REVIEW ARTICLE

Dabigatran: ready for prime time?

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KEY WORDS

atrial fibrillation, dabigatran, thrombin inhibitors, venous thromboembolism

ABSTRACT

Studies in high-risk surgical patients have demonstrated the efficacy of the selective inhibitors of factor Xa and thrombin in preventing venous thromboembolism. Because of their predictable dose-response, which eliminates the need for routine laboratory monitoring, they may be more convenient for patients requiring long-term therapy, and have the potential to improve the quality of anticoagulation. The results from 2 large trials of dabigatran (a thrombin inhibitor) compared to warfarin, in patients with atrial fibrillation and those with acute symptomatic venous thromboembolism, have recently become available. These trials provide convincing evidence of the efficacy of dabigatran in preventing patient-important clinical outcomes when compared to warfarin. In this paper we critically review these trials and discuss the feasibility of replacing warfarin with dabigatran for these indications.

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Introduction The new selective inhibitors of activated factor X and thrombin are effective in preventing venous thromboembolism (VTE) in high-risk patients when compared to enoxaparin, which is the current standard of care.[1] While these studies provided unequivocal evidence of efficacy, the greatest potential for the new oral agents lies in long-term therapy where their favorable characteristics (namely, a predictable dose-response, which obviates the need for routine laboratory monitoring and the lower potential for food and drug interactions) may lead to improved outcomes when compared to standard anticoagulation with warfarin. The results of 2 large phase III trials of long-term treatment with dabigatran involving patients with atrial fibrillation (AF)[2] and acute VTE[3] have recently become available. In this commentary, we critically review these trials and discuss if we should replace warfarin with dabigatran for these indications.

The pharmacology of dabigatran etexilate has been reviewed in several recent publications.[4-6] Briefly, dabigatran etexilate is an orally active, direct thrombin inhibitor. It is a pro-drug with a low bioavailability (about 6%) and is converted to its active metabolite in the gut and liver. Plasma concentrations peak in 2 h and the half-life after oral administration is 12 to 17 h. 80% of the drug is excreted unchanged by the kidneys. It is therefore contraindicated in patients with severe renal insufficiency (creatinine clearance <30 ml/min). Dabigatran etexilate is a substrate for the efflux transporter, P-glycoprotein (P-gp), and blood levels of dabigatran are increased by up to 50% with concomitant administration of moderate inhibitors of P-gp, amiodarone, and verapamil. Quinidine is a potent P-gp inhibitor and should not be administered with dabigatran.

The RE-LY study The RE-LY study (Randomized Evaluation of Long-term Anticoagulation Therapy) asked the question: In patients with AF and an indication for oral anticoagulation, is dabigatran noninferior to warfarin for reducing the occurrence of stroke and systemic embolism?[2] Over 18,000 patients with AF were recruited in this global trial and randomized to receive either 110 mg of dabigatran twice daily, 150 mg dabigatran twice daily, or adjusted-dose warfarin (target international normalized ratio [INR] 2–3). Patients and healthcare providers were blinded to the dose of dabigatran while the warfarin arm was open-label. Patients were followed up for a median of 2 years. The primary outcome was the first occurrence of stroke or systemic embolism. The primary safety outcome was the occurrence of major hemorrhage. Secondary outcomes were stroke, systemic embolism, and death. Outcomes were adjudicated using standard definitions by an independent committee of clinicians who were blinded to treatment assignment. To establish the noninferiority

