ◦ Fibrinolytic agents within 48 hours of study entry ◦ Uncontrolled HTN (systolic BP above 180 mm Hg and/or diastolic BP greater than 100 mm Hg) ◦ Recent malignancy or radiation therapy (within 6 months) and not expected to survive 3 years • Contraindication to warfarin treatment • Reversible causes of AF (e.g., cardiac surgery, pulmonary embolism, untreated hyperthyroidism) • Scheduled for pulmonary vein ablation or surgery for cure of AF • Severe renal impairment (estimated CrCl of 30 mL/minute or less) • Active infective endocarditis • Active liver disease, including but not limited to: ◦ persistent ALT, AST, alkaline phosphatases greater than twice the ULN ◦ active hepatitis C (positive HCV RNA) ◦ active hepatitis B (HBs antigen–positive, anti-HBc IgM–positive) ◦ Active hepatitis A • Women who are pregnant or of childbearing age who refuse to use a medically acceptable form of contraception throughout the study • Anemia (Hb < 100 g/L) or thrombocytopenia (platelet count < 100 x 10^9/L) • Patients with transaminase elevations (ALT, AST) upon exposure to ximelagatran (Exanta) • Patients who received an investigational drug in the past 30 days • Patients considered unreliable by the investigator or who may have a life expectancy less than the expected duration of the trial because of concomitant disease or who have any condition that, in the opinion of the investigator, would not allow safe participation in the study (e.g., drug addiction, alcohol abuse)

table continues

Table 5 Inclusion and Exclusion Criteria for the Patient Population in Clinical Trials of New Oral Anticoagulants *(continued)*

Rivaroxaban[35]

Inclusion Criteria	Exclusion Criteria
ROCKET-AF • Nonvalvular AF • History of prior ischemic stroke, TIA, or non-CNS systemic embolism believed to be cardioembolic in origin or two or more of the following risk factors: ◦ Heart failure and/or left ventricular ejection fraction ≤35% ◦ HTN (defined as use of antihypertensive medications within 6 months before the screening visit or persistent systolic BP above 140 mm Hg or diastolic BP above 90 mm Hg) ◦ Age ≥75 years ◦ DM (defined as a history of type-1 or type-2 DM or use of antidiabetic medications within 6 months before screening visit) ◦ Female subjects must be postmenopausal (for at least 2 years); surgically sterile; abstinent; or, if sexually active, must be practicing an effective method of birth control before entry and throughout the study. Females of childbearing age must have a negative serum β-hCG pregnancy test at screening.	• Hemodynamically significant mitral valve stenosis • Prosthetic heart valve (annuloplasty with or without prosthetic ring; commissurotomy and/or valvuloplasty permitted) • Planned cardioversion (electrical or pharmacological) • Transient AF caused by a reversible disorder (e.g., thyrotoxicosis, pulmonary embolism, recent surgery, MI) • Known presence of atrial myxoma or left ventricular thrombus • Active endocarditis • Active internal bleeding • History of or condition associated with increased bleeding risk including, but not limited to: ◦ major surgical procedure or trauma within 30 days before the randomization visit ◦ clinically significant gastrointestinal bleeding within 6 months before the randomization visit ◦ history of intracranial, intraocular, spinal, or atraumatic intra-articular bleeding ◦ chronic hemorrhagic disorder ◦ known intracranial neoplasm, arteriovenous malformation, or aneurysm • Planned invasive procedure with potential for uncontrolled bleeding, including major surgery • Platelet count < 90,000/μL at screening visit • Sustained uncontrolled HTN: systolic BP ≥180 mm Hg or diastolic BP ≥100 mm Hg • Severe, disabling stroke (modified Rankin score of 4 to 5, inclusive) within 3 months or any stroke within 14 days before the randomization visit • TIA within 3 days before the randomization visit • Indication for anticoagulant therapy for a condition other than AF (e.g., venous thromboembolism) • Treatment with: ◦ aspirin >100 mg daily ◦ aspirin in combination with thienopyridines within 5 days before randomization ◦ IV antiplatelet drugs within 5 days before randomization ◦ Fibrinolytic agents within 10 days before randomization ◦ *Note:* aspirin ≤100 mg monotherapy allowed and thienopyridine monotherapy allowed. • Anticipated need for chronic treatment with NSAIDs • Systemic treatment with a strong inhibitor of CYP3A4, such as ketoconazole or protease inhibitors, within 4 days before randomization, or planned treatment during the time period of the study • Treatment with a strong inducer of CYP3A4, such as rifampin/rifampicin, within 4 days before randomization, or planned treatment during the time period of the study • Anemia (Hb < 10 g/dL) at screening visit • Pregnancy or breastfeeding • Any other contraindication to warfarin • Known HIV infection at time of screening • Calculated CrCl < 30 mL/minute at the screening visit • Known significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis), or ALT > 3 x ULN

