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Background—The aim of this study was to compare the management and prognosis of major bleeding in patients treated with dabigatran or warfarin.

Methods and Results—Two independent investigators reviewed bleeding reports from 1034 individuals with 1121 major bleeds enrolled in 5 phase III trials comparing dabigatran with warfarin in 27 419 patients treated for 6 to 36 months. Patients with major bleeds on dabigatran (n=627 of 16 755) were older, had lower creatinine clearance, and more frequently used aspirin or non-steroid anti-inflammatory agents than those on warfarin (n=407 of 10 002). The 30-day mortality after the first major bleed tended to be lower in the dabigatran group (9.1%) than in the warfarin group (13.0%; pooled odds ratio, 0.68; 95% confidence interval, 0.46–1.01; *P*=0.057). After adjustment for sex, age, weight, renal function, and concomitant antithrombotic therapy, the pooled odds ratio for 30-day mortality with dabigatran versus warfarin was 0.66 (95% confidence interval, 0.44–1.00; *P*=0.051). Major bleeds in dabigatran patients were more frequently treated with blood transfusions (423/696, 61%) than bleeds in warfarin patients (175/425, 42%; *P*<0.001) but less frequently with plasma (dabigatran, 19.8%; warfarin, 30.2%; *P*<0.001). Patients who experienced a bleed had shorter stays in the intensive care unit if they had previously received dabigatran (mean 1.6 nights) compared with those who had received warfarin (mean 2.7 nights; *P*=0.01).

Conclusions—Patients who experienced major bleeding on dabigatran required more red cell transfusions but received less plasma, required a shorter stay in intensive care, and had a trend to lower mortality compared with those who had major bleeding on warfarin.

Clinical Trial Registration—URL: http://www.ClinicalTrials.gov. Unique identifiers: NCT00262600, NCT00291330, NCT00680186, NCT00329238 and NCT00558259. **(*Circulation*. 2013;128:2325-2332.)**

Key Words: anticoagulants ■ atrial fibrillation ■ hemorrhage ■ mortality ■ venous thrombosis

The oral thrombin inhibitor dabigatran etexilate (hereafter referred to as dabigatran) has been approved in >80 countries for stroke prevention in atrial fibrillation based on the superior stroke reduction with dabigatran 150 mg twice daily and non-inferior stroke prevention with dabigatran 110 mg twice daily as compared with well-managed warfarin (target international normalized ratio, 2–3; median time in therapeutic range, 67.3%) in the Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate (RE-LY) trial.[1] Major bleeding occurred with a similar incidence in patients treated with dabigatran 150 mg twice daily compared with warfarin but was less frequent in patients treated with dabigatran 110 mg twice daily. A lower rate of bleeding was also seen with dabigatran 150 mg twice daily compared with warfarin (international normalized ratio, 2.0–3.0) in patients with venous thromboembolism.[2] In a pooled analysis of three trials of primary prevention of venous thromboembolic events in patients after total hip or total knee replacement, the risk of major bleeding was similar with dabigatran 150 mg and 220 mg once daily compared with the low-molecular-weight heparin, enoxaparin.[3]

Clinical Perspective on p 2332

Most vitamin K antagonists have a long half-life (acenocoumarol, 10 h; warfarin, 36–48 h; phenprocoumon, 120–150 h),

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but their anticoagulant effects can be reversed within 10–20 minutes by prothrombin complex concentrates (PCCs) and within 6–12 h by vitamin K.[4] Dabigatran does not have an antidote but has a half-life of 12–14 h,[5] and withholding the drug for 1–2 days is sufficient to restore hemostasis in most cases of mild to moderate bleeding. In patients with life-threatening bleeding, more rapid restoration of hemostasis might be achieved by the use of hemodialysis to remove the drug,[6–8] activated charcoal to prevent gastrointestinal absorption of recently ingested drug,[9] and the administration of PCCs,[10] activated PCCs,[11] or recombinant activated factor VII (rFVIIa)[12] to enhance thrombin generation. Evidence concerning the efficacy of these approaches is, however, limited to experimental and animal studies and isolated case reports.[10,13] Shortening of coagulation time is not always equivalent with restoration of hemostasis. A monoclonal antibody that selectively and rapidly neutralizes dabigatran has been developed, but results from clinical trials are not yet available.[14] In the absence of an effective antidote, many clinicians are concerned that dabigatran-treated patients who experience severe bleeding cannot be adequately managed.[15–17]

The objective of this study was to describe the management of major bleeding and outcomes after bleeding in large phase III trials evaluating the efficacy and safety of long-term (≥6 months) dabigatran compared with warfarin.