TABLE 1 Salient characteristics of the RE-LY and RE-COVER studies

Trial characteristic	RE-LY	RE-COVER
design	randomized, controlled, noninferiority trial	randomized, controlled, noninferiority trial
allocation concealment	yes	yes
blinding	patients, care providers, and outcome assessors (dabigatran dose); outcome assessors (dabigatran and warfarin)	patients, care providers, and outcome assessors
setting	international (44 countries), multicenter (951 centers)	international (29 countries), multicenter (228 centers)
patients	18,113 patients, mean age 71 years, 64% male, had AF (at screening or within 6 months) and were at risk of stroke (past stroke/TIA, LVEF <40%, heart failure symptoms, ≥75 years of age, or if 65–74, had associated diabetes mellitus, hypertension or coronary artery disease principal exclusions were: any stroke in the 14 days prior to enrollment, severe stroke in the last 6 months, increased risk of hemorrhage, creatinine clearance <30 ml/min, and active liver disease	2564 patients, median age 55, 59% male, had acute, symptomatic, objectively verified proximal deep vein thrombosis of the legs or pulmonary embolism, for whom 6 months of oral anticoagulation was considered appropriate principal exclusions were: symptoms >14 days, pulmonary embolism with hemodynamic instability or requiring thrombolytic therapy, increased risk of hemorrhage, creatinine clearance <30 ml/min, and active liver disease
interventions	dabigatran, 110 mg or 150 mg twice daily, orally, or warfarin (dose adjusted to INR of 2–3)	dabigatran 150 mg twice daily orally, or warfarin (dose adjusted to INR of 2–3)
outcomes	primary efficacy: composite of stroke or systemic embolism primary safety: major hemorrhage	symptomatic VTE or VTE-related death other outcomes: major bleeding
follow-up and adherence	99.9% follow-up (intention-to-treat population); rates of drug discontinuation were 20.7%, 21.2%, and 16.6% for dabigatran 110 mg, 150 mg, and warfarin, respectively. Mean time in therapeutic range for warfarin treated patients was 64%.	99% (modified intention-to-treat, i.e., only those who received at least 1 dose of the study drugs); rates of drug discontinuation were 16% in the dabigatran group and 14.5% in the warfarin group. The mean time in therapeutic range for warfarin treated patients was 60%.
main results	Both doses of dabigatran were noninferior to warfarin and the 150 mg dose of dabigatran was superior to warfarin. Rates of major hemorrhage were lower with dabigatran treatment.	dabigatran was noninferior to warfarin for efficacy (recurrent VTE)

Abbreviations: AF – atrial fibrillation, INR – international normalized ratio, LVEF – left ventricular ejection fraction, TIA – transient ischemic attack, VTE – venous thromboembolism

of dabigatran, the investigators prespecified that the upper bound of the one-sided 97.5% confidence interval (CI) of the relative risk (RR) for the primary outcome with dabigatran compared to warfarin needed to fall below 1.46. This represents half the 95% CI of the RR with control therapy compared to warfarin, estimated from a meta-analysis of oral anticoagulation vs. control therapy in patients with AF.[7] The study was designed to have more than 80% power to demonstrate noninferiority of each dose of dabigatran compared with warfarin. The salient features of the study are summarized in TABLE 1.

Follow-up was complete in all but 20 patients. Rates of discontinuation of dabigatran were marginally greater than that of warfarin (TABLE 1). In the warfarin arm, the mean percentage of the study period during which the INR was in the therapeutic range was 64%. About 70% of the enrolled patients had a $CHADS_2$ score ≥2 and the stroke rate in the warfarin arm was 1.57% per year. The main results are summarized in TABLE 2. Both doses of dabigatran were noninferior to warfarin for the primary outcome (P <0.001), and the 150 mg dose of dabigatran was superior to warfarin (RR 0.66, 95% CI 0.53–0.82; P <0.001). Rates of hemorrhagic stroke with either dabigatran dose were about a third of that with warfarin therapy. The rate of major bleeding were lower than warfarin with the 110 mg bid dose of dabigatran, but was not different from warfarin with the 150 mg bid dose of dabigatran (TABLE 2). All categories of major bleeding were higher with warfarin with one exception: major gastrointestinal bleeding was significantly higher with the 150 mg bid dose of dabigatran when compared to warfarin. (TABLE 2) The 150 mg bid dabigatran dose, compared to the 110 mg bid dose, reduced the risk of the primary outcome compared to the lower dose (RR 0.73, 95% CI 0.58–0.91; P = 0.005) but also caused a trend toward an increased risk of major bleeding (RR 1.16, 95% CI 1.00–1.34; P = 0.052). Dabigatran did not cause any excess of significant liver enzyme elevation compared to warfarin. There was a considerable increase in the risk of myocardial infarction (MI) in both the 110 mg bid dose arm (RR 1.35, 95% CI 0.98–1.87; P = 0.07), and the 150 mg bid arm (RR 1.38, 95% CI 1.00–1.91; P = 0.048). Another notable problem with dabigatran was the higher incidence of dyspepsia (11.8%, 11.3%, and 5.8% in the 110 mg dabigatran group, 150 mg dabigatran group, and the warfarin group, respectively).

