Vascular Health and Risk Management

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Rivaroxaban in atrial fibrillation

This article was published in the following Dove Press journal:
Vascular Health and Risk Management
29 August 2012
Number of times this article has been viewed

Mariano A Giorgi[1,2]
Lucas San Miguel[3]

[1]Cardiology Service, Centro de Educación Médica e Investigaciones Clínicas "Norberto Quirno", [2]Department of Pharmacology, School of Medicine, Universidad Austral, [3]Department of Cardiology and Cardiovascular Surgery, FLENI, Buenos Aires, Argentina

Abstract: Warfarin is the traditional therapeutic option available to manage thromboembolic risk in atrial fibrillation. The hemorrhagic risk with warfarin depends mainly on the international normalized ratio (INR). Data from randomized controlled trials show that patients have a therapeutic INR (2.00–3.00) only 61%–68% of the time while taking warfarin, and this target is sometimes hard to establish. Many compounds have been developed in order to optimize the profile of oral anticoagulants. We focus on one of them, rivaroxaban, comparing it with novel alternatives, ie, dabigatran and apixaban. The indication for rivaroxaban in nonvalvular atrial fibrillation was evaluated in ROCKET-AF (Rivaroxaban-once daily, Oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation). In this trial, rivaroxaban was associated with a 12% reduction in the incidence of the primary endpoint compared with warfarin (hazard ratio 0.88; 95% confidence interval [CI] 0.74–1.03; $P < 0.001$ for noninferiority and $P = 0.12$ for superiority). However, patients remained in the therapeutic range for INR only 55% of the time, which is less than that in RE-LY (the Randomized Evaluation of Long-Term Anticoagulation Therapy, 64%) and in the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation, 66%). This shorter time spent in the therapeutic range has been one of the main criticisms of the ROCKET-AF trial, but could actually reflect what happens in real life. In addition, rivaroxaban exhibits good pharmacokinetic and pharmacoeconomic properties. Novel anticoagulants are a viable and commercially available alternative to vitamin K antagonists nowadays for the prevention of thromboembolic complications in atrial fibrillation. Rivaroxaban is an attractive alternative, but the true picture of this novel compound in atrial fibrillation will only become available with more widespread use.

Keywords: atrial fibrillation, anticoagulants, rivaroxaban

Introduction

The "perfect" anticoagulant should have a relatively fast onset of action, reversibility, a linear relationship between pharmacokinetics and pharmacodynamics, and the fewest possible drug–drug interactions. Until recently, the main commercially available therapeutic option to manage thrombotic risk in atrial fibrillation was the vitamin K antagonists, which did not comply with all the necessary requirements of a good anticoagulant. In fact, use of vitamin K antagonists has been associated with many subjects not achieving or surpassing therapeutic levels and having an increased bleeding risk. Both situations are related to deficits in the vitamin K antagonists, including high variability in plasma levels due to vulnerable pharmacokinetics (food and drug interactions), implying the need for frequent monitoring

Correspondence: Mariano A Giorgi
Centro de Educación Médica e Investigaciones Clínicas "Norberto Quirno", Av Galván 4202, Buenos Aires, Argentina
Email marianoagiorgi@hotmail.com

through the use of the international normalized ratio (INR). Many compounds have been developed as part of efforts to optimize the profile of oral anticoagulants. We will focus in one of them, rivaroxaban, comparing it with novel alternatives.