Methods

The Research Ethics Board of McMaster Faculty of Health Sciences – Hamilton Health Sciences approved the project without the need for patient consent. The data that were used for these analyses did not contain any personal identifiers.

The study is based on pooled data from trial populations with atrial fibrillation (RE-LY trial)[1] or venous thromboembolism (RE-COVER,[2] RE-COVER II,[18] RE-MEDY,[19] and RE-SONATE[19] trials; Table 1). Patient data from these trials were merged into a common dataset. The comparator in all studies was warfarin, with the exception of RE-SONATE which compared dabigatran with placebo. Patients in the placebo group in RE-SONATE did not experience any major bleeding and were not included. Cases eligible for our analysis experienced centrally adjudicated major bleeding on treatment or within 3 days of temporary or permanent discontinuation of treatment. The purpose of this 3-day rule was to ensure that active drug was likely to be in the circulation at the time of onset of bleeding. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria[20] in all 5 trials. The protocols for the trials only recommended general supportive measures in case of major bleeding on dabigatran. For nonresponsive patients with a life-threatening bleed the protocols listed fresh frozen plasma, activated prothrombin complex concentrate, or recombinant factor VIIa as options to be considered at the discretion of the treating physician.

We calculated creatinine clearance with the Cockcroft Gault formula[21] using the creatinine level on admission or, if this was unavailable, the most recent creatinine level prior to the bleeding event. For the data extraction we used study databases and the bleeding and serious adverse event narratives. Event narratives were obtained from Boehringer Ingelheim (Ridgefield, CT\). A computer algorithm had been used to automatically generate major bleeding event narratives, whereas a medical writer had prepared narratives for life threatening bleeding. Investigators at each site had prepared the serious adverse event narratives.

Assessment of Resources Used for Bleeding Management

Data on resource use and the short-term consequences of major bleeding in the RE-LY trial were obtained from the Population Health Research Institute (Hamilton, Canada). Using the RE-LY trial database we retrieved data on the number of units of blood products given and proportion of major bleeds treated with the different products; the proportion of events requiring hospitalization, the length of stay in intensive care and in step-down unit, the decrease in hemoglobin from baseline to the first hemoglobin level recorded during the event and from then to the lowest level during the event, and the proportion of patients with associated discontinuation of study medication or of aspirin. For the venous thromboembolism trials we obtained data on blood product use from the event narratives (verified against the databases from the sponsor).

Assessment of Outcome of Bleeding

Two of the authors (A.M. and H.-G.H.) reviewed independently all narratives and extracted data on patient characteristics, concomitant medication with aspirin or clopidogrel, type of bleeding, treatments given for the bleeding, length of stay in the hospital, and death after the bleeding. Data from the narratives on deaths were verified against the individual study databases at Boehringer Ingelheim. It was not possible to blind the reviewers to the anticoagulant treatment because this information was contained in the narratives.

For AF patients with intracranial hemorrhage, data on the modified Rankin Scale on presentation and during follow up were obtained from the RE-LY database as a measure of disability caused by the bleeding. Information on discharge destination after hospitalization

Table 1. Overview of Patients and Major Bleeding Events in the Phase III Long-Term Treatment Trials

Study	RE-LY		RE-COVER	RE-COVER II	RE-MEDY	RE-SONATE
Randomized, n	18113		2539	2568	2856	1343
Duration of treatment, months, median	24		6	6	18	6
Patients with major bleeds, n	1162		44	37	38	2
Major bleeding events, n	1378		47	40	40	2
Narratives available, n	1006		46	28	39	2
Major bleeds, %/year*						
Dabigatran 150 mg BID	3.32	2.71†	3.2	2.4	0.7	0.6
Warfarin, INR 2.0–3.0	3.57		3.8	3.4	1.4	NA‡

BID indicates twice daily; INR, international normalized ratio; NA, not applicable; and RE-LY, Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate.

