Treatment of Acute Venous Thromboembolism With Dabigatran or Warfarin and Pooled Analysis

Sam Schulman, MD, PhD; Ajay K. Kakkar, MB, BS, PhD; Samuel Z. Goldhaber, MD; Sebastian Schellong, MD; Henry Eriksson, MD, PhD; Patrick Mismetti, MD; Anita Vedel Christiansen, MSc Pharm; Jeffrey Friedman, MD; Florence Le Maulf, BSc (Hons), MSc; Nuala Peter, BSc (Hons), MSc; Clive Kearon, MB, PhD; for the RE-COVER II Trial Investigators*

***Background*—**Dabigatran and warfarin have been compared for the treatment of acute venous thromboembolism (VTE) in a previous trial. We undertook this study to extend those findings.

***Methods and Results*—**In a randomized, double-blind, double-dummy trial of 2589 patients with acute VTE treated with low-molecular-weight or unfractionated heparin for 5 to 11 days, we compared dabigatran 150 mg twice daily with warfarin. The primary outcome, recurrent symptomatic, objectively confirmed VTE and related deaths during 6 months of treatment occurred in 30 of the 1279 dabigatran patients (2.3%) compared with 28 of the 1289 warfarin patients (2.2%; hazard ratio, 1.08; 95% confidence interval [CI], 0.64–1.80; absolute risk difference, 0.2%; 95% CI, −1.0 to 1.3; $P<0.001$ for the prespecified noninferiority margin for both criteria). The safety end point, major bleeding, occurred in 15 patients receiving dabigatran (1.2%) and in 22 receiving warfarin (1.7%; hazard ratio, 0.69; 95% CI, 0.36–1.32). Any bleeding occurred in 200 dabigatran (15.6%) and 285 warfarin (22.1%; hazard ratio, 0.67; 95% CI, 0.56–0.81) patients. Deaths, adverse events, and acute coronary syndromes were similar in both groups. Pooled analysis of this study RE-COVER II and the RE-COVER trial gave hazard ratios for recurrent VTE of 1.09 (95% CI, 0.76–1.57), for major bleeding of 0.73 (95% CI, 0.48–1.11), and for any bleeding of 0.70 (95% CI, 0.61–0.79).

***Conclusion*—**Dabigatran has similar effects on VTE recurrence and a lower risk of bleeding compared with warfarin for the treatment of acute VTE.

***Clinical Trial Registration*—**URL: www.clinicaltrials.gov. Unique identifiers: NCT00680186 and NCT00291330.
(*Circulation*. 2014;129:764-772.)

Key Words: antagonists & inhibitors ■ hemorrhage ■ recurrence ■ thrombin ■ venous thromboembolism ■ warfarin

Venous thromboembolism (VTE) is increasingly prevalent despite efforts to prevent the disease. The number of adults with VTE in the United States is projected to double from 0.95 million in 2006 to 1.82 million in 2050, mainly as a result of the expansion and aging of the population.[1] Vitamin K antagonists have been the mainstay in the treatment of VTE after an initial course of parenteral anticoagulation. Recent studies have demonstrated that novel oral thrombin or factor Xa inhibitors can be used for long-term anticoagulation in patients with VTE,[2–4] atrial fibrillation,[5–7] or acute coronary syndromes[8] without the need for laboratory monitoring or dose adjustments. The inconvenience of vitamin K antagonists for both patients and health-care providers is thereby avoided. Another goal is to decrease

Editorial see p 725
Clinical Perspective on p 772

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

Received June 13, 2013; accepted November 11, 2013.

From the Department of Medicine, McMaster University and Thrombosis and Atherosclerosis Research Institute, Hamilton, ON, Canada (S. Schulman, C.K.); Department of Hematology, Karolinska University Hospital, Stockholm, Sweden (S.S.); Thrombosis Research Institute and University College London, London, UK (A.K.K.); Brigham and Women's Hospital, Harvard Medical School, Boston, MA (S.Z.G.); Medical Division 2, Municipal Hospital Friedrichstadt, Dresden, Germany (S. Schellong); Department of Medicine, Sahlgrenska University Hospital-Östra, Gothenburg, Sweden (H.E.); Department of Vascular Pathology, Bellevue Hospital, Saint Etienne, France (P.M.); Clinical Research, Boehringer Ingelheim, Copenhagen, Denmark (A.V.C.); Boehringer Ingelheim, Ridgefield, CT (J.F.); Boehringer Ingelheim, Reims, France (F.L.M.); and Boehringer Ingelheim, Biberach and der Riss, BDM, Germany (N.P.).

*The investigators are listed in the online-only Data Supplement.

Guest Editor for this article was Frans J. Van de Werf, MD.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.113.004450/-/DC1.

Correspondence to Sam Schulman, MD, PhD, Thrombosis Service, HHS-General Hospital, 237 Barton St E, Hamilton, ON L8L 2X2, Canada. E-mail schulms@mcmaster.ca

© 2013 American Heart Association, Inc.

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.113.004450**

the bleeding risk associated with vitamin K antagonists,[9] which is important because warfarin has been implicated in 33% of emergency hospitalizations for adverse drug events.[10]

Dabigatran etexilate (hereafter referred to as dabigatran) is an orally administered direct thrombin inhibitor with an efficacy similar to that of warfarin in the treatment and secondary prevention of VTE and with a reduced risk for major and clinically relevant nonmajor bleeding (hereafter referred to as clinically relevant bleeding).[4,11] On the basis of the low rate of recurrent VTE observed during recruitment to the first trial (RE-COVER), we initiated this study (RE-COVER II) to confirm the results and to allow more precise subgroup analyses using pooled data from the 2 trials.