Standard management options for thromboembolic risk

Thromboembolic risk

Atrial fibrillation is the most common arrhythmia, and its incidence and prevalence increases with age, with about 10% of patients older than 75 years having the disorder.[1,2] The real figures could be worse, considering that 25%–30% of people aged 65 years or older could have sustained silent atrial fibrillation.[3] In fact, according to a study of elderly patients in whom a pacemaker or a cardiac defibrillator had been recently implanted, detection of subclinical tachyarrhythmia was associated with a five-fold increased risk of developing clinical atrial fibrillation.[4] The main adverse consequence of atrial fibrillation is that it increases the risk of stroke by five-fold.[5] The annual incidence of stroke in patients with atrial fibrillation depends on the type of atrial fibrillation (paroxysmal, persistent, or permanent), ranging from 1.2% to 1.9%,[6] and the clinical characteristics of patients. There are many scoring systems available to assess the risk of stroke in atrial fibrillation. One of the most widely used is the CHADS2 (Cardiac heart failure, Hypertension, Age, Diabetes, and Stroke) score[7] that considers age $>$ 75 years (1 point), prior stroke or transient ischemic attack (2 points), diabetes mellitus (1 point), and heart failure (1 point). According to new European Society of Cardiology guidelines, long-term oral anticoagulation is a class IA indication in all patients with atrial fibrillation with a CHA2DS2 score $>$ 1, except in those with lone atrial fibrillation or the presence of contraindications.[8] Another useful system is the CHA(2)DS(2)-VASC score, which considers demonstrated cardiac failure or left ventricular ejection fraction $<$ 40% (1 point), hypertension (1 point), age $\geq$ 75 (2 points), diabetes (1 point), prior stroke, transient ischemic attack, or thromboembolism (2 points), vascular disease (1 point), age 65–74 years (1 point), and female gender (1 point) as risk factors for thromboembolism.[8–10] Patients with one definitive risk factor (previous stroke/transient ischemic attack and age $\geq$ 75 years) or a CHA(2)DS(2) score $\geq$ 2 must be considered for oral anticoagulation if there are no contraindications.[8] Patients with a score of 1 could be managed either with oral anticoagulants or aspirin 75–325 mg/day.[3] The CHA(2)DS(2) is also useful for identifying elderly patients who remain at higher risk despite use of anticoagulant therapy.[11]

Older options for management of thromboembolic risk

Until recently, the only oral compounds licensed to manage the thromboembolic complications of atrial fibrillation in the long term were the vitamin K antagonists and aspirin. Of all the vitamin K antagonists available, warfarin has been the most prescribed worldwide. In general terms, warfarin and related compounds (phencoumarol, acenocoumarol) exert their anticoagulant effect by inhibiting γ-glutamyl carboxylation of factors II, VII, IX, and X.[12] The efficacy of antithrombotics in atrial fibrillation (especially nonvalvular) is well established. A meta-analysis of 29 trials including 28,044 patients reported that, at a mean 1.5 years of follow-up, adjusted doses of warfarin and antiplatelet drugs (ie, aspirin) reduced the risk of stroke by 64% and 22%, respectively.[13] Compared with aspirin, vitamin K antagonists reduce the risk of ischemic stroke by 40%–50%.[12,14] Alongside the impressive reduction in stroke or systemic embolism achieved with vitamin K antagonists is the risk of hemorrhage. Compared with antiplatelet agents, warfarin doubles the risk of intracranial bleed and noncentral nervous system hemorrhage.[13] The hemorrhagic risk of warfarin (especially intracranial bleed) depends mainly on INR and age.[15] The recommended INR target in atrial fibrillation to prevent thrombotic events is 2.00–3.00.[8] Data from randomized controlled trials show that patients have an appropriate INR on 61%–68% of occasions whilst on warfarin.[15–18] However, in a less controlled setting, as happens in the real world, patients were found to have an INR in the therapeutic range less than 60% of the time.[19] An example of the narrow therapeutic INR margin for warfarin was shown in the study by Hylek et al,[20] which reported that 56% of patients had an INR within the therapeutic range of 2.00–3.00, 29% had INR $<$ 2.00, and 15% had INR $>$ 3.00. A recent meta-analysis showed that 44% of hemorrhagic events occurred in patients with INR levels $>$ 3.00, and 48% of thromboembolic episodes were observed in subjects with INR $<$ 2.00.[21] Regarding the influence of age, the older the population, the greater the probability of being outside the therapeutic INR range.[18–20] Recently, a new bleeding risk score known as HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly [$>$65 years], Drugs/alcohol concomitantly) has provided a practical tool for assessment of bleeding risk in individuals with atrial fibrillation.[22] The majority of patients with atrial

fibrillation are elderly, and this is the most vulnerable group when warfarin is prescribed. However, a large prospective observational study demonstrated that the absolute rate of major bleeding in patients aged ≥80 years is acceptably low with careful management of anticoagulation.[21,23]