The RE-COVER study The primary objective of the RE-COVER study was to determine if

TABLE 2 Results of the RE-LY study

Comparisons	Outcomes	Event rates (%/year)	RR (95% CI)	NNT/NNH[a] (CI)
dabigatran 110 mg twice daily vs. warfarin	efficacy			
	stroke or systemic embolism	1.53 vs. 1.69	0.91 (0.74–1.11)	noninferior
	any stroke	1.44 vs. 1.57	0.92 (0.74–1.13)	–
	ischemic (or unspecified) stroke	1.34 vs. 1.20	1.11 (0.89–1.40)	–
	all-cause mortality	3.75 vs. 4.13	0.91 (0.80–1.03)	–
	safety			
	major bleeding	2.71 vs. 3.36	0.80 (0.69–0.93)	77 (48–213)
	life-threatening bleeding	1.22 vs. 1.80	0.68 (0.55–0.83)	86 (62–163)
	intracranial bleeding	0.23 vs. 0.74	0.31 (0.20–0.47)	98 (84–127)
	hemorrhagic stroke	0.12 vs. 0.38	0.31 (0.17–0.56)	192 (159–299)
	minor bleeding	13.16 vs. 16.37	0.79 (0.74–0.84)	16 (12–19)
	gastrointestinal major bleeding	1.12 vs. 1.02	1.10 (0.86–1.41)	–
	myocardial infarction	0.72 vs. 0.53	1.35 (0.98–1.87)	–
dabigatran 150 mg twice daily vs. warfarin	efficacy			
	stroke or systemic embolism	1.11 vs. 1.69	0.66 (0.53–0.81)	86 (63–156)
	any stroke	1.01 vs. 1.57	0.64 (0.51–0.81)	89 (65–168)
	ischemic (or unspecified) stroke	0.92 vs. 1.20	0.76 (0.60–0.98)	179 (104–2083)
	all-cause mortality	3.64 vs. 4.13	0.88 (0.77–1.00)	–
	safety			
	major bleeding	3.11 vs. 3.36	0.93 (0.81–1.07)	–
	life-threatening bleeding	1.45 vs. 1.80	0.81 (0.66–0.99)	143 (82–2778)
	intracranial bleeding	0.30 vs. 0.74	0.40 (0.27–0.60)	114 (93–169)
	hemorrhagic stroke	0.10 vs. 0.38	0.26 (0.14–0.49)	179 (153–258)
	minor bleeding	14.84 vs. 16.37	0.91 (0.85–0.97)	33 (20–102)
	gastrointestinal major bleeding	1.51 vs. 1.02	1.50 (1.19–1.89)	NNH 102 (55–258)
	myocardial infarction	0.74 vs. 0.53	1.38 (1.00–1.91)	NNH 238 (104–∞)

a NNT and NNH were calculated from the published data.

Abbreviations: CI – confidence interval, NNT/NNH – numbers needed to treat/numbers needed to harm, for 2 years of treatment with dabigatran, RR – relative risk

treatment with dabigatran was noninferior to warfarin, for the prevention of recurrent symptomatic VTE or VTE-related death in patients who have acute VTE.[3] About 2500 patients recruited from centers around the world were randomly assigned to receive either 150 mg dabigatran, given twice daily or adjusted-dose warfarin. Patients were eligible to participate if they were over 18 years of age, had acute, symptomatic, objectively diagnosed VTE (either deep vein thrombosis of the legs or pulmonary embolism), and if at least 6 months therapy with warfarin was considered appropriate treatment. Similar to the RE-LY study, patients considered to be at high risk of bleeding and those with severe renal insufficiency were excluded. Patients initially received an approved parenteral anticoagulant (unfractionated or low-molecular-weight heparin) prior to randomization to study treatment. Patients were then allocated to receive either warfarin or dabigatran 150 mg bid or matching placebos using a double-blind, double-dummy design. Anticoagulation was monitored using point-of-care coagulometers that were programmed in accordance with the randomization schedule to provide a true or sham INR value. Parenteral anticoagulants were discontinued after at least 5 days of therapy and when the true or sham INR were ≥2 on 2 consecutive days. Treatment was continued for 6 months. The primary outcome of interest was the occurrence of symptomatic VTE or death due to VTE. Major bleeding was the principal safety outcome. Bleeding was defined in accordance with the International Society on Thrombosis and Hemostasis criteria.[8] Outcome adjudicators were blinded to treatment assignment. The study had 90% power to exclude a hazard ratio of 2.75 and an absolute increase in the risk of 3.6% for the primary outcome with dabigatran. The noninferiority margin represented a preservation of more than 57% (for assessment of hazard ratio) of the lower boundary of the 95% CI of the expected benefit of warfarin over no anticoagulation. All patients who received at least 1 dose of the study drug were included in the analysis for the primary outcome ("modified intention-to-treat").