Methods

Study Design

The design of this trial was essentially identical to that of the first study with dabigatran for the treatment of acute VTE.[4] Briefly, we used a randomized, double-blind, double-dummy design to compare dabigatran 150 mg twice daily with warfarin, adjusted to maintain an international normalized ratio (INR) of 2.0 to 3.0 during 6 months, after initial parenteral anticoagulation. The study was designed, conducted, and funded and the data were analyzed by Boehringer Ingelheim and the steering committee, the members of which vouch for the completeness and accuracy of the data and the analyses reported here. The protocol and all amendments were approved by the institutional review board at each participating clinical center, and all patients provided informed consent. A central adjudication committee, the members of which were unaware of the treatment assignments, classified all suspected outcome events, bleeding events, and deaths. An independent data and safety monitoring board periodically reviewed the efficacy and safety outcomes. The steering committee wrote the manuscript and made the decision to submit it for publication.

Study Patients

We recruited patients at 208 study sites in 31 countries worldwide. The inclusion and exclusion criteria were the same as previously described[4] except that baseline aminotransferases had to exceed 3 times rather than 2 times the local upper limit of the normal for patients to be excluded. The diagnosis of proximal deep vein thrombosis or pulmonary embolism was established objectively before randomization. Additional screening for asymptomatic deep vein thrombosis and pulmonary embolism was performed within 72 hours after randomization.[4]

Random Assignment and Treatment

Patients were randomized by use of an interactive voice response system and a computer-generated randomization scheme in blocks of 4. The randomization was stratified according to the presence or absence of symptomatic pulmonary embolism or active cancer. Patients were assigned in a 1:1 ratio to receive active fixed-dose dabigatran 150 mg twice daily and warfarin-like placebo or active warfarin and dabigatran-like placebo. Treatment with a parenteral anticoagulant (unfractionated heparin or low-molecular-weight heparin) was generally started before randomization. On the day of randomization, warfarin or warfarin-like placebo was added to the parenteral treatment and adjusted to achieve an INR of 2.0 to 3.0 with the use of a point-of-care instrument that provided an encrypted INR. An interactive voice-response system provided a true or sham INR. This was the single-dummy phase, which lasted for at least 5 days and until the true or sham INR had been ≥2.0 for 2 consecutive measurements. Then, parenteral anticoagulation was stopped and the first dose of dabigatran was given within 2 hours before the time that the next dose of subcutaneous parenteral therapy would have been due or at the time of discontinuation of intravenous unfractionated heparin. The study drugs were then given for 6 months from randomization (double-dummy phase).

Follow-Up and Outcome Measures

We assessed the patients at 7 days and monthly for 6 months. An additional visit occurred 30 days after treatment completion unless the patient had discontinued study medication prematurely or was enrolled in a trial of extended treatment with anticoagulants.

Suspected recurrent VTE had to be objectively verified, preferably with the same method as for the index event. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis criteria.[12] Other bleeding was classified as clinically relevant nonmajor bleeding (defined in the online-only Data Supplement, available with the full text of this article) or as nuisance bleeding. The protocol stated as hierarchically equal safety outcomes major bleeding, major or clinically relevant nonmajor bleeding, and any bleeding. We had not planned for independent central adjudication of acute coronary syndromes, but this decision was revised by the steering committee and performed at the end of the trial, after database lock but while the committee was still blinded to the treatment allocation. Other adverse events, laboratory measures, and adherence (quantified by capsule counts) were assessed routinely.

Statistical Analysis

The trial was designed to demonstrate that dabigatran was as effective as (ie, noninferior to) warfarin and to compare the safety of the 2 drug regimens during 6 months of treatment of acute VTE. We determined the sample size on the basis of an expected rate of recurrent VTE of 2% in each group during 6 months,[2,13,14] while requiring a power of 90% to exclude a hazard ratio of 2.75, an absolute risk increase of 3.6 percentage points for the primary outcome with dabigatran, and a 1-sided α level of 0.025. With a possible 20% loss to follow-up during 6 months allowed for, the required sample size was 2550 patients, with 1275 patients per group and a total of at least 46 events. The noninferiority margins in this study were similar to those in contemporary VTE trials for both the hazard ratio[3,11,15] and the absolute risk increase,[11,16–19] although in more recently designed trials, the noninferiority margin for the risk estimate has decreased to 1.8 (relative risk in the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy [AMPLIFY])[20] and 1.5 (hazard ratio in Hokusai-VTE).[21]

The population analyzed for efficacy consisted of all randomized patients who took at least 1 dose of the study drug. The primary analysis for efficacy was a comparison between the groups of the time to the first occurrence of the composite end point of symptomatic VTE or death associated with VTE in the 6 months after randomization. This was assessed by the hazard ratio, calculated with the use of the Cox model; the difference in risk was calculated with the use of Kaplan-Meier estimates. Both summary statistics were adjusted for the presence or absence of pulmonary embolism and active cancer at baseline. The interaction between active cancer and symptomatic pulmonary embolism was also included in the Cox model. We tested for noninferiority by comparing the upper boundary of the 95% confidence interval (CI) for the hazard ratio with the predefined margin of 2.75 and for the difference in absolute risk with the predefined margin of 3.6 percentage points. If noninferiority was confirmed with both criteria, testing for superiority of dabigatran was to be performed.

The safety population also consisted of all randomized patients who took at least 1 dose of the study drug, but this analysis was according to the actual treatment received and was from the first dose of trial treatment until 6 days after the trial treatment. We excluded the 6-day period after the last dose if patients were enrolled in a trial on extended treatment.