The appropriate dose of warfarin to achieve an INR of 2.00–3.00 is sometimes hard to establish, particularly during the first months of therapy. The effect of warfarin is influenced by food, pharmacogenomic factors, and drug–drug interactions. Like many vitamin K antagonists, ingestion of vitamin K-rich foods can affect the INR value and, therefore, the efficacy of warfarin.[12] The presence of polymorphisms at the level of warfarin metabolism, ie, cytochrome P450 (CYP) CYP 2C9 and site of action, ie, vitamin K epoxide reductase are also strongly related to variability in INR values.[24] This has led to development of multiple dosing schemes, and clinical and pharmacogenetic data.[25] Other sources of INR variability are drugs that interact with warfarin. Many nonsteroidal anti-inflammatory drugs increase the bleeding risk due to their antiplatelet activity. Others modify warfarin metabolism by inhibition of CYP2C9 (ie, amiodarone, fluconazole, and efavirenz, which increase INR) or by induction of this metabolic pathway (ie, barbiturates and phenytoin, that reduce the anticoagulant effect of warfarin).[26] Warfarin and other vitamin K antagonists have a slow onset of anticoagulant effect due to their mechanism of action.[12] The synthesis of vitamin K-dependent coagulation factors is reduced 2–3 days after initiation of therapy, and this fact determines the slow return to normal INR values after drug discontinuation.[12]

Novel alternatives to vitamin K antagonists

The new paradigm of anticoagulation is centered on identification of molecules that block the coagulation cascade in a more direct fashion, and selection of molecules with more predictable pharmacokinetics.[27] The main groups of novel oral compounds act as direct thrombin inhibitors (ie, ximelagatran, dabigatran, and AZD0837) or as activated factor X inhibitors (ie, LY517717, YM150, DU176b, apixaban, rivaroxaban, betrixaban, edoxaban, and eribaxaban).[28,29] At the time of this review, dabigatran and rivaroxaban were already licensed for use in atrial fibrillation. Apixaban was awaiting the decision of regulatory agencies.

Dabigatran

Dabigatran is a reversible, orally administered direct thrombin inhibitor that has been recently licensed in several countries for the prevention of thromboembolic complications in patients with atrial fibrillation. Regarding its pharmacokinetics, it is rapidly absorbed (requiring tartaric acid), has low oral bioavailability, has non-CYP metabolism, and its half-life is 7–17 hours.[27] The background to its approval as an alternative to vitamin K antagonists in the management of atrial fibrillation was its safety in comparison with warfarin (using an open-label dose adjustment procedure) in 18,113 patients with atrial fibrillation over a mean follow-up period of 2 years.[30] Two dose regimens of dabigatran were evaluated, ie, 110 mg and 150 mg twice daily. In this trial, warfarin-treated patients remained in the therapeutic INR range 64% of the time whilst on treatment, so the data from this study were similar to those from previous registries and randomized controlled trials. Regarding the primary efficacy endpoint (stroke or systemic embolism), both doses of dabigatran were noninferior to warfarin. However, the 150 mg dose of dabigatran was superior to warfarin (relative risk 0.66, 95% confidence interval [CI] 0.53–0.82) and the 110 mg dose was not (relative risk 0.91, 95% CI 0.74–1.11). Bleeding rates (major, minor, life-threatening, and intracranial bleeding) were higher in the warfarin group than in either of the dabigatran groups. Nevertheless, the risk of major bleeding was similar between the warfarin and 150 mg dabigatran groups, and was significantly lower in the 110 mg dabigatran group compared with warfarin. In spite of the reported net benefits, alarm was raised in the medical community because of an increased incidence of myocardial infarction on both dabigatran dose regimens compared with warfarin. This unexpected finding was statistically significant for the 110 mg arm and showed a trend for the 150 mg arm.