Of the 2564 patients randomized, 25 did not receive the study drug and were excluded from the analysis. A similar proportion of patients in either arm discontinued the study drug (TABLE 1).

TABLE 3 Results of the RE-COVER study

Outcomes	Event rates, n (%)[a]		HR (95% CI)
efficacy	dabigatran	warfarin	
VTE or related death	30 (2.4)	27 (2.1)	1.10 (0.65–1.84)
symptomatic venous thrombosis	16 (1.3)	18 (1.4)	0.87 (0.44–1.71)
symptomatic nonfatal pulmonary embolism	13 (1.0)	7 (0.6)	1.85 (0.74–4.64)
all-cause mortality	21 (1.6)	21 (1.7)	0.98 (0.53–1.79)
safety			
major bleeding	20 (1.6)	24 (1.9)	0.82 (0.45–1.48)
major or clinically relevant nonmajor bleeding	71 (5.6)	111 (8.8)	0.63 (0.47–0.84)[b]
any bleeding event	205 (16.1)	277 (21.9)	0.71 (0.59–0.85)[c]
gastrointestinal bleeding	53	35	–

a event rates for the 6-month study period
b NNT (95% CI) for 6 months of treatment = 31 (21–71)
c NNT (95% CI) for 6 months of treatment = 17 (11–30)

Abbreviations: HR – hazard ratio, others – see TABLE 2

The adjudicated primary outcome occurred in 30 (2.4%) patients in the dabigatran group and 27 (2.1%) patients in the warfarin group (hazard ratio 1.10, 95% CI 0.65–1.84; P <0.001 for noninferiority). The rates of major bleeding were 1.6% and 1.9% in the dabigatran and warfarin groups, respectively. There was a significant reduction in the rate of major or clinically relevant nonmajor bleeding with dabigatran (5.6% vs. 8.8%, hazard ratio 0.63, 95% CI 0.47–0.84; P = 0.002). As with the RE-LY study, the number of gastrointestinal bleeding episodes was greater with dabigatran than warfarin (53 vs. 35). Likewise, dyspepsia occurred over 4 times as frequently with dabigatran as with warfarin (3.1% vs. 0.7%). There was no increase in the frequency of MI or hepatic enzyme elevation with dabigatran. The RE-COVER results are summarized in TABLE 3.

Discussion RE-LY was a large, pragmatic trial, reflecting contemporary practice among typical patient populations, and is therefore generalizable to clinical practice. Unlike other new anticoagulants, dabigatran at either dose *reduces* the risk of major bleeding without compromising efficacy.[9,10] The higher dose provided greater protection from stroke and systemic embolism compared to warfarin. Similarly, RE-COVER demonstrated the noninferiority of dabigatran for the treatment of acute VTE when compared to warfarin. The consistent efficacy of fixed-dose treatment with dabigatran in preventing thrombotic events is encouraging and is most likely the result of stable blood dabigatran levels, achieved and maintained during the course of therapy. Since the half-life of dabigatran is 12 to 17 h, the twice-daily dosing schedule also contributed to the maintenance of stable blood levels. In contrast, warfarin therapy is associated with substantial variations in anticoagulation, with less than two-thirds of time spent in the therapeutic INR range. The efficacy of dabigatran was consistent across patient subgroups. Particularly, efficacy was similar among patients with different baseline stroke risk (estimated by the $CHADS_2$ score), and was independent of whether patients were warfarin naïve or had received long-term warfarin therapy prior to enrollment. Unlike the results of RE-LY, the 150 mg bid dose was not *more* efficacious than warfarin in RE-COVER. While this could have been due to the play of chance, the longer duration of treatment in RE-LY (2 years vs. 6 months in RE-COVER) may have accentuated the differences between dabigatran and warfarin.