After the trial results were known, the steering committee decided to present pooled data of the primary and secondary efficacy and safety outcomes from this and the previous trial that compared dabigatran and warfarin for treatment of acute VTE. Minor corrections of the numerators were made, as explained in the online-only Data Supplement. The hazard ratios were obtained from a Cox model assuming different baseline hazards for the 2 studies and a common treatment effect. Statistical analyses were performed with SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

From June 2008 through October 2010, we randomized 2589 patients; 66% were from Europe or North America, and 20% were from Asia. Fourteen patients in the dabigatran group and 7 in the warfarin group did not receive any study medication (10 did not meet the inclusion criteria or met the exclusion criteria, 9 withdrew consent, and 2 had an adverse event; Figure I in the online-only Data Supplement). Therefore, 1279 patients in the dabigatran group and 1289 patients in the warfarin group were included in the analysis of efficacy. One patient was assigned to receive warfarin but received dabigatran throughout the study. One patient in each group mistakenly received the opposite treatment for the first month, after which time the mistake was corrected. None of these 3 patients had any VTE,

Table 1. Characteristics of the Patients and Treatments*

Characteristic	Dabigatran (n=1280)	Warfarin (n=1288)	*P* Value
Age, y	54.7±16.2	55.1±16.3	0.39
Median	56	57	
Range	18–92	18–93	
Female sex, n (%)	499 (39)	512 (39.8)	0.69
Race, n (%)†			1.00
White	993 (77.6)	999 (77.6)	
Black	19 (1.5)	19 (1.5)	
Asian	267 (20.9)	270 (21.0)	
Weight, kg	83.2±19.7	82.9±19.6	0.69
Median	80	81	
Range	36–184	35–210	
Body mass index, kg/m^2	28.4±5.8	28.4±5.8	0.89
Estimated creatinine clearance, mL/min‡	108.2±43.7	107.1±41.1	0.50
Type of index event, n (%)			0.85
Deep vein thrombosis only	877 (68.5)	873 (67.8)	
Pulmonary embolism only	298 (23.3)	297 (23.1)	
Both deep vein thrombosis and pulmonary embolism	104 (8.1)	117 (9.1)	
Neither deep vein thrombosis nor pulmonary embolism§	1 (0.1)	1 (0.1)	
Cancer at baseline, n (%)	50 (3.9)	50 (3.9)	0.98
Previous venous thromboembolism, n (%)	247 (19.3)	203 (15.8)	0.02
Concomitant use of acetylsalicylic acid, n (%)	130 (10.2)	112 (8.7)	0.20
Parenteral anticoagulation			
Total duration of treatment, d	9.4±3.8	9.6±4.1	
Treatment after randomization in the single-dummy phase, d‖	6.8±3.4	7.1±3.7	
Unfractionated heparin, n (%)	198 (15.5)	207 (16.1)	
Low-molecular-weight heparin, n (%)	1133 (88.5)	1147 (89.1)	
Fondaparinux, n (%)	32 (2.5)	21 (1.6)	
Double-dummy phase¶			
Exposure to study drug, d	164.4±47.6	164.0±48.5	
Adherence to study regimen, n (%)#	1251 (97.7)	1266 (98.3)	
Time that INR was in the therapeutic range, %	NA	56.9±21.9	

INR indicates international normalized ratio; and NA, not applicable

*Plus-minus values are mean±SD. The numbers in the 2 groups represent the number of patients treated with dabigatran or warfarin rather than the number randomized to the treatment (1 patient who was assigned to receive dabigatran mistakenly received warfarin during the entire study, and 1 per group received the opposite treatment the first month). The *P* values were calculated with the use of Student *t* test for creatinine clearance and body mass index, the Wilcoxon-Mann-Whitney test for age and weight, the Fisher exact test for race and type of index event, and the χ^2 test for sex, cancer, concomitant use of acetylsalicylic acid, and previous venous thromboembolism.

†Race was determined by the investigator; data were missing for 1 patient in the dabigatran group.

‡Creatinine clearance was estimated according to the Cockcroft-Gault method.

§In the case of 1 patient in each group, the diagnosis of venous thromboembolism was made locally and was subsequently not confirmed by the central adjudication committee.

‖In the single-dummy phase, patients received a parenteral anticoagulant agent and warfarin or warfarin-like placebo. Some patients received >1 parenteral anticoagulant during this phase.

¶In the 6-month double-dummy phase, patients received only the oral treatment (dabigatran and warfarin-like placebo or warfarin and dabigatran-like placebo).

#Adherence was assumed if a pill count of dabigatran or the dabigatran placebo indicated an intake of between 80% and 120% of the prescribed dose.

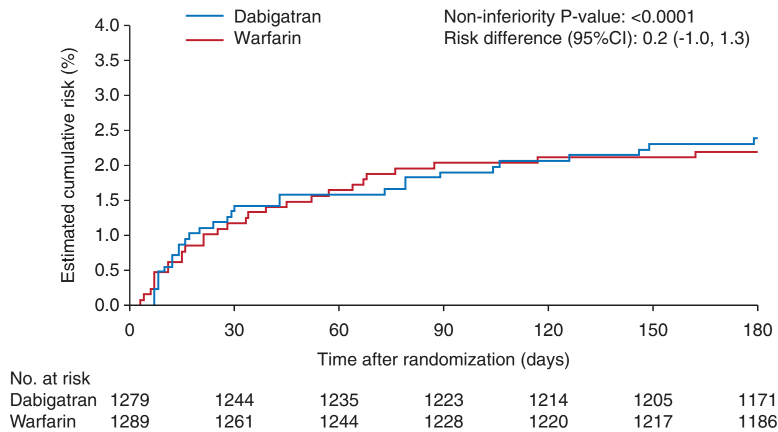


Figure 1. Cumulative risk of recurrent venous thromboembolism or related death during 6 months of treatment among patients randomly assigned to dabigatran or warfarin.

bleeding, or serious adverse events. In the safety analysis, we therefore had 1280 patients in the dabigatran group and 1288 patients in the warfarin group. There were no significant differences between the groups in baseline characteristics except for a higher proportion with previous VTE in the dabigatran group (Table 1).