Apixaban

Apixaban is another novel compound under consideration for use in atrial fibrillation. It is a reversible, orally administered factor Xa inhibitor with good oral bioavailability, is metabolized by CYP3A4, and has a half-life of 8–15 hours.[27] The trial that provides evidence for the use of apixaban in atrial fibrillation as an alternative to vitamin K antagonists was ARISTOTLE,[31] that randomized 18,206 patients to warfarin according to INR (using a blind system that provided a mock INR value) or apixaban 5 mg twice daily. The primary endpoint was the occurrence of stroke or systemic embolism. Patients treated with warfarin were in the therapeutic INR range 66% of the time during a median follow-up of 1.8 years. Compared with warfarin, apixaban decreased the risk of stroke or systemic embolism by 21% (relative risk 0.79, 95% CI 0.66–0.95). Apixaban also reduced the risk of hemorrhagic

stroke by 49% and of major bleeding by 31% (relative risk 0.69, 95% CI 0.60–0.80).

Rivaroxaban

This molecule binds selectively, reversibly, and directly to the active site of factor Xa, blocking interaction with its substrates.[32] It is the unique member of a new class of oxazolidinedione-based molecules with very high bioavailability.[32] Its pharmacokinetic features are shown in Table 1. Rivaroxaban is a substrate of the P-glycoprotein system and is transported through membranes.[33] Although rivaroxaban does not induce or inhibit any CYP system,[34] it is metabolized by CYP3A4 and CYP2J2 and, therefore, the concomitant use of potent inhibitors of these systems and of P-glycoprotein (ie, ketoconazole, itraconazole, or ritonavir) induced a 2.5-fold increase in the bioavailability of rivaroxaban.[34] The opposite occurred when rifampicin, a strong inducer of such enzymatic systems, was added, with a 50% reduction in bioavailability.[34] The presence of food increases both time taken to reach peak plasma concentration (by approximately 4 hours) and peak plasma levels (by about 30%).[35] Because renal excretion is the main elimination pathway, rivaroxaban should be used with caution when creatinine clearance is <50 mL per minute, and it is recommended to use 15 mg twice daily during the first weeks of treatment and 15 mg once daily thereafter.[33] Another factor related to the renal elimination of rivaroxaban is the decline in renal function associated with age. In spite of an observed two-fold increase in terminal elimination half-life in elderly subjects,[36] there is no recommendation for dose adjustment related to age.[33] The evidence suggests that the correlation between pharmacokinetics and anticoagulant effect is quite linear,[36–38] so there is no formal recommendation to monitor treatment with rivaroxaban routinely.

Following a Phase III research program, rivaroxaban secured approval from the European Medicines Agency and the US Food and Drug Administration for use in orthopedic surgery for prevention of venous thromboembolic events. Dose-finding studies revealed that once-daily or twice-daily regimens had similar efficacy and safety profiles.[39] These data were the rationale for the selection of once-daily rivaroxaban 20 mg to be assessed in nonvalvular atrial fibrillation. This indication was evaluated in ROCKET-AF (Rivaroxaban-once daily, oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation).[40] This Phase III trial randomized 14,264 patients with atrial fibrillation to rivaroxaban 20 mg or dose-adjusted warfarin (INR 2.00–3.00). The primary endpoint was occurrence of stroke or nonsystemic embolism. The aim of the

