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ATRIAL FIBRILLATION

A promising new anticoagulant for stroke prevention

Sarah A. Spinler

Stroke is the leading cause of morbidity and mortality in patients with atrial fibrillation. Whereas warfarin reduces the risk of stroke, its interactions with other drugs and food, individual differences in its efficacy and the need for frequent monitoring make its use inconvenient. Dabigatran etexilate might represent a step forward in the care of patients with atrial fibrillation.

Patients with atrial fibrillation (AF) might benefit from treatment with anticoagulants, such as warfarin, which help prevent stroke. However, a substantial number of these patients do not receive warfarin, either because of their poor compliance with monitoring of anticoagulation (measured by the international normalized ratio [INR]) and dietary restrictions, or owing to their physician's concern regarding the increased risk of bleeding associated with the use of this drug.[1] A large, open-label, noninferiority trial, the Randomized Evaluation of Long-term Anticoagulant (RE-LY) trial, compared the rates of stroke or systemic thromboembolism and bleeding in patients treated with warfarin (doses were determined by a local investigator to target INR 2.0–3.0), or with a fixed dose (110 mg or 150 mg twice daily) of a new anticoagulant, dabigatran etexilate, without routine anticoagulation monitoring for a median of 2 years.[2] Results of the RE-LY study indicate superior efficacy of dabigatran 150 mg twice daily with similar risk of major bleeding compared with warfarin, whereas dabigatran 110 mg twice daily demonstrated similar efficacy to warfarin with a lower risk of bleeding.[3]

> "...the frequency of intracranial hemorrhage was more than halved with both dabigatran doses compared with warfarin"

Dabigatran etexilate, an orally active, direct thrombin inhibitor, is a prodrug that is converted by hydrolysis to the active form dabigatran, which has a rapid anticoagulant effect within 2 h following ingestion and an elimination half-life of 12–17 h.[4] As a result, dabigatran does not need to be bridged with an injectable anticoagulant in patients who are at high risk of stroke; in its current formulation, however, it requires twice daily dosing. Of note, clinical use of dabigatran etexilate has been approved in Europe and Canada, but not in the US.

In the RE-LY study, dabigatran or warfarin were administered to 18,113 patients with AF and at least one major risk factor for stroke (history of previous stroke, transient ischemic attack or systemic thromboembolism, an ejection fraction of less than 40%, symptomatic heart failure within the past 6 months, age ≥75 years, or age ≥65 years plus either diabetes mellitus, coronary artery disease or hypertension).[2] The primary end point, either stroke or systemic thromboembolism, as well as a secondary end point, stroke, occurred less often in patients treated with dabigatran 150 mg compared with warfarin, whereas dabigatran 110 mg was noninferior to warfarin.[3] The risk of major bleeding was lower in the dabigatran 110 mg group and similar in the dabigatran 150 mg group, compared with the warfarin group; the risk of life-threatening major bleeding was, however, lower in both dabigatran groups than in the warfarin group. Importantly, the frequency of intracranial hemorrhage was more than halved with both dabigatran doses compared with warfarin. In contrast, the frequency of myocardial infarction was higher in patients treated with dabigatran 150 mg compared with warfarin. In patients treated with dabigatran, no evidence of liver toxicity was observed but the absolute risk of dyspepsia increased by 6%.[3]

The net clinical benefit (a composite of death, stroke, systemic embolism, pulmonary embolism, myocardial infarction, or major bleeding) of dabigatran 150 mg was superior to that of warfarin (relative risk 0.91, 95% CI 0.82–1.00) but similar to that of dabigatran 110 mg (relative risk 0.98, 95% CI 0.89–1.08).[3] The number of patients who needed treatment with dabigatran etexilate for 1 year to prevent various adverse outcomes is reasonable (Table 1). These benefits, however, were observed at a cost of 14–15 myocardial infarctions per 1000 patients treated for 1 year and an excess risk of dyspepsia. Owing to the similarity between the effects of the two doses of dabigatran, the ideal dose for a particular patient cannot be determined on the basis of this data from RE-LY; it might be clarified by publication of an important substudy that evaluates predictors of bleeding and stroke risk.[2]

Table 1 | NNT with dabigatran for 1 year to prevent one adverse event compared with warfarin

Event	NNT*	
	Dabigatran 110 mg twice daily	Dabigatran 150 mg twice daily
Stroke or systemic thromboembolism	NA	172
Stroke	NA	179
Intracranial bleeding	196	227
Major bleeding	154	NA
Life-threatening bleeding	172	286

*Defined as $1/(p_d-p_w)$ where p_d and p_w represent the risk of an adverse event in either dabigatran group and in the warfarin group, respectively. Abbreviation: NA, not applicable as the outcomes were not statistically significant; NNT, number of RE-LY participants[3] who needed to be treated.

