CLINICAL INVESTIGATION

EDITORIAL

Clin. Invest. (2011) 1(1), 3–7

New oral anticoagulants for stroke prevention in atrial fibrillation

John W Eikelboom[1,2] & Jeffrey I Weitz[†1,2,3]

"The approval of dabigatran etexilate as an alternative to warfarin for stroke prevention in atrial fibrillation ushers in a new era for long-term anticoagulation."

[1]Thrombosis & Atherosclerosis Research Institute, 237 Barton Street East Hamilton, Ontario, L8L 2X2, Canada
[2]Department of Medicine, McMaster University, Ontario, Canada
[3]Department of Biochemistry & Biomedical Sciences, McMaster University, Ontario, Canada
[†]Author for correspondence:
Tel.: +1 905 574 8550
Fax: +1 905 575 2646
E-mail: weitzj@taari.ca

We are at the dawn of a new era in oral anticoagulant therapy. For the past 65 years, the only available oral anticoagulants were the vitamin K antagonists, such as warfarin [1]. Although effective, these agents are difficult to administer because the dose varies from patient to patient reflecting, at least in part, common genetic polymorphisms that influence warfarin metabolism, differences in the dietary intake of vitamin K and multiple drug interactions [2]. Consequently, the anticoagulant response to warfarin is so variable that frequent monitoring is necessary to ensure that the level of anticoagulation is therapeutic. Such monitoring is burdensome for patients and physicians and costly for the healthcare system. In addition, even when monitoring is performed, the level of anticoagulation is above or below the therapeutic range in at least half the patients, which places them at risk of bleeding or thrombosis, respectively. Because of these limitations, warfarin is underused, particularly for stroke prevention in patients with atrial fibrillation [3–7]. Therefore, there is an urgent need for new oral anticoagulants that can be given in fixed doses and produce such a predictable level of anticoagulation that monitoring is unnecessary. Finally, this need has been fulfilled.

On 20 October 2010, the US FDA approved dabigatran etexilate, a new oral thrombin inhibitor, as an alternative to warfarin for long-term stroke prevention in patients with nonvalvular atrial fibrillation [101]. Following this, 3 days after the FDA decision, regulatory authorities in Canada also approved dabigatran etexilate for this indication [102], and other countries are likely to follow suit in the near future.

Dabigatran etexilate is a prodrug of the active moiety, dabigatran; a potent, reversible direct inhibitor of thrombin [8]. Unlike warfarin, dabigatran etexilate has a rapid onset of action that obviates the need for bridging with a rapidly acting parenteral anticoagulant, a low potential for food and drug interactions such that dietary restrictions are not needed, and such a predictable anticoagulant effect that it can be given in fixed doses without routine coagulation monitoring (Table 1) [1].

Focusing on patients with nonvalvular atrial fibrillation and at least one risk factor for stroke, the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial compared two doses of dabigatran etexilate (110 or 150 mg twice daily) with warfarin, which was dose-adjusted to achieve a target international normalized ratio (INR) of 2 to 3, in 18,113 such patients recruited from 951 centers in 44 countries [9]. The two doses of dabigatran etexilate were administered in a double-blind fashion, but the comparison between dabigatran and warfarin was open label. Because dabigatran is primarily renally excreted, patients with a creatinine clearance below 30 ml/min were not included in the trial. The primary efficacy outcome was stroke or systemic embolism and the main safety outcome was major bleeding. Key outcomes were adjudicated by committees blinded to treatment allocation.

Compared with warfarin, dabigatran etexilate 150 mg twice-daily reduced stroke or systemic embolism by a third (relative risk [RR]: 0.65; 95% confidence interval [CI]: 0.52–0.81; $p < 0.001$) with a similar rate of major bleeding (RR: 0.93; 95% CI: 0.81–1.07; $p = 0.31$), whereas dabigatran etexilate 110 mg twice daily was

Table 1. Advantages of dabigatran over warfarin and other vitamin K antagonists.