Table 1 Pharmacokinetic characteristics of rivaroxaban, apixaban, and dabigatran

	Rivaroxaban	Apixaban	Dabigatran etexilate
Absorption	• Rapid • Slightly delayed by food	• Rapid	• Rapid • Better with acid environment (pills containing tartaric acid) • Slightly delayed by high-fat diet
Relative bioavailability	• 66%–80%	• 66%	• 6.5%
t_{max}	• 0.5–4 hours • Slightly delayed by food	• 0.5–3 hours	• 1.25–3 hours • Delayed after surgery
C_{max}	• Slight interindividual variability (mostly after foods)	• Not affected by food • Increased by after multiple doses	• Interindividual variability (mostly after surgery)
Fat and elimination	• 90% circulates unchanged in plasma • Is metabolized by CYP3A4 (18%), CYP2J2 (14%), hydrolases (14%) to inactive metabolites • 66% via renal elimination: 36% unchanged • 28% via fecal elimination: 7% unchanged • 6% nonreported	• 50%–70% unchanged via fecal elimination • 25%–30% unchanged via renal elimination • Metabolized mainly by CYP3A4 and 1A1/2	• Conversion to dabigatran by hydrolysis via esterases in plasma or liver • 80% unchanged via renal elimination • 20% conjugated with glucuronic acid and eliminated via feces • Not metabolized by CYPs
Plasma protein binding	• About 95%	• About 87%	• About 35%
$t_{1/2}$	• About 3.2–11 hours	• About 8–15 hours	• About 7–17 hours
Drug–drug interactions	• Potent CYP3A4 inhibitors (ketoconazole)	• Potent CYP3A4 inhibitors (ketoconazole)	• P-glycoprotein inducers (rifampicin)

Adapted with permission from Informa Healthcare: *Expert Opin Pharmacother*. (Giorgi MA, Cohen Arazi H, Gonzalez CD, de Girolamo G. Changing anticoagulant paradigms for atrial fibrillation: dabigatran, apixaban, and rivaroxaban. *Expert Opin Pharmacother*. 2011;12:567–577.), Copyright (2011).[27]
Abbreviation: CYP, cytochrome P450.

study was to test the noninferiority of rivaroxaban versus warfarin. The study prespecified that the primary analysis would be performed on the per-protocol population of patients, ie, all subjects who received at least one dose of the study drug and were followed up while receiving the study medication or within 2 days of discontinuation. In the event that noninferiority was achieved, a test for superiority would be performed on the safety population, which comprised patients who received at least one dose of the study drug and were followed up for events while they were receiving the study drug or within 2 days of discontinuation. Both analyses were performed in the intent-to-treat patient population. The median treatment duration was 590 days and the median follow-up was 707 days. For the primary analysis (per-protocol population), rivaroxaban produced a 21% reduction in the risk of stroke or systemic embolism (hazards ratio 0.79, 95% CI 0.66–0.96; $P < 0.001$ for noninferiority). In the as-treated safety cohort, rivaroxaban also reduced the rate of the primary endpoint by 21% (hazard ratio 0.79, 95% CI 0.65–0.95; $P = 0.01$ for superiority). Finally, for the intent-to-treat population, rivaroxaban was associated with a 12% reduction in incidence of the primary endpoint compared with warfarin (hazard ratio 0.88; 95% CI 0.74–1.03; $P < 0.001$ for noninferiority and $P = 0.12$ for superiority). The annual incidences of the primary endpoint and its components for rivaroxaban and warfarin are shown in Table 2. Regarding safety, the incidence of major bleeding was similar between the treatment groups, and intracranial bleeding was less frequently observed in the rivaroxaban arm.[41]