*The differences between dabigatran 150 mg bid and warfarin were not statistically different in any of the studies.

†For dabigatran 110 mg BID, which only was used in the RE-LY trial, % major bleeds/year was significantly lower than with warfarin (relative risk, 0.80; 95% confidence interval, 0.69–0.93).

‡The comparator in this study was placebo, and there were no major bleedings in that group.

for the bleeding event was also collected from this database as an indirect indicator of the overall disability.

Statistical Analyses

The analyses of resource use were based on all major bleeding events, whereas the analyses of outcomes after a major bleed were based on the first event per patient. Comparisons between dabigatran 110 mg and 150 mg twice daily as well as between the combined dabigatran groups and warfarin were performed with χ^2 test or Fisher exact test for categorical data and Student *t* test or nonparametric Wilcoxon test for continuous variables. Cumulative risk for death was estimated with Kaplan–Meier analysis. Odds ratio (OR) for mortality 30 days after the bleeding event was calculated by logistic function regression to adjust for sex, age, weight, renal function, and additional antithrombotic therapy, using SAS Proc logistic (SAS version 9.2, Cary, NC) and reporting Wald χ^2 *P* values and confidence intervals. Sensitivity analyses were performed for the main outcomes (7- and 30-day mortality, transfusions of blood or plasma, vitamin K administration, and nights in intensive care setting) with major bleeding occurring on active treatment. Furthermore, we analyzed when appropriate with correction for multiple events using the generalized estimating equation for estimation of the parameters of a generalized linear model with a possible unknown correlation between outcomes.

Results

Baseline Characteristics

The number of patients randomized in the 5 studies, the number of major bleeding events, patients with bleeding, narratives reviewed, and event rates are summarized in Table 1. In the RE-LY trial patients were randomized 2:1 to dabigatran versus warfarin. In total, 1121 major bleeding events occurred in 1034 patients for whom we reviewed the narratives, usually consisting of an event narrative and a serious adverse event narrative.

Characteristics of the patients, for whom the narratives were reviewed, and their concomitant antithrombotic medications are shown in Table 2. The location of bleeding events is shown in Table I in the online-only Data Supplement. The discrepancy between the 1034 narrated events and the 1507 bleeds reported from the studies is attributable to our stricter cut-off for the interval between last dose and onset of bleeding.

There were no statistically significant differences between the characteristics of the patient population with major bleeding in the narratives from all phase III trials and the 1162 patients with major bleeding previously reported from the RE-LY trial[1] (not shown). Patients with major bleeding during treatment with dabigatran were significantly older (75.3 years) and had lower creatinine clearance (median 53 mL/min) than those with major bleeding during treatment with warfarin (71.8 years; 62 mL/min). Furthermore, a larger proportion of the patients treated with dabigatran who experienced bleeding had received concomitant treatment with aspirin (30.9%) or a nonsteroid anti-inflammatory agent (12.9%) than those treated with warfarin (24.6% and 8.4%, respectively).

Resources and Management Strategies Used for Major Bleeding

Blood Transfusions and Drop in Hemoglobin

For 365 (33%) major bleeding events in the 5 trials no blood products or other hemostatic agents were given (dabigatran 110 mg – 100 of 293 events [34%], dabigatran 150 mg – 126 of 403 events [31%], warfarin – 139 of 425 events [33%]). The difference was not significant for any comparison between the three groups. Red blood cell transfusion alone (ie, without any other blood products, coagulation factors, vitamin K, or local hemostatic intervention) was given more often in dabigatran treated patients, for 395 bleeding events (35%; dabigatran 110 mg – 137 of 293 bleeds [47%], dabigatran 150 mg – 173 of 403 bleeds [43%], warfarin – 85 of 425 bleeds [20%]); the differences are significant for all comparisons of dabigatran versus warfarin with a similar pattern in the RE-LY study alone (Table 3). The median number of red cell units transfused per patient did not differ between the groups.