Treatment and Follow-Up

The median duration of initial parenteral anticoagulation was 9.4 days in the dabigatran group and 9.6 days in the warfarin group (Table 1). In the warfarin group, the mean time in the therapeutic range (INR, 2.0–3.0) was 57%, increasing from 51% in month 1 and 56% in month 2 to between 59% and 62% per month during months 3 through 6. The INR was below the therapeutic range 24% of the time and above the therapeutic range 19% of the time.

The study drug was stopped before planned treatment completion in 188 patients (14.7%) in the dabigatran group (102 because of an adverse event, 39 because of nonadherence, 6 because of loss to follow-up, 33 because of withdrawal of consent, and 8 for other reasons) and in 182 patients (14.1%) in the warfarin group (101 because of an adverse event, 37 because of nonadherence, 3 because of loss to follow-up, 38 because of withdrawal of consent, and 3 for other reasons). The planned observation time for analysis of efficacy was not completed in 125 patients (9.8%) in the dabigatran group (47 because of an adverse event, 31 because of nonadherence, 11 because of loss to follow-up, 32 because of withdrawal of consent, and 4 for other reasons) and in 116 patients (9.0%) in the warfarin group (44 because of an adverse event, 26 because of nonadherence, 6 because of loss to follow-up, 39 because of withdrawal of consent, and 1 for other reasons). After 6 months of treatment, 61 patients from the dabigatran group and 65 from the warfarin group gave additional informed consent and were randomly assigned a second time to receive treatment with dabigatran or warfarin as extended secondary prophylaxis as part of the double-blind RE-MEDY study.

Efficacy

Recurrent nonfatal or fatal VTE was confirmed after central adjudication in 30 patients in the dabigatran group (2.3%) and in 28 patients in the warfarin group (2.2%; hazard ratio, 1.08; 95% CI, 0.64–1.80; Figure 1). The difference in risk was 0.2 percentage points (95% CI, −1.0 to 1.3) in favor of warfarin. Dabigatran was noninferior to warfarin for the prevention of recurrent or fatal VTE ($P<0.001$ for both hazard ratio and difference in absolute risk criteria). Efficacy results were consistent in all the predefined subgroups (data not shown). The results by the components of the primary end point are shown in Table 2.

Safety

Fifteen patients in the dabigatran group (1.2%) and 22 patients in the warfarin group (1.7%) had major bleeding events (hazard ratio, 0.69; 95% CI, 0.36–1.32; Figure 2). The difference in risk was –0.6 percentage points (95% CI, −1.6 to 0.3). The sites of major bleeding events in the dabigatran group were gastrointestinal (6 events), intracranial (2), retroperitoneal (2), urogenital (2), intra-articular (1), and other (3), and the sites in the warfarin group were gastrointestinal (10 events), urogenital (7), intracranial (2), intramuscular (1), and other (4). Some patients had major bleeding from >1 site. We observed major or clinically relevant nonmajor bleeding less often in the dabigatran group than in the warfarin group (hazard ratio, 0.62; 95% CI, 0.45–0.84) and similarly any bleeding less often in the dabigatran group than in the warfarin group (hazard ratio, 0.67; 95% CI, 0.56–0.81; Table 2). The incidence of different categories of adverse events was similar in the 2 treatment groups (Table 2). Dyspepsia was the only drug-related adverse event that was more common in the dabigatran group (1.0%) than in the warfarin group (0.2%).

Pooled Analysis

For the 2 studies combined, the pooled hazard ratio for recurrent VTE was 1.09 (95% CI, 0.76–1.57) for dabigatran compared with warfarin, with no suggestion that this differed according to whether patients presented with or without symptomatic pulmonary embolism or with or without cancer. Pooled event rates for components of the efficacy and safety outcomes are shown in Table 3. With age analyzed as a continuous variable, there was evidence that the efficacy of dabigatran compared with warfarin was somewhat lower in younger patients and higher in older patients ($P=0.099$ for interaction; Figure 3A), with equal efficacy at ≈60 years of age. At all ages, the 95% CI for the estimated hazard ratio included 1.0, suggesting that the difference in efficacy was not statistically significant at any age. The corresponding analysis for the safety outcome of clinically relevant bleeding showed

Table 2. Efficacy and Bleeding Outcomes

Outcome	Dabigatran (n=1279)	Warfarin (n=1289)	Hazard Ratio (95% CI)*
Efficacy analysis†			
Primary end point of venous thromboembolism or related death, n subjects (%)			
During 6 mo	30 (2.3)	28 (2.2)	1.08 (0.64–1.80)
During the study period plus an additional 30-d follow-up‡	34 (2.7)	30 (2.3)	1.13 (0.69–1.85)
Secondary end point, n subjects (%)			
Symptomatic deep vein thrombosis	25 (2.0)	17 (1.3)	1.48 (0.80–2.74)
Symptomatic nonfatal pulmonary embolism	7 (0.5)	13 (1.0)	0.54 (0.21–1.35)
Death related to pulmonary embolism	3 (0.2)§	0 (0.0)	
All deaths	25 (2.0)	25 (1.9)	0.98 (0.56–1.71)
Safety analysis‖			
Major bleeding event, n subjects (%)	15 (1.2)	22 (1.7)	0.69 (0.36–1.32)
Fatal event, n events	0	1 (0.1)	
Bleeding into critical organ, n events	6	4	
Intracranial	2	2	
Retroperitoneal	2	0	
Intra-articular	1	0	
Intramuscular	0	1	
Other	1	1	
Event resulting in fall in hemoglobin level or need for blood transfusions, n subjects (%)¶	13 (1.0)	19 (1.5)	
Major or clinically relevant nonmajor bleeding event, n subjects (%)	64 (5.0)	102 (7.9)	0.62 (0.45–0.84)
Any bleeding event, n subjects (%)	200 (15.6)	285 (22.1)	0.67 (0.56–0.81)
Sites of bleeding, n events#			
Intracranial	2	6	
Intraocular	5	14	
Retroperitoneal	3	1	
Intra-articular	3	0	
Pericardial	0	1	
Intramuscular	6	20	
Gastrointestinal	48	33	
Urogenital	51	75	
Nasal	43	76	
Other	160	255	
Any adverse event, n subjects (%)	852 (66.6)	916 (71.1)	
Serious adverse event, n subjects (%)	156 (12.2)	153 (11.9)	
Event leading to discontinuation of study drug, n subjects (%)	100 (7.8)	100 (7.8)	1.00 (0.76–1.32)
Acute coronary syndromes, n (%)**	4 (0.3)	2 (0.2)	
Myocardial infarction	4 (0.3)	2 (0.2)	
ALT >3× ULN plus bilirubin >2× ULN, n subjects (%)	1 (0.1)	2 (0.2)	