In spite of these results, it is important to note that patients on warfarin in this trial remained within the therapeutic INR range only 55% of time, which is clearly less than for the RE-LY (64%)[30] and ARISTOTLE (66%)[31] studies. This fact has been one of the main criticisms of the findings of ROCKET-AF[41] due to the fact that rivaroxaban was compared with the "worst" warfarin-treated group, which could maximize differences between treatments. However, as suggested by one of the ROCKET-AF investigators,[42] the lower than observed time spent in the therapeutic INR range could actually reflect what happens in real life. Other concerns related to the assumptions made for declaring noninferiority and the use of a prespecified per-protocol analysis.[43] These factors are closely related to the estimated event rate in the trial, and are directly linked to the performance of the comparator. In this case, less time spent in the therapeutic range indicated poorer performance in terms of clinical efficacy. Table 2 shows that, for all clinical endpoints, warfarin-treated patients in ROCKET-AF had worse outcomes than those in the other two trials. This is one of the main weaknesses of the evidence supporting use of rivaroxaban (0.7–0.8 more stroke cases per 100 patients). In addition, the observed event rate for patients in the rivaroxaban arm was higher than the event rates for dabigatran and apixaban. Taking into account all these pros and cons, the US Food and Drug Administration approved rivaroxaban for the prevention of stroke in patients with atrial fibrillation.[44] The commercial packages include 20 mg doses to be used once daily during treatment.

Conclusion

Novel anticoagulants have become a viable and commercially available alternative to vitamin K antagonists nowadays for

Table 2 Phase III trials comparing novel anticoagulants versus dose-adjusted warfarin

Design	RE-LY (n = 18,113)			ROCKET-AF (n = 14,264)[-]		ARISTOTLE (n = 18,201)	
	Open-label			Double-blind		Double-blind	
	Dabigatran 150 mg BID	Dabigatran 110 mg BID	Warfarin (TTR 64%)	Rivaroxaban 20 mg OD	Warfarin (TTR 55%)	Apixaban 5 mg BID	Warfarin (TTR 66%)
	Event rate/100 patient year						
Primary endpoint*	1.11[ʃ]	1.53[ʃ]	1.69	2.1[ʃ]	2.4	1.27[ʃ]	1.6
Stroke (total)	1.44[ʃʃ]	1.01[ʃ]	1.57	2.6[ʃʃ]	3.12	1.19[ʃ]	1.51
Hemorrhagic	0.1[ʃ]	0.12[ʃ]	0.38	0.41[ʃ]	0.71	0.24[ʃ]	0.57
Ischemic or nonspecified	0.92[ʃ]	1.34[ʃʃ]	1.2	1.34[ʃʃ]	1.42	0.97[ʃʃ]	1.05
Major bleeding	3.11[ʃʃ]	2.71[ʃ]	3.36	3.6[ʃʃ]	3.4	2.13[ʃ]	3.08
Intracranial bleeding	0.3[ʃ]	0.23[ʃ]	0.74	0.5[ʃ]	0.7	0.33[ʃ]	0.8
Major GI bleeding	1.51[ʃ]	1.12[ʃʃ]	1.02	3.2[ʃ]	2.2	0.76[ʃʃ]	0.86
Total mortality	3.64[ʃʃ]	3.75[ʃʃ]	4.13	2.95[ʃʃ]	3.53	3.52[ʃ]	3.94

Notes: [-]Data for the ROCKET-AF trial are from the primary analysis of the per-protocol population; *stroke or systemic embolism; [ʃ]statistically significant difference compared with warfarin; [ʃʃ]statistically insignificant difference compared with warfarin.

Abbreviations: ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; GI, gastrointestinal; OD, once daily; BID, twice daily; TTR, time in therapeutic range; ROCKET-AF, Rivaroxaban-once daily, Oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy.

the prevention of thromboembolic complications in atrial fibrillation. Despite being "nonperfect" anticoagulants, they have many advantages. First, all the new compounds have been proven to be at least noninferior to warfarin for the prevention of thromboembolic complications. Second, they have shown an acceptable safety profile. Third, INR monitoring is not required, so many patients who were previously not anticoagulated for logistical reasons (ie, living in rural areas) can now be treated effectively. Finally, the more stable and predictable pharmacokinetic and pharmacodynamic characteristics of these novel compounds enables more patient-friendly dosing in comparison with the vitamin K antagonists. This is particularly important for elderly patients who are often on polypharmacy and would benefit from simplified dosification.