table continues

Table 5 Inclusion and Exclusion Criteria for the Patient Population in Clinical Trials of New Oral Anticoagulants *(continued)*

Apixaban[31,34]

Inclusion Criteria	Exclusion Criteria
AVERROES	
• Patients not receiving warfarin with a documented reason for being deemed unsuitable for therapy by treating physician • Age ≥ 50 years • AF (≤6 months prior to enrollment) plus one additional risk factor: ◦ Prior stroke or TIA ◦ Age ≥ 75 years ◦ Arterial HTN (receiving treatment) ◦ DM (receiving treatment) ◦ Heart failure (NYHA class ≥ 2) ◦ LVEF ≤ 35% ◦ PAD	• Valvular disease requiring surgery • Need for anticoagulation or aspirin • Serious bleeding event 6 months or less before enrollment • High risk for bleeding (e.g., active PUD, platelet count < 100,000/mm^3, Hb < 10 g/dL, stroke within previous 10 days, blood dyscrasias) • Current alcohol use or psychological problems • Life expectancy < 1 year • Severe renal insufficiency (Sr.Cr > 2.5 mg/dL or CrCl < 25 mL/minute) • AST or ALT >2 x ULN, or total bilirubin >1.5 x ULN • Allergy to aspirin
ARISTOTLE AF (≤12 months prior to enrollment) plus one additional risk factor: • Prior stroke, TIA, or systemic embolism • Age ≥ 75 years • Arterial HTN (requiring treatment) • DM • Symptomatic HF or LVEF ≤ 40% within previous 3 months	• AF due to reversible causes • Moderate-to-severe mitral stenosis • Comorbid conditions requiring anticoagulation • Stroke within previous 7 days • Concomitant aspirin administration at doses > 165 mg • Concomitant aspirin and clopidogrel administration • Renal insufficiency (Sr.Cr > 2.5 mg/dL or CrCl < 25 mL/minute)

AF = atrial fibrillation; ALT = alanine aminotransferase; AST= aspartate aminotransferase; BP = blood pressure; CNS = central nervous system; CrCl = creatinine clearance; CYP = cytochrome P450; DM = diabetes mellitus; Hb = hemoglobin; hCG = human chorionic gonadotropin; HTN = hypertension; IgM = immunoglobulin M; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; NYHA = New York Heart Association; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; PUD = peptic ulcer disease; Sr.Cr = serum creatinine; T. bili = total bilirubin; TIA = transient ischemic attack; ULN= upper limit of normal.

Data from Connelly et al.,[31–33] Granger et al.,[34] and Patel et al.[35]

paring the three new agents against warfarin, apixaban was more likely to be the cost-effective treatment (45.1%) when compared with dabigatran (40%) and rivaroxaban (14.9%). Pooled data from ARISTOTLE, RE-LY and ROCKET-AF were used for the efficacy and safety analysis. The modeled cohort included patients 70 years of age and older, a $CHADS_2$ score of 1 or higher, a CrCl of 50 mL/minute or greater, and no previous contraindications to anticoagulation therapy.