Advantages	Consequences
Rapid onset of action	No need for bridging with a rapidly acting parenteral anticoagulant
Predictable anticoagulant effect	No need for routine coagulation monitoring
Low potential for food interactions	No dietary precautions
Low potential for drug interactions	Few drug restrictions

associated with a similar rate of stroke or systemic embolism (RR: 0.90; 95% CI: 0.74–1.10; p < 0.001 for noninferiority) and a reduction by a fifth in major bleeding (RR: 0.80; 95% CI: 0.70–0.93; p = 0.003) [9]. Both doses of dabigatran etexilate reduced intracranial hemorrhage by two-thirds compared with warfarin (Table 2). Compared with warfarin, the effects of dabigatran etexilate on stroke or systemic embolism were consistent in all subgroups examined, including $CHADS_2$ score at baseline, age, sex, creatinine clearance, history of prior stroke, adequacy of INR control and concomitant use of aspirin [9–11]. For major bleeding, however, there was an interaction between age and treatment such that patients aged less than 75 years had reduced rates of major bleeding with both doses of dabigatran etexilate compared with warfarin, whereas those aged over 75 years had similar rates of major bleeding with dabigatran etexilate 110 mg twice daily and higher rates of major bleeding with dabigatran 150 mg twice daily [12]. This interaction was restricted to extracranial bleeding, which was mostly gastrointestinal bleeding; compared with warfarin, both doses of dabigatran were associated with a reduced rate of intracranial bleeding irrespective of age, including in patients aged over 75 years [12].

Both doses of dabigatran etexilate were associated with numerically higher rates of myocardial infarction than warfarin, but this was outweighed by the substantially larger reduction in stroke (Table 2). The responsible mechanisms remain uncertain but this phenomenon might simply reflect superior efficacy of warfarin for prevention of myocardial infarction [13]. Both doses of dabigatran etexilate were also associated with a higher rate of dyspepsia than with warfarin, which contributed to more premature discontinuation of the drug. After 2 years of follow up, 21% of patients randomized to receive dabigatran etexilate discontinued treatment compared with 17% of those randomized to warfarin [9].

> "Both dabigatran and rivaroxaban provide patients and physicians with a major advance over warfarin because the new drugs reduce intracranial bleeding and are more convenient to administer."

The results of the RE-LY trial offer the potential to tailor the dose regimen of dabigatran etexilate in patients with atrial fibrillation according to their risk of stroke or bleeding. Because of its superior efficacy for stroke prevention over warfarin, the dabigatran etexilate 150 mg twice daily regimen is likely to be the optimal choice for the majority of atrial fibrillation patients. However, the dabigatran etexilate 110 mg twice daily regimen may be better for patients over the age of 80 years and for those at risk of gastrointestinal bleeding. Patients with severe renal impairment (creatinine clearance <30 ml/min) were excluded from the RE-LY trial; such patients may be best treated with warfarin, which is not cleared through the kidneys.

Table 2. Main results of the Randomized Evaluation of Long-Term Anticoagulant Therapy trial.

Event	Dabigatran 110 mg (n = 6015)		Dabigatran 150 mg (n = 6076)		Warfarin (n = 6022)		Dabigatran 110 mg b.i.d. vs warfarin		Dabigatran 150 mg b.i.d. vs warfarin	
	n	%/year	n	%/year	n	%/year	RR (95% CI)	p-value	RR (95% CI)	p-value
Stroke/SEE	183	1.54	134	1.11	202	1.71	0.90 (0.74–71.10)	0.30	0.65 (0.52–50.81)	<0.001
CV death	289	2.43	274	2.28	317	2.69	0.90 (0.77–71.06)	0.21	0.85 (0.72–70.99)	0.04
MI	98	0.82	97	0.81	75	0.64	1.29 (0.96–91.75)	0.09	1.27 (0.94–91.71)	0.12
Major bleeding	342	2.87	399	3.32	421	3.57	0.80 (0.70–70.93)	0.003	0.93 (0.81–81.07)	0.32
GI bleeding	137	1.15	188	1.56	126	1.07	1.08 (0.85–81.38)	0.52	1.48 (1.18–11.85)	0.001
Intracranial bleeding	27	0.23	38	0.32	90	0.76	0.30 (0.19–10.45)	<0.001	0.41 (0.28–20.60)	<0.001