In the RE-LY database the decrease in hemoglobin from baseline to the time of bleeding was greater in patients randomized to receive dabigatran compared with warfarin (dabigatran, 38.0 g/L, warfarin, 30.7 g/L; *P*=0.02). A decrease in hemoglobin from baseline was also noticed for patients in the dabigatran and warfarin treatment arms who did not have any bleeding event. For the dabigatran 110 mg group, the mean reduction in hemoglobin at 12 months was 0.6 g/L greater (95% confidence interval [CI], 0.14–1.06) than that for warfarin (*P*=0.011). For the dabigatran 150 mg group, the corresponding figures were 1.1 g/L (95% CI, 0.63–1.57; *P*<0.0001).

Table 2. Characteristics of the 1034 Patients With 1121 Major Bleeding Events and Reviewed Narratives

	D 110 mg	D 150 mg	Warfarin	*P* Value D 110 vs D 150	*P* Value* D vs W
Patients randomized and treated, n	6015	10 740	10 002		
Patients with major bleed, n	262	365	407		
Age, years, mean (SD)	75.9 (6.6)	75.1 (7.8)	71.8 (10.3)	0.22	<0.0001
Male sex, n (%)	170 (64.9)	234 (64.1)	268 (65.9)	0.83	0.67
Body weight, kg (SD)	81.4 (18.8)	82.1 (20.2)	81.2 (20.5)	0.62	0.63
Creatinine, μmol/L, median (range)	106 (44–968)	105 (43–800)	96 (17–577)		
Creatinine clearance, median (range)	52 (5–155)	55 (5–199)	62 (7–239)	0.05	<0.0001
Aspirin, n (%)	93 (35.5)	101 (27.7)	100 (24.6)	0.040	0.026
Clopidogrel, n (%)	3 (1.1)	9 (2.5)	7 (1.7)	0.38	1.0
Triple therapy, n (%)	10 (3.8)	13 (3.6)	14 (3.4)	0.92	0.93
NSAID	39 (15.9)	42 (11.5)	34 (8.4)	0.21	0.023

D indicates dabigatran; D110, dabigatran 110 mg twice daily; D150, dabigatran 150 mg twice daily; NSAID, nonsteroid anti-inflammatory agent; SD, standard deviation; and W, warfarin.

*The tests used were *t* test for age and body weight, Pearson χ^2 for sex, aspirin, clopidogrel, and triple therapy, or Fisher exact test when a numerator was <10.

Table 3. Hemostatic Products Used for Major Bleeding, as Derived From the RE-LY Database

	D 110 mg	D 150 mg	Dabigatran	Warfarin	*P* Value D 110 vs D 150	*P* Value D vs Warfarin	*P* Value D 110 vs Warfarin	*P* Value D 150 vs Warfarin
Patients with major bleeds, n (%)	342 (100)	399 (100)	741 (100)	421 (100)				
Patients treated with blood transfusion, n (%)	194 (56.7)	245 (61.4)	439 (59.2)	210 (49.9)	0.20	0.002	0.06	<0.001
Blood transfused, units, median (IQR)	2.0 (2.0)	3.0 (2.0)	3.0 (2.0)	3.0 (2.0)	0.11	0.35	0.11	0.88
Patients treated with FFP, n (%)	61 (17.8)	86 (21.6)	147 (19.8)	127 (30.2)	0.21	<0.001	<0.001	0.005
FFP transfused, units (median, IQR)	2.0 (2.0)	4.0 (2.5)	4.0 (2.0)	4.0 (2.0)	—	—	—	—
Patients treated with cryoprecipitate, n (%)	3 (0.9)	5 (1.3)	8 (1.1)	7 (1.7)	0.62	0.40	0.34	0.63
Cryoprecipitate transfused, units (median, IQR)	1.0 (0.0)	2.0 (3.0)	2.0 (3.0)	2.5 (3.0)	—	—	—	—
Patients treated with platelets, n (%)	13 (3.8)	15 (3.8)	28 (3.8)	20 (4.8)	0.98	0.42	0.52	0.48
Platelets transfused, units (median, IQR)	2.5 (1.5)	2.0 (3.0)	2.0 (2.0)	3.0 (4.0)	—	—	—	—
Patients treated with vitamin K, n (%)	29 (8.5)	41 (10.3)	70 (9.4)	115 (27.3)	0.40	<0.001	<0.001	<0.001
Patients treated with PCC, n (%)	3 (0.9)	2 (0.5)	5 (0.7)	5 (1.2)	0.53	0.36	0.68	0.29
Patients treated with recombinant factor VIIa, n (%)	1 (0.3)	7 (1.8)	8 (1.1)	3 (0.7)	0.05	0.53	0.42	0.17
Patients treated with other coagulation factor replacement, n (%)	0 (0.0)	3 (0.8)	3 (0.4)	4 (1.0)	0.11	0.25	0.07	0.76