QALYs were 8.47, 8.41, 8.26, and 7.97 for apixaban, dabigatran, rivaroxaban, and warfarin, respectively. The estimated total cost of treatment was $85,326 for apixaban; $82,719 for dabigatran; $78,738 for rivaroxaban; and $77,813 for warfarin. Although this analysis provides some insight for the prescribers, prospective real-world studies are lacking to determine which drug would be the most cost-effective treatment for patients.[47]

Conflicting data exist regarding cost-effectiveness for the new agents, because the estimated cost efficacy trials are indirect comparisons. Apixaban had a lower estimated incremental cost-effectiveness ratio (ICER) than dabigatran when each was compared with warfarin in two separate Markov decision models: $11,400 vs. $25,000 per QALY, respectively.[44,58] Rivaroxaban had the lowest ICER per QALY in the most recent U.S. analysis: $3,190 for rivaroxaban vs. $11,150 for dabigatran, and $15,026 for apixiban.[47]

In summary, comparisons are difficult to make because of the differences in study design and patient populations. Dabigatran and apixaban have demonstrated improved efficacy compared with warfarin. Rivaroxaban was non-inferior to warfarin in an ITT analysis. Apixaban demonstrated a reduced incidence of major bleeding, compared with warfarin, and is also the only new anticoagulant that is associated with lower all-cause mortality rates when compared with warfarin (see Table 4).[31–35]

CONCLUSION

Three new oral anticoagulants (dabigatran, rivaroxaban, and apixaban) provide several advantages over warfarin, including their predictable pharmacokinetic profile, the fact that no routine monitoring is needed, and the incidence of fewer drug–food interactions. Although renal function, bleeding, and compliance may still need to be monitored in patients, the ease of use may improve persistence with their anticoagulant regimen.[63]

Some limitations to the use of these newer anticoagulants include the lack of a reversal agent, an inability to use them in specific patient populations (such as those with severe renal impairment), a lack of coagulation tests to quantify their effect, and little experience with drug–drug and drug–disease interactions. Information about the impact of noncompliance, especially given the short half-lives of these agents, is also lacking.

Taking their limitations into consideration, the new agents still offer several advantages when used appropriately in selected patients. Their role is likely to grow as more data become

available regarding their long-term use, drug–drug interactions and use in specific patient populations.