ALT indicates alanine aminotransferase; CI confidence interval; and ULN, upper limit of normal.

*The hazard ratio was estimated with the use of the Cox model, including treatment, active cancer at baseline, symptomatic pulmonary embolism at baseline, and the interaction between active cancer and symptomatic pulmonary embolism at baseline as factors.

†The efficacy analysis was based on the number of randomly assigned patients who received at least 1 dose of the study drug. Events that occurred within 6 months after randomization were counted as events in the analysis, regardless of early discontinuation of study drug.

‡The extension of the study period to the end of follow-up was prespecified as the primary analysis for the hazard ratio in the statistical analysis plan of the trial. Because this period is >6 months, it does not reflect the true incidence of the end point after anticoagulation was discontinued because >60 patients in each group were enrolled in an extended-treatment study with double-blind design and additional patients received open-label anticoagulants.

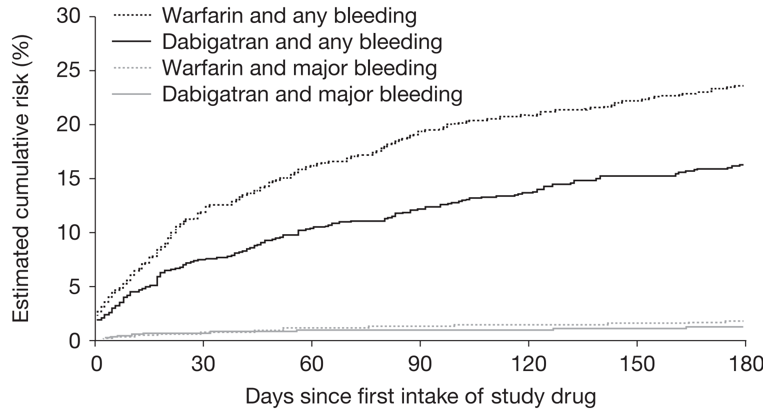
§Two fatal events occurred during the single-dummy phase, that is, before dabigatran was started.

‖The safety analysis of bleeding events was performed on the basis of the number of patients treated with dabigatran (1280) or warfarin (1288) rather than the number assigned to the treatment (see footnote for Table 1). Events that occurred from first to last intake of any study drug plus a 6-day washout period were included.

¶Included in this category were patients in whom there was a reduction in hemoglobin level of at least 20 g/L or patients who required a transfusion of at least 2 U whole blood or red cells.

#Patients may have had >1 type or site of bleeding event.

**Included in this category are acute coronary syndromes classified as definite or likely by the independent adjudication committee.



No. at risk							
Dabigatran and major bleeding	1280	1206	1176	1150	1130	1109	991
Warfarin and major bleeding	1288	1209	1178	1151	1135	1118	974
Dabigatran and any bleeding	1280	1128	1072	1029	995	965	858
Warfarin and any bleeding	1288	1083	1007	951	918	890	778

Figure 2. Cumulative risks of a first event of major bleeding (data lines) and of any bleeding among patients randomly assigned to dabigatran or warfarin.

that the risk reduction with dabigatran was influenced by age (P=0.010 for interaction; Figure 3B); the risk reduction was higher with dabigatran (compared with warfarin) in younger patients, and at ≈85 years of age, the effect changed, so the risk reduction with warfarin tended to become higher (compared with dabigatran).

Sex, ethnicity, geographical region, body mass index, creatinine clearance, history of previous VTE, or concomitant use of P-glycoprotein inhibitors, acetylsalicylic acid, or nonsteroid anti-inflammatory drugs did not influence the treatment effect (tests of interaction not statistically significant at the 5% level; Figure II in the online-only Data Supplement).

Table 3. Efficacy and Safety Outcomes in Pooled Analysis of RE-COVER[4] and RE-COVER II on Treatment of Acute Venous Thromboembolism

