

## CORRESPONDENCE



## Dabigatran versus Warfarin in Patients with Atrial Fibrillation

**TO THE EDITOR:** Although Connolly et al. (Sept. 17 issue)<sup>1</sup> have demonstrated a modest advantage for dabigatran over warfarin in atrial fibrillation, we think the benefit could be even greater.

Warfarin has many adverse properties. Vitamin K content varies widely in foods. Warfarin inhibits the synthesis of sequential enzymes in the coagulation cascade, which imparts a drastically steep dose–response relationship. The binding of warfarin to plasma proteins and its metabolism by cytochrome P-450 enzymes facilitate drug interactions. These properties result in variability in anticoagulant control, which is associated with bleeding, thrombosis, and increased risk of death.<sup>2–5</sup>

Dabigatran lacks these undesirable properties. But the adoption of “one size fits all” dosing has probably undermined the performance of dabigatran in the trial for the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY). Dabigatran appeared to be more efficacious in patients who weighed less and in patients with impaired renal function (in whom the drug accumulates), pointing to significant interpatient variability in response. Individualized dosing, based on weight and estimated creatinine clearance, might improve the drug’s risk–benefit ratio. Dosing could be further refined with the use of a single measurement of the drug level drawn at steady state, if necessary. Such an approach should be studied.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** The RE-LY investigators report that dabigatran, a thrombin inhibitor, was associated with similar or better outcomes in patients with atrial fibrillation, as compared with warfarin. They also report that myocardial infarction occurred at a rate of 0.72 to 0.74% per year for dabigatran (with respective dosing of 110 mg or 150 mg twice daily) versus 0.53% per year for warfarin (P=0.07 for comparison with the 110-mg dose and P=0.048 for comparison with the 150-mg dose). Although the difference of 0.2% per year

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appears small, in the United States there are approximately 2.3 million adults with atrial fibrillation,<sup>1</sup> and a substantial number of myocardial infarctions might therefore result from long-term use of dabigatran. Dabigatran has been reported to increase urinary thromboxane excretion in patients not receiving aspirin, suggesting a paradoxical platelet-activating effect.<sup>2</sup> In a study of deep-vein thrombosis comparing the effectiveness of ximelagatran, another thrombin inhibitor, with that of a combination of enoxaparin and warfarin, the rate of serious coronary events associated with the former was 0.81%, versus 0.08% for the latter ( $P=0.006$ ).<sup>3</sup> In that trial, concomitant aspirin administration was discouraged. In another study, administration of ximelagatran in combination with aspirin helped to prevent a recurrence of myocardial infarction.<sup>4</sup> In a subgroup analysis in the RE-LY trial, aspirin use did not significantly affect the rate of thromboembolism. However, coronary thrombosis is induced by platelet aggregation rather than thromboembolism. Possible platelet-activating effects of dabigatran require further investigation.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** Connolly et al., in comparing the use of warfarin and dabigatran in patients with atrial fibrillation, found that the yearly incidence of major bleeding in the warfarin group was 3.36%. This rate is much higher than that previously reported by the same author (1.78 to 2.92%)<sup>1</sup> and than that reported for warfarin groups in clinical trials of anticoagulants such as ximelagatran (1.8%)<sup>2</sup> and idraparinix (1.4%)<sup>3</sup> in the treatment of atrial fibrillation. We surmise that

the high percentage of patients concomitantly treated with aspirin in the recent report by Connolly et al. (about 20%) contributed substantially to the unusually high incidence of bleeding. A favorable risk–benefit ratio for the use of aspirin with warfarin has been reported only for patients with mechanical heart valves,<sup>4</sup> not for atrial fibrillation, and the combination increases the risk of bleeding. In one study, patients with atrial fibrillation who received aspirin in combination with warfarin had almost double the rate of bleeding in patients who received warfarin alone (17.7% vs. 9.3%).<sup>3</sup> Subgroup analysis by Connolly et al. should help to establish whether concomitant administration of aspirin with warfarin was responsible for the high rate of major bleeding.

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Drs. Moia and Mannucci report receiving lecture fees from Boehringer and Bayer. No other potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** The results of the RE-LY study indicate that we may finally have a fixed-dose anticoagulant that is effective in the treatment of nonvalvular atrial fibrillation. Establishing the role of dabigatran will require subgroup analyses in elderly patients, in whom nonvalvular atrial fibrillation is most prevalent and for whom the benefits of warfarin are now established.<sup>1</sup> We also need to consider the high bleeding rate observed with warfarin use and its relationship to high concomitant use of antiplatelet agents.<sup>2</sup> Publication of the risk of fatal bleeding by group would be helpful to clinicians.<sup>3</sup>

Discontinuation rates were high, particularly in the dabigatran group (21%, vs. 17% for the warfarin group). We assume that patients who

stopped receiving treatment without having had a stroke or systemic embolism (the primary outcomes) remained in the intention-to-treat-analysis. Subsequent antithrombotic selections across study groups should be considered for their possible influence on the small absolute differences between groups. Presumably, patients who stop taking dabigatran could be switched to warfarin. It is unclear whether dabigatran or less effective antiplatelet agents were administered after cessation of treatment with warfarin.