Treatment with dabigatran was associated with a substantial reduction in the rates of major and minor bleeding with dabigatran. The number needed to treat to prevent a major bleeding event with the 110 mg dose of dabigatran was 77 (TABLE 2). Because of the smaller numbers and event rates, data on bleeding was less robust in the RE-COVER study. Nevertheless, the lower rates of major or clinically significant nonmajor bleeding with dabigatran observed in this study are consistent with the overall data (TABLE 3). The reduction in bleeding with dabigatran, particularly intracranial bleeding is impressive and likely due to the steadier anticoagulant levels achieved with dabigatran, since there is good evidence that the risk of intracranial bleeding increases with increasing INR levels.

Dyspepsia was the most common side effect of dabigatran in both trials. Dabigatran was also associated with a trend towards a greater risk of gastrointestinal bleeding. These side-effects were consistently observed in the double-blind (RE-COVER) as well as the open-label (RE-LY) designs. Both these side-effects have been attributed to the tartaric acid content of the dabigatran capsules. An acid pH is required to facilitate the absorption of dabigatran, and it remains to be seen if changes in the tartaric acid content of the capsules can reduce the rates of dyspepsia and gastrointestinal bleeding, while preserving bioavailability (and efficacy). Finally, the small (0.2% per year) increase in the rate of MI is unexplained. It has been postulated that the more frequent occurrence of MI may relate greater efficacy of warfarin, compared to dabigatran in protecting against coronary events. There might, however, be alternative explanations and so careful surveillance should be performed in future phase III and post-marketing studies.

Two other anticoagulants, rivaroxaban and apixaban, are in advanced stages of development as potential replacements for vitamin K antagonists. Studies with these agents have shown promising efficacy in the short-term in comparison to enoxaparin in preventing VTE,[11-13] and against placebo in the intermediate-term in comparison to placebo in patients with acute coronary syndromes.[9,10] But these agents have been associated with an increased bleeding risk when used over a period of 6 months in comparison to placebo. Further, none of these agents have been

compared with warfarin for conditions requiring long-term anticoagulation.

Conclusion Dabigatran presents a safe, efficacious and convenient alternative to warfarin in the treatment of patients with AF and acute VTE. These are the 2 most common indications for warfarin in current practice. Patients with mechanical heart valves will possibly be the next big battleground for dabigatran (and the other new oral agents) and warfarin. Fixed-dose chronic oral anticoagulant therapy with dabigatran represents an important advance in long-term anticoagulation therapy, and the results from these 2 pivotal trials may herald the beginning of the end for vitamin K antagonist-based oral anticoagulation.

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ARTYKUŁ POGLĄDOWY

Doustna antykoagulacja – czy nadszedł już czas dabigatranu?

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dabigatran, inhibitory trombiny, migotanie przedsionków, żylna choroba zakrzepowo-zatorowa

STRESZCZENIE

Badania obejmujące chorych obciążonych dużym ryzykiem wykazały skuteczność wybiórczych inhibitorów czynnika Xa i trombiny w zapobieganiu żylnej chorobie zakrzepowo-zatorowej w okresie okołooperacyjnym. W związku z przewidywalną odpowiedzią w zależności od dawki, która eliminuje potrzebę rutynowego monitorowania laboratoryjnego, ich stosowanie może być wygodniejsze dla chorych wymagających długiego leczenia i może poprawić jakość antykoagulacji. Niedawno opublikowano wyniki 2 dużych badań z użyciem dabigatranu (inhibitora trombiny) w porównaniu z warfaryną u chorych z migotaniem przedsionków i ostrą objawową żylną chorobą zakrzepowo-zatorową. Dostarczyły one przekonujących danych na temat skuteczności dabigatranu w zapobieganiu ważnym dla chorych klinicznym punktom końcowym, w porównaniu z warfaryną. W niniejszym artykule podsumujemy wyniki tych badań i omówimy możliwość zastąpienia warfaryny dabigatranem w tych wskazaniach.

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