	Dabigatran (n=2553)	Warfarin (n=2554)	Hazard Ratio (95% CI)*
Outcome: efficacy			
Primary end point of venous thromboembolism or related death, n subjects (%)			
During 6 mo	60 (2.4)	55 (2.2)	1.09 (0.76–1.57)
During the study period plus an additional 30-d follow-up	68 (2.7)	62 (2.4)	1.09 (0.77–1.54)
Symptomatic deep vein thrombosis†	40 (1.6)	34 (1.3)	
Symptomatic nonfatal pulmonary embolism†	18 (0.7)	18 (0.7)	
Death related to pulmonary embolism†	2 (0.1)	3 (0.1)	
All deaths	46 (1.8)	46 (1.8)	1.0 (0.67–1.51)
Outcome: safety			
From the start of any study drug (single- and double-dummy periods)			
Major bleeding event, n subjects (%)	37 (1.4)	51 (2.0)	0.73 (0.48–1.11)
Intracranial bleeding	2 (0.1)	5 (0.2)	
Major or clinically relevant nonmajor bleeding event, n subjects (%)	136 (5.3)	217 (8.5)	0.62 (0.50–0.76)
Any bleeding event, n subjects (%)	411 (16.1)	567 (22.2)	0.70 (0.61–0.79)
From the start of the oral drug only (double-dummy period only)			
Major bleeding event, n subjects (%)	24 (1.0)	40 (1.6)	0.60 (0.36–0.99)
Intracranial bleeding	2 (0.1)	4 (0.2)	
Major or clinically relevant nonmajor bleeding event, n subjects (%)	109 (4.4)	189 (7.7)	0.56 (0.45–0.71)
Any bleeding event, n subjects (%)	354 (14.4)	503 (20.4)	0.67 (0.59–0.77)
Acute coronary syndrome, n subjects (%)			
Any	9 (0.4)	5 (0.2)	
Myocardial infarction	8 (0.3)	4 (0.2)	

RE-COVER indicates Efficacy and Safety of Dabigatran Compared to Warfarin for 6-Month Treatment of Acute Symptomatic Venous Thromboembolism; and RE-COVER II, Phase III Study Testing Efficacy & Safety of Oral Dabigatran Etexilate Versus Warfarin for 6-Month Treatment for Acute Symptomatic Venous Thromboembolism.

*The hazard ratio was estimated with the use of the Cox model with factor treatment stratified by study, assuming different baseline hazards per study.

†These are the events contributing to the primary end point. In the case of a patient suffering 2 different events, the first event is counted (a detailed explanation is given in the online-only Data Supplement).

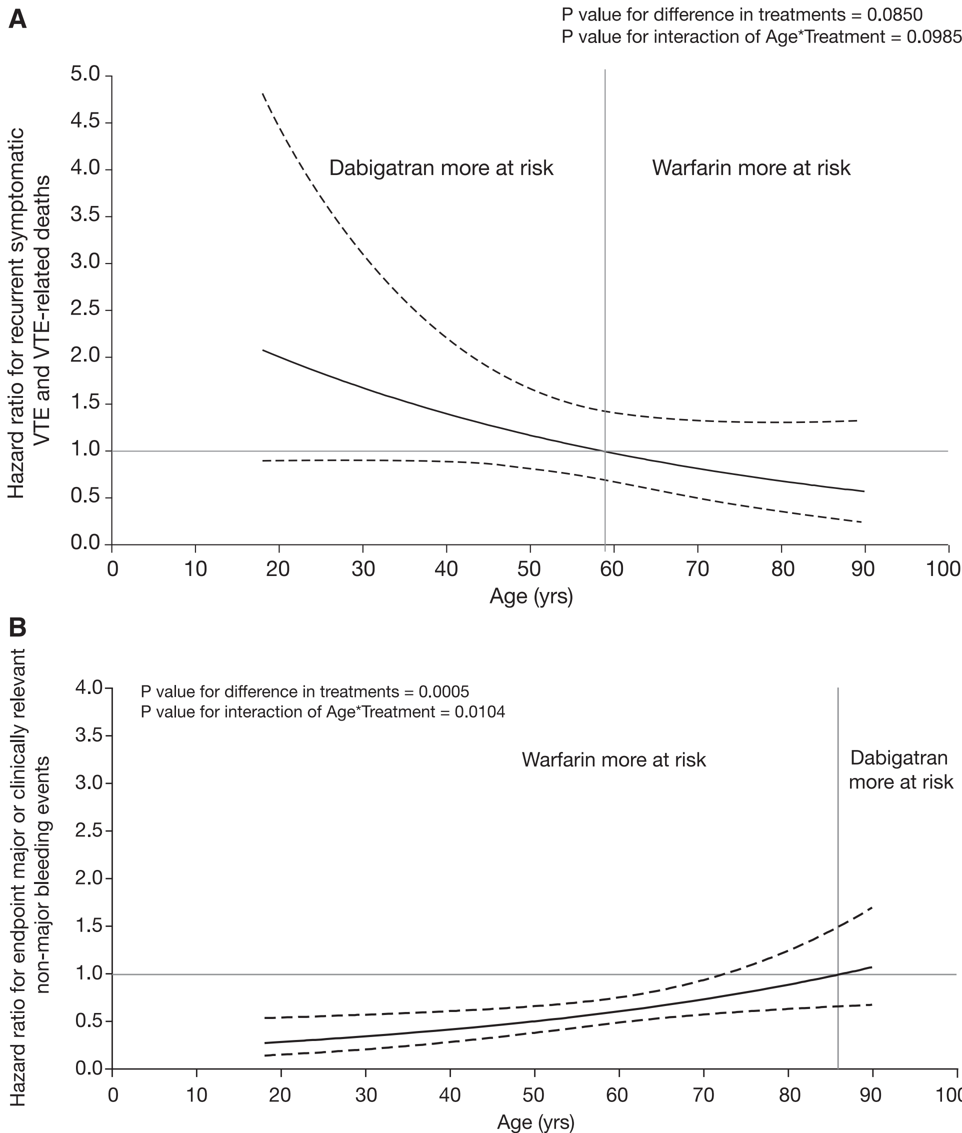


Figure 3. Hazard ratios with dabigatran, depending on age as a continuous variable, for the primary efficacy outcome (**A**) and for major or clinically relevant nonmajor bleeding (**B**). Pooled analysis of RE-COVER[4] and RE-COVER II. VTE indicates venous thromboembolism.

Likewise, these variables or a history of bleeding did not influence the risk for major bleeding or any bleeding with dabigatran compared with warfarin (data not shown).