Rivaroxaban is a particularly attractive alternative because it can be administered once daily. Although there is no study comparing rivaroxaban with dabigatran or apixaban available as yet, rivaroxaban shows good pharmacokinetic properties, and could be a safe option in patients with renal failure. In terms of clinical performance, rivaroxaban has been shown to perform worse than the other novel agents in the prevention of systemic stroke and embolism. However, a potential advantage of rivaroxaban could be its pharmacoeconomic performance. Given that there are some data showing that dabigatran is a cost-effective alternative to warfarin in patients with atrial fibrillation[45] and that dabigatran needs to be administered twice daily and rivaroxaban once daily, this could represent a potential advantage. However, the true picture of rivaroxaban in atrial fibrillation will only become available with its more widespread use.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Schnabel RB, Sullivan LM, Levy D, et al. Developments of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet*. 2009;373:739–745.
2. Wolf PA, Benjamin EJ, Belanger AJ, Kannel WB, Levy D, D'Agostrino DB. Secular trends in the prevalence of atrial fibrillation: the Framingham Study. *Am Heart J*. 1996;131:790–795.
3. Mohammed I, Mohmand-Borkowski A, Burke J, et al. Stroke prevention in atrial fibrillation. *J Cardiovasc Med*. 2012;13:72–85.
4. Healey JS, Connolly SJ, Gold MR, Kowey PR. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366:120–129.
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Heart Study. *Stroke*. 1991;22:983–988.
6. Nieuwlaat R, Prins MH, Le Heuzey JY, et al. Prognosis, disease progression, and treatment of atrial fibrillation patients during 1 year: follow-up of the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J*. 2008;29:1181–1189.
7. Gage BF, Waterman AD, Shannon B, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870.
8. European Heart Journal. Guidelines for the management of atrial fibrillation. The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Available at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf. Accessed July 2, 2012.
9. Lip GY, Niewlaat R, Pisters R, Lane D, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–272.
10. Lip GY, Halperin JL. Improving stroke risk stratification in atrial fibrillation. *Am J Med*. 2010;123:484–488.
11. Poli D, Lip G, Antonucci E, Grifoni E, Lane D. Stroke risk stratification in a "real world" elderly anticoagulated atrial fibrillation population. *J Cardiovasc Electrophysiol*. 2011;22:25–30.
12. Brunton LL, Parker LK. Blood coagulation and anticoagulant, thrombolytic, and antiplatelet drugs. In: *Goodman and Gilman's Manual of Pharmacology and Therapeutics*. New York, NY: McGraw-Hill; 2008.
13. Hart RG, Pearce LA, Aguilare MI. Metaanalysis: antithrombotic therapy to prevent stroke in patients who have non-valvular atrial fibrillation. *Ann Intern Med*. 2007;146:857–867.
14. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians evidence-based practice guidelines. 8th ed. *Chest*. 2008;133:546S–592S.
15. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in patients taking warfarin. *Ann Intern Med*. 1994;120:897–902.
16. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted dose warfarin versus low intensity, fixed dose warfarin plus aspirin for high risk patients with atrial fibrillation: stroke prevention in atrial fibrillation III randomised clinical trial. *Lancet*. 1996;348:633–638.
17. The ACTIVE Writing Group on behalf of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367:1903–1912.
18. Mant J, Hobbs R, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomized controlled trial. *Lancet*. 2007;370:493–503.
19. Cios DA, Baker WL, Sander SD, Phung OJ, Coleman CI. Evaluating the impact of study-level factors on warfarin control in US-based primary studies: a meta-analysis. *Am J Health Syst Pharm*. 2009;66:916–925.
20. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation*. 2007;115:2689–2696.
21. Poli D, Antonucci E, Grifoni E, Abbate R, Gensini GF, Prisco D. Bleeding risk during oral anticoagulation in atrial fibrillation patients older than 80 years. *J Am Coll Cardiol*. 2009;54:999–1002.
22. Pisters R, Lane DA, Nieuwlaart R, de Vos CB, Crihns HJ, Lip GY. A novel user friendly score (HAS-BLED) to assess one-year risk of major bleeding in atrial fibrillation patients: The Euro Heart Survey. *Chest*. 2010;18:1093–1100.
23. Oake N, Fergusson DA, Forster AJ. Frequency of adverse events in patients with poor anticoagulation: a metaanalysis. *Can Med Assoc J*. 2007;176:1589–1594.
24. Wu AH. Use of genetic and non-genetic factors in warfarin dosing algorithms. *Pharmacogenomics*. 2007;7:851–861.
25. The International Warfarin Pharmacogenetics Consortium. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med*. 2009;360:753–764.
26. Bauer LA. Clinical pharmacokinetics and pharmacodynamics concepts. In: Bauer LA, editor. *Clinical Pharmacokinetics Handbook*. New York, NY: McGraw-Hill; 2006.