Finally, it will be important to gauge the value of the benefits and convenience of dabigatran as compared with its cost and lack of reversibility at the time of acute bleeding.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** The investigators in the RE-LY trial report a reduced risk of hemorrhage in patients with atrial fibrillation who are treated with 110 mg of dabigatran twice daily as compared

with those treated with warfarin. The investigators also report a reduced risk of stroke and embolism in those treated with 150 mg of dabigatran twice daily. In this trial, the incidence of both thrombotic and hemorrhagic events in patients treated with warfarin far exceeds the incidence of these events in patients in the European Action on Anticoagulation (EAA) study<sup>1</sup> (Table 1); the incidence of these events is also higher in patients treated with either dose of dabigatran than in the EAA study. In that study, patients underwent randomization to computer-assisted or physician-determined dosing, but because there was no significant difference in clinical events in the patients with atrial fibrillation in the study groups, the results have been pooled for this analysis. Connolly et al. studied an average of only 6.3 patients per center, whereas the EAA investigators averaged 185 patients with atrial fibrillation per center.

The effectiveness and safety of warfarin depend on reliable control of the international normalized ratio (INR), but the authors do not provide any information about local calibration of the international sensitivity index<sup>2,3</sup> or external assessments of the INR.<sup>4</sup>

Dabigatran may prove useful in atrial fibrillation therapy, but on the basis of this evidence, it cannot take the place of warfarin.

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**Table 1. Incidence of Stroke, Hemorrhage, and Death among Patients in the RE-LY Trial versus Patients in the EAA Study.\***

Variable	RE-LY Trial of Dabigatran vs. Warfarin		EAA Study of Warfarin	
			Warfarin	
	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	Warfarin
Total no. of patients	6015	6076	6022	5939
No. of centers	951	951	951	32
No. of patients per center	6.3	6.4	6.3	185.6
Events per year (%)				
Stroke	1.44	1.01	1.57	0.30
Bleeding				
Minor	13.16	14.84	16.37	2.7
Major	2.71	3.11	3.36	0.86
Death	3.75	3.64	4.13	0.75

\* RE-LY denotes Randomized Evaluation of Long-Term Anticoagulation Therapy, and EAA European Action on Anticoagulation.

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**TO THE EDITOR:** The editorial by Gage that accompanies the report by Connolly et al. highlights the difficulties associated with the use of warfarin therapy in the treatment of patients with atrial fibrillation and considers the use of the new thrombin inhibitor dabigatran.<sup>1</sup> But the author failed to highlight the significant difference in price between warfarin and dabigatran. In Ireland, a month's supply of warfarin in a dose of 5 mg per day costs approximately €2.13 (about \$3.55), whereas a month's supply of dabigatran (Pradaxa, Boehringer Ingelheim) in a dose of 110 mg twice daily costs €143.70 (about \$239.55). Warfarin has regularly been in the top 15 most frequently prescribed medicines, and more than 32,400 patients in Ireland take it. If just 50% of these patients were to switch to dabigatran, the drug acquisition cost would be roughly €27 million (about \$45 million) per year, or about 10% of the total cost of cardiovascular medicines. Clearly, there will be cost offsets, since anticoagulation monitoring will not be necessary and the rate of clinical events will be reduced. Many countries will conduct a formal health technology assessment before providing reimbursement for the drug in the treatment of atrial fibrillation. The editorial suggests that we can rely on RE-LY, but many decision makers will ask, can we afford RE-LY?

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No potential conflict of interest relevant to this letter was reported.

1. Gage BF. Can we rely on RE-LY? *N Engl J Med* 2009;361:1200-2.

**THE AUTHORS REPLY:** We agree with Houston and Zarychanski that the benefits of dabigatran over warfarin in the RE-LY trial are probably due in part to reduced variability in anticoagulant con-

trol. The availability of two effective doses will allow for individualized therapy. Since 80% of the dabigatran dose is excreted by the kidney, we are evaluating the importance of the assessment of renal function in dose selection with the use of information on plasma concentration.

Tomoda alludes to the possible platelet-activating effects of dabigatran. Although rates of myocardial infarction were higher among patients taking dabigatran than among those taking warfarin, this may be due to a superior effect of warfarin in the prevention of myocardial infarction. The question of whether dabigatran activates platelets is being evaluated in a substudy.