The timing of the initiation of oral anticoagulant therapy in relation to the parenteral anticoagulant differs between warfarin and dabigatran owing to differences in their onset of action. Therefore, 2 safety comparisons were made: from the start of any study drug (from single-dummy period) and from the start of oral drug only (double-dummy period, after warfarin had reached therapeutic levels). Regardless of the calculation, pooled data from RE-COVER and RE-COVER II consistently showed a profile of less bleeding with dabigatran than with warfarin (Table 3).

Discussion

This study, RE-COVER II, confirms the results of RE-COVER, with noninferiority of dabigatran to warfarin in the prevention of recurrent VTE and with superiority of dabigatran for clinically relevant bleeding and for any bleeding. There is also a similar trend for fewer major bleedings with dabigatran. The RE-COVER II and RE-COVER studies differed in ethnic composition of the study populations, with more Asians in the current trial (20% versus 3%). There were also fewer patients with previous VTE in the present study (18% versus 26% in RE-COVER). In the pooled analysis of dabigatran versus warfarin, which included 1602 patients treated for symptomatic pulmonary embolism, efficacy was maintained with dabigatran (Figure II in the online-only Data Supplement).

Subgroup analyses of the pooled data indicated no need for dose adjustment of dabigatran according to demographic characteristics or concomitant medication use. The only level at which drug interactions with dabigatran have been described is with the permeability glycoprotein,[22] which transports dabigatran into the intestinal lumen. Although only 100 patients received dabigatran and a permeability glycoprotein inhibitor in the pooled analysis, there was no apparent increase in bleeding in this subset. Similarly, we did not find any evidence of an increased risk in bleeding with dabigatran in patients >75 years of age, with creatinine clearance of 30 to 49 mL/min, or with previous bleeding events.

The incidence of acute coronary syndromes was numerically higher with dabigatran than with warfarin, although not

statistically significant, as also seen in other recent trials.[11,23] The absolute risk increase was 0.2%, which should be balanced against the lower risk of intracranial hemorrhage that has been consistently observed with dabigatran compared with warfarin.[5,11]

The results in the RE-COVER trials can now be compared with those of the factor Xa inhibitors apixaban (AMPLIFY),[20] rivaroxaban (EINSTEIN DVT study,[3] EINSTEIN PE study),[24] and edoxaban (Hokusai-VTE)[21] for similar patient populations. Dabigatran and edoxaban were started after initial treatment with a parenteral anticoagulant and then given at a fixed dose and thus have not been studied as monotherapy for the treatment of VTE. Apixaban and rivaroxaban were given without mandatory initial parenteral anticoagulant but at a higher dose for 1 or 3 weeks, respectively, and then lowered to a maintenance dose. All 4 drugs showed noninferiority versus warfarin in terms of efficacy. In RE-COVER,[4] RE-COVER II, and Hokusai-VTE, there was a significant reduction in the combination of major and clinically relevant nonmajor bleeding (hazard ratio, 0.63, 0.62, and 0.81, respectively) but not of major bleeding alone. In the pooled analysis, we found a marginally significant reduction of major bleeding while the patients were actually treated with dabigatran (double-dummy period). There was a significant reduction in major bleeding with rivaroxaban in the pulmonary embolism population (hazard ratio, 0.49)[24] and in both major and clinically relevant nonmajor bleeding with apixaban (relative risk, 0.31 and 0.48, respectively).[20] There was never a risk estimate exceeding 1.0 for any of the 4 new anticoagulants in any of the subcategories of bleeding, supporting the safety of these drugs.

For patients with pronounced symptoms of VTE or with a large thrombus burden for whom the clinician feels that initial hospitalization with parenteral anticoagulation is indicated, dabigatran would be an alternative to other approved oral anticoagulants when the patient is ready for discharge home. Conversely, when the symptoms or thrombosis burden on first examination are limited and the patient is suitable for outpatient management with only oral therapy, dabigatran as opposed to rivaroxaban is not recommended because it has not been evaluated for monotherapy.

Conclusions

The 2 studies on the short-term treatment of VTE show that dabigatran is noninferior to warfarin for the prevention of recurrent VTE. The risk for clinically relevant bleeding or any bleeding is significantly lower with dabigatran.

Source of Funding

The RE-COVER and RE-COVER II studies were funded by Boehringer-Ingelheim.

Disclosures

Dr Schulman reports receiving consulting fees from Boehringer Ingelheim and grant support from Bayer Healthcare. Dr Kakkar discloses consultancy for Sanofi Aventis, Pfizer, Eisai Inc, GSK, Bayer Healthcare, Boehringer Ingelheim, Daiichi Sankyo, and Bristol-Myers Squibb, as well as payment for lectures (including speakers' bureaus) from Sanofi Aventis, Pfizer, Eisai Inc, GSK, Bayer Healthcare, Boehringer Ingelheim, Daiichi Sankyo, and Bristol-Myers Squibb. His institution has received grants from Sanofi Aventis, Pfizer, Eisai Inc, GSK, Bayer Healthcare, Boehringer Ingelheim, Daiichi Sankyo, and Bristol-Myers Squibb. Dr Goldhaber reports receiving clinical research support from Sanofi Aventis, Bristol-Myers Squibb, and Boehringer Ingelheim, plus consulting fees from Sanofi Aventis, Boehringer Ingelheim, Merck, Possis, Bristol-Myers Squibb, Genentech, and Medscape. Dr. Schellong reports receiving speaker fees and consulting honoraria from Bayer Healthcare, Boehringer Ingelheim, and GlaxoSmithKline and consulting fees from Sanofi Aventis. Dr Eriksson reports receiving consultant fees and lecture fees from Boehringer Ingelheim, Pfizer, Bayer Healthcare, Leo Pharma, and Bristol-Meyers Squibb. Dr Mismetti reports receiving consulting fees and lecture fees from Boehringer Ingelheim, Sanofi Aventis, and GlaxoSmithKline. A.V. Christiansen, F. Le Maulf, Dr Friedman, and N. Peter are employees of Boehringer Ingelheim. Dr Kearon reports receiving consulting fees from Boehringer Ingelheim.