Owing to the open-label design of the RE-LY study, the frequency of monitoring was different in the main treatment arms. To minimize the risk of its adverse effects, warfarin treatment necessitates monthly INR testing and discussion of medication changes, diet, bleeding events and other lifestyle changes with a healthcare provider. Such close monitoring, however, is not recommended during dabigatran therapy, as the dose of dabigatran is fixed and not adjusted to changes in the INR. While dabigatran does increase the INR and the activated partial thromboplastin time to some extent, the effects are variable and depend on reagent, and have not been used in clinical trials to make dosing adjustments.[4] As a consequence, and because the RE-LY study was unblinded, patients in the dabigatran group were followed up less often (regular visits at 14 days, 1 month, 3 months, 6 months, 9 months, 1 year and then every 4 months) than those in the warfarin group (regular visits plus monthly INR testing).[2] To avoid reporting bias, events were adjudicated by a blinded committee.[2] The advantage of this design is that the use of dabigatran was similar to that likely to occur in clinical practice. In addition, if monthly INR testing was performed in the dabigatran arm as well, with sham dose changes to simulate warfarin management, the safety of permitting unmonitored use of dabigatran for more than 1 month could not have been confirmed.

The monthly monitoring of warfarin-treated patients revealed that their INR values remained within the therapeutic range during 64% of the study period. This value is similar to the frequency of warfarin-treated patients' visits at anticoagulation clinics (63%) that has been reported in a meta-analysis.[5] However, the majority of warfarin management in the US occurs via 'usual care', rather than in anticoagulation clinics, which results in a markedly decreased duration of time (51%) spent within the therapeutic range.[5] Therefore, the risk of warfarin-related adverse outcomes, such as bleeding or stroke, might be even higher and dabigatran's benefit even greater in general practice than in the RE-LY study. In addition, the safety of warfarin in RE-LY may have been overestimated, as more than 50% of patients in each group were already safely receiving long-term vitamin K antagonist therapy at baseline,[3] and initiation of warfarin in anticoagulation naive patients is associated with instability of the INR and a high bleeding risk.[6]

Importantly, the study results do not imply that dabigatran etexilate 110 mg is safe for patients with risk factors for bleeding as those with any contraindication to warfarin treatment were excluded from participating.[2] Other important subgroups of patients were also excluded, such as those with valvular heart disease, prosthetic heart valves, or a creatinine clearance rate ≤30% (of note, 80% of dabigatran is cleared by the kidney[4]).[2] Therefore, dabigatran treatment should be avoided in these subgroups of patients with AF until more information is available.

Clinicians should also consider dabigatran's interactions with other drugs. Dabigatran is a medium-affinity substrate for the transporter P-glycoprotein; therefore, the European product labeling contraindicates concomitant administration of quinidine, a strong inhibitor of P-glycoprotein, with cautions for other strong P-glycoprotein inhibitors, such as verapamil and clarithromycin.[7] Furthermore, as amiodarone increases the concentration of dabigatran by 50%,[7] the European labeling recommends to administer no more than 150 mg of dabigatran etexilate per day when given concomitantly with this drug and to consider dose adjustments for patients who have received amiodarone previously[7] as it persists in the body for months to years following discontinuation of the treatment. In contrast, coadministration of dabigatran etexilate with digoxin, another substrate for P-glycoprotein, does not have any significant effect on serum concentrations of either drug.[7] Detailed information regarding these interactions and management strategies for the concomitant use of potentially interacting drugs is necessary to assure safety.

In summary, dabigatran etexilate, an oral, rapid-acting anticoagulant that does not necessitate routine anticoagulation monitoring, offers the advantages of enhanced or similar efficacy and a lower frequency of intracranial hemorrhage without an increased risk of major bleeding compared with warfarin.

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