b.i.d.: Twice daily; CI: Confidence interval; CV: Cardiovascular; GI: Gastrointestinal; MI: Myocardial infarction; N: Number; RR: Relative risk; SEE: Systemic embolic event.

Although the Canadian Health Authorities approved both doses of dabigatran etexilate, the FDA only approved the 150 mg twice daily dose. The FDA decision not to approve the lower dose appeared to be based on the premise that physicians would choose the lower dose regimen because of concerns about bleeding, thereby depriving patients of the efficacy advantages of the dabigatran 150 mg twice daily dose regimen over warfarin. Moreover, building on the results of pharmacokinetic modeling studies, the FDA also approved a dabigatran etexilate 75 mg twice daily dose for patients with a creatinine clearance of 15 to 30 ml/min despite the fact that such patients were excluded from the RE-LY trial, and that the efficacy and safety of this dose regimen has never been evaluated in patients with atrial fibrillation.

The approval of dabigatran etexilate as an alternative to warfarin for stroke prevention in atrial fibrillation ushers in a new era for long-term anticoagulation. Not only does dabigatran afford improved efficacy and safety compared with warfarin but dabigatran is also more convenient because it can be given in fixed doses without routine coagulation monitoring. However, dabigatran does have some disadvantages (Table 3). Unlike warfarin, which is given once daily, dabigatran etexilate must be given twice daily, which could reduce adherence and result in discontinuation of treatment. The dyspepsia associated with dabigatran, which can often be alleviated by taking the drug with meals and possibly by the concomitant use of a proton-pump inhibitor, also may reduce adherence. In addition, in contrast to warfarin, dabigatran etexilate is not suitable for use in patients with end-stage renal disease and the drug lacks an antidote (Table 3).

Can we do better than dabigatran for stroke prevention in atrial fibrillation? Several other new oral anticoagulants are in advanced stages of development for this indication. Those agents, which include rivaroxaban, apixaban and edoxaban, are oral factor Xa inhibitors [1] and share many of the advantages of dabigatran over warfarin. In contrast to dabigatran, however, this class of drugs is not associated with dyspepsia nor does there appear to be an increased risk of myocardial infarction with these agents. These features are highlighted by the results of the recent AVERROES trial, which compared apixaban 5 mg twice daily (reduced dose of 2.5 mg twice daily in patients who met at least two or the following three criteria: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dl or 133 µmol/l) with aspirin (81–324 mg once daily) in 5600 atrial fibrillation patients who were not eligible for warfarin [14]. Apixaban reduced the rate of stroke and systemic embolism by approximately a half with no increase in major or intracranial bleeding, no difference in myocardial infarction and a significantly lower drug discontinuation rate [103].

The Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF trial) results were reported on 15 November 2010 at the American Heart Association Meeting [15,104]. The trial enrolled 14,264 patients with nonvalvular atrial fibrillation and at least two additional risk factors for stroke or with a prior history of stroke, transient ischemic attack or systemic embolism from 1178 sites in 45 countries. Rivaroxaban 20 mg once daily (15 mg once daily in patients with a creatinine clearance of 30 to 49 ml/min), was noninferior to dose-adjusted warfarin (target INR of 2 to 3) for the prevention of stroke or systemic embolism (hazard ratio [HR]: 0.79; 95% CI: 0.65–0.95; p = 0.015) with no increase in major bleeding (HR: 1.04; 95% CI: 0.90–1.20; p = 0.576). Compared with warfarin, rivaroxaban reduced intracranial hemorrhage by a third (HR: 0.67;

Table 3. Disadvantages of dabigatran compared with warfarin and other vitamin K antagonists.