REFERENCES

1. Lloyd-Jones D, Adams RJ, Brown TM, et al. Executive summary: Heart disease and stroke statistics—2010 update. A report from the American Heart Association. *Circulation* 2010;121:948–954.
2. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: The Framingham Heart Study. *Circulation* 2004;110:1042–1046.
3. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: A report from the American Heart Association. *Circulation* 2011;123(4):e18–e209.
4. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;114:119–125.
5. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: Results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864–2870.
6. Lip GY, Frison L, Halperin JL, Lane DA. Identifying patients at high risk for stroke despite anticoagulation: A comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke* 2010;41:2731–2738.
7. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 Suppl):e531S–575S.
8. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;127:1916–1926.
9. Wann LS, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran): A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2011;123:1144–1150.
10. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation—developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;14:1385–1413.
11. Furie KL, Goldstein LB, Albers GW, et al. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: A science advisory for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2012;43:3442–3453.
12. Xarelto (rivaroxaban), package insert. Titusville, N.J.: Janssen; March 2013.
13. Eliquis (apixaban), package insert. Princeton, N.J.: Bristol-Myers Squibb; December 2012.
14. Pradaxa (dabigatran), package insert. Ridgefield, Conn.: Boehringer Ingelheim; Apr 2013.
15. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013;369(13):1206–1214.
16. Zehnder JL. Drugs used in disorders of coagulation. *In:* Katzung BG, Masters SB, Trevor AJ, eds. *Basic & Clinical Pharmacology*, 12th ed. New York: McGraw-Hill; 2012.
17. Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e44S–88S.
18. Schwarz UI, Ritchie MD, Bradford Y, et al. Genetic determinants of response to warfarin during initial anticoagulation. *N Engl J Med* 2008;358:999–1008.
19. Genetic testing to aid in warfarin (Coumadin) dosing. *Pharmacists Lett* 2007;231002.
20. Takahashi H, Echizen H. Pharmacogenetics of warfarin elimination and its clinical implications. *Clin Pharmacokinet* 2001;40:587–603.
21. Porter RS, Sawyer WT. Warfarin. *In:* Evans WE, Schentag JJ, SJ, Jusko WJ, ed. *Applied Pharmacokinetics Principles of Therapeutic Drug Monitoring*, 3rd ed. Vancouver, Wash: Applied Therapeutics; 1992:31.1–31.46.
22. Warrell DA, Cox TM, Firth JD. *Oxford Textbook of Medicine*, 4th ed. Oxford, U.K.: Oxford University Press; 2003.
23. De Caterina R, Husted S, Wallentin L, et al. Anticoagulants in heart disease: Current status and perspectives. *Eur Heart J* 2007; 28:880–913.
24. Stangier J, Clemens A. Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor. *Clin Appl Thromb Hemost* 2009;15(Suppl 1):9S–16S.
25. Norgard NB, Dinicolantonio JJ, Topping TJ, Wee B. Novel anticoagulants in atrial fibrillation stroke prevention. *Ther Adv Chronic Dis* 2012;3:123–136.
26. Liesenfeld KH, Lehr T, Dansirikul C, et al. Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. *J Thromb Haemost* 2011;9:2168–2175.
27. Baron TH, Kamath PS, McBane RD. Management of antithrombotic therapy in patients undergoing invasive procedures. *N Engl J Med* 2013;368:2113–2124.
28. van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 2010;103:1116–1127.
29. Chang DN, Dager WE, Chin AI. Removal of dabigatran by hemodialysis. *Am J Kidney Dis* 2013;61:487–489.
30. Kalus JS. Pharmacologic interventions for reversing the effects of oral anticoagulants. *Am J Health Syst Pharm* 2013;70:S12–S21.
31. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;364:806–817.
32. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361:1139–1151.
33. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Newly identified events in the RE-LY trial. *N Engl J Med* 2010;363:1875–1876.
34. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–992.
35. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–891.
36. van Walraven C, Jennings A, Oake N, et al. Effect of study setting on anticoagulation control: A systematic review and metaregression. *Chest* 2006;129:1155–1166.
37. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: An analysis of the RE-LY trial. *Lancet* 2010;376:975–983.
38. Alonso-Coello P, Zhou Q, Guyatt G. Home-monitoring of oral anticoagulation vs. dabigatran: An indirect comparison. *Thromb Haemost* 2012;108:647–653.
39. Pink J, Lane S, Pirmohamed M, Hughes DA. Dabigatran etexilate versus warfarin in management of non-valvular atrial fibrillation in UK context: Quantitative benefit-harm and economic analyses. *BMJ* 2011;343:d6333.
40. Kansal AR, Sorensen SV, Gani R, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in UK patients with atrial fibrillation. *Heart* 2012;98:573–578.
41. Langkilde LK, Bergholdt Asmussen M, Overgaard M. Cost-effectiveness of dabigatran etexilate for stroke prevention in non-valvular atrial fibrillation: Applying RE-LY to clinical practice in Denmark. *J Med Econ* 2012;15:695–703.
42. Parkash R, Wee V, Gardner MJ, et al. The impact of warfarin use on clinical outcomes in atrial fibrillation: A population-based study. *Can J Cardiol* 2007;23:457–461.
43. Sorensen SV, Kansal AR, Connolly S, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: A Canadian payer perspective. *Thromb Haemost* 2011;105:908–919.
44. Kamel H, Johnston SC, Easton JD, Kim AS. Cost-effectiveness