27. Giorgi MA, Cohen Arazi H, Gonzalez CD, de Girolamo G. Changing anticoagulant paradigms for atrial fibrillation: dabigatran, apixaban, and rivaroxaban. *Expert Opin Pharmacother*. 2011;12:567–577.
28. Chaudhari D, Bhuriya R, Arora R. Newer anticoagulants as alternate to warfarin in atrial fibrillation: a changing paradigm. *Am J Ther*. 2011;18:e1–e11.
29. Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral venous thrombin and factor Xa inhibitors in development. *Clin Pharmacokinet*. 2009;48:1–22.
30. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.
31. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.
32. Perzborn E, Strassburger J, Wilmen A, et al. In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939 – an oral, direct factor Xa inhibitor. *J Thromb Haemost*. 2005;3:514–521.
33. European Medicines Agency. CHMP Assessment Report for Xarelto. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf. Accessed on July 17, 2012.
34. Weinz C, Radtke M, Schmeer K, et al. In vitro metabolism of BAY 59-7939 – an oral, direct factor Xa inhibitor (Abstract 195). *Drug Metab Rev*. 2004;36 Suppl 1:98.
35. Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Effect of food, an antacid, and the H2 antagonist ranitidine on the absortion of BAY 59-7939 (rivaroxaban), an oral, direct factor Xa inhibitor, in healthy subjects. *J Clin Pharmacol*. 2006;46:549–558.
36. Kubitza D, Becka M, Roth A, Mueck W. Dose-escalation study of the pharmacokinetics and pharmacodynamics of rivaroxaban in healthy elderly subjects. *Curr Med Res Opin*. 2008;24:2757–2765.
37. Kubitza D, Becka M, Wensing G, Voith B, Zuehlsdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939 – an oral, direct factor Xa inhibitor – after multiple dosing in healthy male subjects. *Eur J Clin Pharmacol*. 2005;61:873–880.
38. Kubitza D, Becka M, Voith B, Zuehlsdorf M, Wensing G. Safety, pharmacodynamics, and pharmacokinetics of single dose of BAY 59-7939, an oral, direct factor Xa inhibitor. *Clin Pharmacol Ther*. 2005;78:412–421.
39. Ufer M. Comparative efficacy and safety of the novel oral anticoagulants dabigatran, rivaroxaban and apixaban in preclinical and clinical development. *J Thromb Haemost*. 2010;103:572–585.
40. The Executive Steering Committee, on behalf of the ROCKET AF Study Investigators. Rivaroxaban-once daily, oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation: rationale and design of the ROCKET AF Study. *Am Heart J*. 2010;159:340–347.
41. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.
42. Mitka M. FDA advisory decision highlights some problems inherent in pragmatic trials. *JAMA*. 2011;306:1851–1852.
43. Fleming TR, Emerson S. Evaluating rivaroxaban for nonvalvular atrial fibrillation – regulatory considerations. *N Engl J Med*. 2011;365:1557–1559.
44. United States Food and Drug Administration. FDA approves Xarelto to prevent stroke in people with common type of abnormal heart rhythm. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm278646.htm. Accessed July 2, 2012.
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.