Disadvantages	Consequences
Need for twice daily administration	Potential for reduced compliance
Methods to monitor anticoagulation not well established	Clinicians are uncertain about the anticoagulant effect of dabigatran in patients who experience events (e.g., stroke) during treatment and in those undergoing invasive procedures[†]
Primarily renally excreted	Not suitable for use in patients with severe renal impairment[‡]
No antidote	Increased risk of bleeding in patients who require urgent invasive procedures and increased risk of adverse outcomes in those who develop severe bleeding

[†]A standardized dilute thrombin time test (Hemoclot, Hyphen Biomed, France) has been developed to measure the anticoagulant effect of dabigatran, but the test has not been fully validated nor is it widely available. Dabigatran prolongs the activated partial thromboplastin time, but the results plateau with higher levels of the drug. Nonetheless, a normal test indicates no residual anticoagulant effect of dabigatran.
[‡]On 20 October 2010 the US FDA approved dabigatran etexilate given at a dose of 75 mg twice daily in patients with a creatinine clearance of 15–30 ml/min.

95% CI: 0.47–0.94) and was associated with a similar rate of myocardial infarction. However, the median time that the INR was in therapeutic range was 58%, which is lower than that reported in other randomized trials and meta-analyses [9,16–19] and implies suboptimal warfarin management in the control group, which may have biased the efficacy outcomes in favor of rivaroxaban. Against this concept, however, was the observation that rivaroxaban was noninferior to warfarin in North America where the median time that the INR was in the therapeutic range was approximately 66%.

> "We truly are at the dawn of a new era in long-term anticoagulation management."

For now, dabigatran etexilate is the only new oral anticoagulant licensed for use as an alternative to warfarin for stroke prevention in atrial fibrillation. Once rivaroxaban is approved for this indication, however, clinicians will have to make treatment decisions on the basis of indirect comparisons of trial results, as head-to-head comparisons are lacking. Both dabigatran and rivaroxaban provide patients and physicians with a major advance over warfarin because the new drugs reduce intracranial bleeding and are more convenient to administer. Rivaroxaban is attractive because it offers the additional benefits of once-daily administration, no dyspepsia and no increase in myocardial infarction. It is likely, however, that clinicians will choose dabigatran over rivaroxaban for many of their patients because at a dose of 150 mg twice daily, dabigatran exhibited superior efficacy for stroke prevention compared with warfarin. In countries where the dabigatran 110 mg twice daily dose is licensed, this dose is likely to be preferred over rivaroxaban for use in elderly patients at high risk of bleeding because this lower dose dabigatran regimen exhibited a safety profile superior to that of warfarin. Nonetheless, with the convenience of once-daily dosing and the absence of dyspepsia, rivaroxaban may also be a good choice for selected patients. As we gain experience with dabigatran and rivaroxaban, ongoing Phase III trials comparing apixaban or edoxaban with warfarin for stroke prevention in patients with atrial fibrillation are expected to report the results in 2011 and 2012, respectively, providing us with even more treatment options [105,106]. We truly are at the dawn of a new era in long-term anticoagulation management.

Financial & competing interests disclosure

Jeffrey I Weitz is a consultant for Bristol Myers Squibb, Boehringer Ingelheim, Pfizer, Bayer, Sanofi-Aventis, Daiichi-Sankyo, Takeda, Merck, and The Medicines Company. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Bibliography

1 Eikelboom JW, Weitz JI. Update on antithrombotic therapy. New anticoagulants. *Circulation* 121, 1523–1532 (2010).

2 Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 133(6 Suppl.), S160–S198 (2008).

3 Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. *J. Manag. Care Pharm.* 15(3), 244–252 (2009).

4 Fang MC, Go AS, Chang Y *et al.* Warfarin discontinuation after starting warfarin for atrial fibrillation. *Circ. Cardiovasc. Qual. Outcomes* 3(6), 624–631 (2010).