Moia and Mannucci draw attention to the higher rate of major bleeding among patients in the RE-LY trial who were taking warfarin as compared with patients taking warfarin in other anticoagulant trials. This difference results in part from the greater use of aspirin in our study. It also results from the fact that in our study a drop in hemoglobin levels of  $\geq 20$  g per liter was considered a major bleeding episode, whereas in previous studies, such as the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events — W (ACTIVE-W),<sup>1</sup> this degree of decline in hemoglobin levels was not considered a major bleeding episode.

We agree with the many issues raised by Worthington and Gattellari. The annual rates of fatal hemorrhage were 0.19 in patients taking 110 mg of dabigatran, 0.23 in patients taking 150 mg of dabigatran, and 0.32 in patients taking warfarin. The corresponding relative risks for 110 mg of dabigatran versus warfarin were 0.60 (95% confidence interval [CI], 0.36 to 1.00;  $P=0.05$ ), and those for 150 mg of dabigatran versus warfarin were 0.72 (95% CI, 0.44 to 1.17;  $P=0.19$ ). Patients discontinuing therapy remained in the intention-to-treat analysis.

Poller et al. draw attention to the difference between the rates of stroke and hemorrhage in the RE-LY trial as compared with their EAA study. They conclude that the much lower event rates in their study make the evidence from RE-LY insufficient to warrant the use of dabigatran as a replacement for warfarin. Comparing data between studies is notoriously unreliable, as enrolled patients may have different characteristics and concomitant therapies. Event definitions may also differ between studies. We note that patients in the EAA study were substantially younger (by an average of 5 years) than the patients in RE-LY. The

EAA report does not provide patients' CHADS<sub>2</sub> scores or a definition of major bleeding, but it is likely that both differed from those in RE-LY. Given the risk profile of patients enrolled in RE-LY and the outcome definitions used, the event rates in RE-LY are consistent with previous reports.<sup>1,2</sup> Furthermore, the time in the therapeutic range achieved in RE-LY is similar to that reported by the EAA investigators, indicating that differences in event rate are not due to the way in which warfarin administration is managed. Therefore, the advantages of dabigatran over warfarin shown in the RE-LY trial are probably applicable to a wide population of patients with atrial fibrillation requiring oral anticoagulation.

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Since publication of their article, the authors report no further potential conflict of interest.

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**THE EDITORIALIST REPLIES:** Thank you for providing the cost of dabigatran in Ireland and for raising the issue of affordability. Dabigatran is

not available in the United States, but a 1-month supply of dabigatran can be purchased through Canadian pharmacies for \$339 (U.S. dollars) — about 10 times the monthly cost of warfarin therapy (including the cost of monitoring). For a typical participant in the RE-LY trial, the number needed to treat to prevent 1 (nonhemorrhagic) stroke with dabigatran (150 mg twice daily) is 357. Using these estimates, the cost per stroke averted with dabigatran (rather than warfarin) averages approximately \$1.3 million (U.S. dollars). For patients with twice the average risk of stroke (e.g., CHADS<sub>2</sub> score<sup>1</sup> of 3 to 4), the number needed to treat and the cost per stroke averted would be halved.

However, these calculations do not take into account the costs and morbidity associated with stroke. The cost of care for a stroke patient averages \$28,500 in the initial 12 months,<sup>2,3</sup> and the lifetime cost of stroke is several times greater.<sup>3</sup> Thus, although dabigatran is unlikely to be cost-saving, it might be cost-effective, at least in carefully selected patients.

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Since publication of his article, the author reports no further potential conflict of interest.

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## Sex Hormone–Binding Globulin and Risk of Type 2 Diabetes

**TO THE EDITOR:** Ding et al. (Sept. 17 issue)<sup>1</sup> found that sex hormone–binding globulin, which is predominantly expressed in hepatocytes, may protect against type 2 diabetes. What variables in the natural history of diabetes determine circulating levels of sex hormone–binding globulin? Recently, monosaccharide-induced hepatic lipogenesis, but not insulin, was shown to suppress hepatic production of sex hormone–binding globulin in animals.<sup>2</sup> Because this pathway is involved in the pathogenesis of fatty liver, a major risk factor in

type 2 diabetes,<sup>3</sup> we hypothesized that levels of sex hormone–binding globulin decrease, particularly under hepatic steatosis. In subjects who underwent precise measurements of liver-fat and body-fat distribution<sup>4</sup> we observed that besides sex and age, liver fat, but not visceral fat or total body fat, was an independent predictor of levels of sex hormone–binding globulin (Fig. 1A). During a lifestyle intervention, an increase in levels of sex hormone–binding globulin was more strongly associated with a decrease in liver fat (Fig. 1B) as