of dabigatran compared with warfarin for stroke prevention in patients with atrial fibrillation and prior stroke or transient ischemic attack. *Stroke* 2012;43:881–883.
45. Freeman JV, Zhu RP, Owens DK, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med* 2011;154:1–11.
46. *Red Book,* 2011.Thomson Reuters Micromedex Gateway. Available at: www.micromedexsolutions.com/micromedex2/librarian. Accessed January 7, 2013.
47. Harrington AR, Armstrong EP, Nolan PE Jr., Malone DC. Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. *Stroke* 2013;44:1676–1681.
48. Carter NJ, Plosker GL. Rivaroxaban: A review of its use in the prevention of stroke and systemic embolism in patients with atrial fibrillation. *Drugs* 2013;73:715–739.
49. Lindhoff-Last E, Samama MM, Ortel TL, et al. Assays for measuring rivaroxaban: Their suitability and limitations. *Ther Drug Monit* 2010;32:673–679.
50. Samama MM, Martinoli JL, LeFlem L, et al. Assessment of laboratory assays to measure rivaroxaban—an oral, direct factor Xa inhibitor. *Thromb Haemost* 2010;103:815–825.
51. Hart RG, Eikelboom JW, Ingram AJ, Herzog CA. Anticoagulants in atrial fibrillation patients with chronic kidney disease. *Nat Rev Nephrol* 2012;8:569–578.
52. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: A randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011;124:1573–1579.
53. Marlu R, Hodaj E, Paris A, et al. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: A randomised crossover *ex vivo* study in healthy volunteers. *Thromb Haemost* 2012;108:217–224.
54. Lee S, Anglade MW, Pham D, et al. Cost-effectiveness of rivaroxaban compared to warfarin for stroke prevention in atrial fibrillation. *Am J Cardiol* 2012;110:845–851.
55. Barrett YC, Wang Z, Frost C, Shenker A. Clinical laboratory measurement of direct factor Xa inhibitors: Anti-Xa assay is preferable to prothrombin time assay. *Thromb Haemost* 2010;104:1263–1271.
56. Martin AC, Le Bonniec B, Fischer AM, et al. Evaluation of recombinant activated factor VII, prothrombin complex concentrate, and fibrinogen concentrate to reverse apixaban in a rabbit model of bleeding and thrombosis. *Int J Cardiol* 2013;168(4):4228–4233.
57. Wallentin L, Lopes RD, Hanna M, et al. Efficacy and safety of apixaban compared with warfarin at different levels of predicted international normalized ratio control for stroke prevention in atrial fibrillation. *Circulation* 2013;127:2166–2176.
58. Kamel H, Easton JD, Johnston SC, Kim AS. Cost-effectiveness of apixaban vs warfarin for secondary stroke prevention in atrial fibrillation. *Neurology* 2012;79:1428–1434.
59. Lee S, Mullin R, Blazawski J, Coleman CI. Cost-effectiveness of apixaban compared with warfarin for stroke prevention in atrial fibrillation. *PloS One* 2012;7:e47473 (October 9, 2012).
60. Schneeweiss S, Gagne JJ, Patrick AR, Cet al. Comparative efficacy and safety of new oral anticoagulants in patients with atrial fibrillation. C*irc Cardiovasc Qual Outcomes* 2012;5:480–486.
61. Banerjee A, Lane DA, Torp-Pedersen C, Lip GY. Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a 'real world' atrial fibrillation population: A modelling analysis based on a nationwide cohort study. *Thromb Haemost* 2012;107:584–589.
62. Kansal AR, Sharma M, Bradley-Kennedy C, et al. Dabigatran versus rivaroxaban for the prevention of stroke and systemic embolism in atrial fibrillation in Canada: Comparative efficacy and cost-effectiveness. *Thromb Haemost* 2012;108:672–682.
63. Zalesak M, Siu K, Francis K, et al. Higher persistence in newly diagnosed nonvalvular atrial fibrillation patients treated with dabigatran versus warfarin. *Circ Cardiovasc Qual Outcomes* 2013. ■