5 Go AS, Hylek EM, Chang Y *et al.* Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA* 290(20), 2685–2692 (2003).

6 Nieuwlaat R, Capucci A, Camm AJ *et al.* Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur. Heart J.* 26(22), 2422–2434 (2005).

7 Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. *Stroke* 37(4), 1070–1074 (2006).

8 Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor Xa inhibitors in development. *Clin. Pharmacokinet.* 48, 1–22 (2009).

9 Connolly SJ, Ezekowitz MD, Yusuf S *et al.*, and the RE-LY steering committee and investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* 361, 1139–1151(2009).

10 Wallentin L, Yusuf S, Ezekowitz MD *et al.*, on behalf of the RE-LY investigators. 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* 376, 975–983 (2010).

11 Diener H-C, Connolly SJ, Ezekowitz MD *et al.*; for the RE-LY Steering Committee and Investigators. Dabigatran compared with warfarin in patients with atrial fibrillation and prior transient ischaemic attack or stroke: results of Randomized Evaluation of Long-Term Anti-coagulation Therapy (RE-LY). *Lancet Neurol.* 9(12), 1157–1163 (2010).

12 Healey JS, Eikelboom J, Wallentin L *et al.* Effect of age and renal function on the risks of stroke and major bleeding with dabigatran compared with warfarin: an analysis from the RE-LY study. *J. Am. Coll. Cardiol.* 55, 10A (2010) (Abstract).

13 Lip GY, Lance Da. Does warfarin for stroke thromboprophylaxis protect against MI in atrial fibrillation patients? *Am. J. Med.* 123, 785–789 (2010).

14 Eikelboom JW, O'Donnell M, Yusuf S *et al.* Rationale and design of AVERROES: apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment. *Am. Heart J.* 159, 348–353 (2010).

15 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.* 159, 340–347.e1 (2010).

16 Connolly SJ, Pogue J, Eikelboom J *et al.*; ACTIVE W investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation* 118, 2029–2037 (2008).

17 Pengo V, Pegoraro C, Cucchini U, Iliceto S. Worldwide management of oral anticoagulant therapy: the ISAM study. *J. Thromb. Thrombolysis* 21, 73–77 (2006).

18 White HD, Gruber M, Feyzi J *et al.* Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. *Arch. Intern. Med.* 167, 239–245 (2007).

19 van Walraven C, Jennings A, Oake N, Fergusson D, Forster AJ. Effect of study setting on anticoagulation control: a systematic review and metaregression. *Chest* 129, 1155–1166 (2006).

Websites

101 US FDA approves Pradaxa® to prevent stroke in people with atrial fibrillation. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm230241.htm (Accessed 6 November 2010).

102 PRADAX™ (dabigatran etexilate) gains approval in Canada for stroke prevention in atrial fibrillation. www.boehringer-ingelheim.com/news/news_releases/press_releases/2010/27_october_2010_dabigatran.html (Accessed 6 November 2010).

103 O'Riordan M. AVERROES: apixaban yields significant reductions in stroke, no increased bleeding. www.theheart.org/article/1116449.do (Accessed 6 November 2010).

104 O'Riordan M. Off orbit? ROCKET AF: rivaroxaban noninferior to warfarin, but superiority analyses at odds. www.theheart.org/article/1148785.do (Accessed 19 November 2010).

105 Apixaban for the prevention of stroke in subjects with atrial fibrillation (ARISTOTLE). NCT00412984. www.clinicaltrials.gov/ct2/show/NCT00412984?term=ARISTOTLE&rank=1 (Accessed 6 November 2010).

106 Global study to assess the safety and effectiveness of DU-176b vs standard practice of dosing with warfarin in patients with atrial fibrillation (EngageAFTIMI48). NCT00781391. www.clinicaltrials.gov/ct2/show/NCT00781391?term=ENGAGEAFTIMI48&rank=1 (Accessed 6 November 2010).