References

1. Deitelzweig SB, Johnson BH, Lin J, Schulman KL. Prevalence of clinical venous thromboembolism in the USA: current trends and future projections. *Am J Hematol*. 2011;86:217–220.
2. Schulman S, Wåhlander K, Lundström T, Clason SB, Eriksson H; THRIVE III Investigators. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. *N Engl J Med*. 2003;349:1713–1721.
3. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, Bounameaux H, Cohen A, Davidson BL, Piovella F, Schellong S. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363:2499–2510.
4. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361:2342–2352.
5. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.
6. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.
7. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.
8. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, Bhatt DL, Goodman S, Verheugt FW, Flather M, Huber K, Liaw D, Husted SE, Lopez-Sendon J, De Caterina R, Jansky P, Darius H, Vinereanu D, Cornel JH, Cools F, Atar D, Leiva-Pons JL, Keltai M, Ogawa H, Pais P, Parkhomenko A, Ruzyllo W, Diaz R, White H, Ruda M, Geraldes M, Lawrence J, Harrington RA, Wallentin L; APPRAISE-2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med*. 2011;365:699–708.
9. Schulman S, Beyth RJ, Kearon C, Levine MN; American College of Chest Physicians. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(suppl):257S–298S.
10. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med*. 2011;365:2002–2012.
11. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, Kvamme AM, Friedman J, Mismetti P, Goldhaber S; RE-MEDY and RE-SONATE Trials Investigators. Extended use of dabigatran, warfarin or placebo in venous thromboembolism. *N Engl J Med*. 2013;368:709–718.
12. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in

clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692–694.
13. Levine MN, Hirsh J, Gent M, Turpie AG, Weitz J, Ginsberg J, Geerts W, LeClerc J, Neemeh J, Powers P. Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. *Thromb Haemost*. 1995;74:606–611.
14. Schulman S, Rhedin AS, Lindmarker P, Carlsson A, Lärfars G, Nicol P, Loogna E, Svensson E, Ljungberg B, Walter H. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism: Duration of Anticoagulation Trial Study Group. *N Engl J Med*. 1995;332:1661–1665.
15. Büller HR, Cohen AT, Davidson B, Decousus H, Gallus AS, Gent M, Pillion G, Piovella F, Prins MH, Raskob GE. Idraparinux versus standard therapy for venous thromboembolic disease. *N Engl J Med*. 2007;357:1094–1104.
16. Büller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, Prins MH, Raskob G, Segers AE, Cariou R, Leeuwenkamp O, Lensing AW; Matisse Investigators. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med*. 2004;140:867–873.
17. Büller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, Prins MH, Raskob G, van den Berg-Segers AE, Cariou R, Leeuwenkamp O, Lensing AW; Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med*. 2003;349:1695–1702.
18. Fiessinger JN, Huisman MV, Davidson BL, Bounameaux H, Francis CW, Eriksson H, Lundström T, Berkowitz SD, Nyström P, Thorsén M, Ginsberg JS; THRIVE Treatment Study Investigators. Ximelagatran vs low-molecular-weight heparin and warfarin for the treatment of deep vein thrombosis: a randomized trial. *JAMA*. 2005;293:681–689.
19. Kearon C, Ginsberg JS, Julian JA, Douketis J, Solymoss S, Ockelford P, Jackson S, Turpie AG, MacKinnon B, Hirsh J, Gent M; Fixed-Dose Heparin (FIDO) Investigators. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. *JAMA*. 2006;296:935–942.
20. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369:799–808.
21. Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369:1406–1415.
22. Walenga JM, Adiguzel C. Drug and dietary interactions of the new and emerging oral anticoagulants. *Int J Clin Pract*. 2010;64:956–967.
23. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L; Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators. Newly identified events in the RE-LY trial. *N Engl J Med*. 2010;363:1875–1876.
24. Buller HR, Prins MH, Lensing AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, Cohen A, Berkowitz SD, Bounameaux H, Davidson BL, Brenner B, Misselwitz F, Gallus AS, Raskob GE, Schellong S, Segers A. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366:1287–1297.

CLINICAL PERSPECTIVE

This is the second phase III trial with the oral thrombin inhibitor dabigatran for the treatment of acute venous thromboembolism for 6 months. The results of this trial are presented, together with a pooled analysis of both studies. Dabigatran was given at a dose of 150 mg twice daily with no dose adjustments. Patients with a creatinine clearance <30 mL/min were excluded. Because both trials used initial parenteral anticoagulation also in the dabigatran treatment arm, this drug should not be used as monotherapy for acute venous thromboembolism. The similar efficacies of dabigatran and standard treatment with warfarin were confirmed. Bleeding was analyzed as major bleeding, major or clinically relevant nonmajor bleeding, and any bleeding. For the last 2 categories, the risk was significantly reduced in the dabigatran group in both studies. Major bleeding was not significantly reduced in any of the trials separately or pooled when the entire treatment period was included. For the treatment period on oral drug only, that is, after the initial week with parenteral therapy but without dabigatran, there was also in the pooled analysis a borderline significant reduction of major bleeds. Deaths, adverse events, and acute coronary syndromes were similar in both groups. The pattern of lower risk of bleeding is seen with all new anticoagulants compared with vitamin K antagonists. Furthermore, here, as in other studies with the new anticoagulants in venous thromboembolism or in atrial fibrillation, there is a consistent trend to lower the risk of intracranial bleeding.

Go to http://cme.ahajournals.org to take the CME quiz for this article.