D indicates dabigatran; D110, dabigatran 110 mg twice daily; D150, dabigatran 150 mg twice daily; FFP, fresh frozen plasma; IQR, interquartile range; PCC, prothrombin complex concentrate; and RE-LY, Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate.

Hemostatic Treatment

Only a minority of the patients received any hemostatic therapy (ie, plasma, vitamin K, factor concentrates, cryoprecipitate, or platelets). In patients with major bleeding events in the RE-LY database, there was significantly less use of fresh frozen plasma or vitamin K for the dabigatran groups compared with the warfarin group (Table 3). The proportion of patients receiving plasma or vitamin K was similar in the venous thromboembolism studies to those in RE-LY. The use of cryoprecipitate, platelets, PCC, rFVIIa, or other coagulation factors was low overall and did not differ significantly between the dabigatran and warfarin groups.

In all 5 trials vitamin K was given as the only treatment to patients on warfarin for 59 bleeds (14%) and as an adjunct for another 73 bleeds (17%) and less often to patients on dabigatran 110 mg or 150 mg, for 18 (2.6%) and 39 bleeds (5.6%), respectively. Any local or invasive procedure to stop the bleeding was used in 9% of bleeds in patients on dabigatran 110 mg, 12% of bleeds on dabigatran 150 mg, and 14% of bleeds on warfarin (significant difference between dabigatran 110 mg and warfarin; *P*=0.013).

Hemodialysis for drug removal was used in a single case on dabigatran. In this patient, after 6 hours of dialysis, before which massive transfusions with blood, plasma, platelets, cryoprecipitate, 5 doses of rFVIIa, and fibrin glue had been ineffective, the thrombin time shortened from 128 s to 65 s and bleeding ceased. The effect of hemodialysis was assessed as good.[7]

Hospital Resources

Based on RE-LY data, the length of stay in intensive care units was shorter for the dabigatran patients (1.6 nights, mean) than for the warfarin patients (2.7 nights; *P*=0.01). There was, according to the narrative assessments, numerically fewer surgical interventions for the dabigatran patients (12.1%) versus the warfarin patients (15.0%; *P*=0.17) to stop the bleeding (Table 4).

Outcomes After Major Bleeding

Mortality

The crude mortality in the 5 studies at 7 and 30 days after the onset of the first major bleeding event among the dabigatran- and the warfarin-patients was 5.3% vs. 8.4% (*P*=0.045) and 9.1% vs. 13.0% (*P*=0.057), respectively. The Kaplan–Meier analysis indicated a trend to reduced risk for death with dabigatran (110 mg and 150 mg combined) versus warfarin during 30 days from the bleeding (*P*=0.052; Figure). Adjusted for sex, age, weight, renal function at the time of the bleed, and additional antithrombotic therapy, the OR for 30-day mortality in the combined dabigatran treatment groups was 0.66 (95% CI, 0.44–1.00; *P*=0.051). The corresponding adjusted ORs separately for dabigatran 110 mg or dabigatran 150 mg versus warfarin were 0.65 (95% CI, 0.38–1.11) and 0.68 (95% CI, 0.42–1.08), respectively. For the RE-LY population alone, the adjusted OR for 30-day mortality for dabigatran treatment groups combined was 0.56 (95% CI, 0.36–0.86; P=0.009), for dabigatran 150 mg was 0.52 (95% CI, 0.31–0.88), and for dabigatran 110 mg was 0.60 (95% CI, 0.35–1.03). For patients with venous thromboembolism there was no reduction of mortality in the dabigatran group, but the number of events was small. The main difference in cause of death after major bleeding between the patients with atrial fibrillation and venous thromboembolism appeared to be concomitant cancer (5% versus 36%; *P*=0.003).

Disability

Data on the initial and final modified Rankin Scale evaluations were recorded for 78 (55%) of all patients with intracranial

Table 4. Short-Term Consequences of Major Bleeding, as Derived From the RE-LY Database

	D 110 mg	D 150 mg	Dabigatran	Warfarin	*P* Value D 110 vs D 150	*P* Value D vs Warfarin	*P* Value D 110 vs Warfarin	*P* Value D 150 vs Warfarin
Patients with major bleeds, n (%)	342 (100)	399 (100)	741 (100)	421 (100)				
Major bleeding events, n	406	489	895	483				
Hospitalization, event (%)*	208 (51.2)	302 (61.8)	510 (57.0)	273 (56.5)	0.002	0.89	0.11	0.10
Length of stay, days, mean (SD)	8.1 (8.0)	8.5 (9.8)	8.4 (9.1)	8.9 (9.8)	0.61	0.48	0.36	0.68
Nights in ICU/CCU, mean (SD)	1.1 (3.2)	1.9 (4.9)	1.6 (4.3)	2.7 (6.6)	0.02	0.01	0.001	0.10
Nights in step-down unit, mean (SD)	1.1 (2.5)	0.9 (2.5)	1.0 (2.5)	1.0 (2.7)	0.39	0.84	0.75	0.59
Patients with major bleed requiring surgery, n (%)	34 (9.9)	56 (14.0)	90 (12.1)	63 (15.0)	0.09	0.17	0.05	0.76
Patients with major bleed requiring surgery or resulting in death, n (%)	56 (16.4)	76 (19.0)	132 (17.8)	94 (22.3)	0.38	0.06	0.04	0.26
Decrease in Hgb, g/L, mean (SD) – from baseline to time of bleeding	39.7 (29.2)	36.5 (25.4)	38.0 (27.2)	30.7 (24.7)	0.43	0.02	0.02	0.10
Decrease in Hgb g/L, median (IQR) – from time of bleeding to lowest Hgb	0.0 (16.0)	0.0 (14.0)	0.0 (14.0)	1.0 (18.0)	0.84	0.07	0.15	0.09
Discontinuation of study medication, n (%)	42 (12.3)	53 (13.3)	95 (12.8)	62 (14.7)	0.68	0.36	0.33	0.55
Discontinuation of ASA, n (%)	16 (4.7)	20 (5.0)	36 (4.9)	15 (3.6)	0.83	0.30	0.44	0.30
Discharge destination, n (% of hospitalizations)†								
Home	152 (73.1)	234 (77.5)	386 (75.7)	199 (72.9)	0.29	0.39	1.00	0.21
Long-term facility	28 (13.5)	32 (10.6)	60 (11.8)	35 (12.8)	0.33	0.73	0.89	0.44
Another hospital	10 (4.8)	13 (4.3)	13 (2.5)	17 (6.2)	0.83	0.31	0.55	0.35
mRS at presentation, median (IQR)‡	5 (2)	6 (1)	6 (1)	5 (3)	0.13	0.10	0.70	0.03
mRS at follow up, median (IQR)‡	6 (3)	6 (2)	6 (0)	6 (4)	0.45	0.10	0.52	0.11
Difference initial-final mRS, median (IQR)‡	0 (1)	0 (2)	0 (0)	0 (1)	0.78	0.97	0.80	0.81

ASA indicates acetylsalicylic acid; CCU, coronary care unit; D, dabigatran; D110, dabigatran 110 mg twice daily; D150, dabigatran 150 mg twice daily; Hgb, hemoglobin; ICU, intensive care unit; IQR, interquartile range; mRS, modified Rankin Scale; and RE-LY, Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate.

*Pertaining to the patients who were hospitalized for the major bleed. Hospitalization is reported for a major bleeding event, if admission to hospital was between 1 day before event and 7 days after the event.

†In ≈10% of cases the discharge destination was not recorded.

‡The mRS evaluations were only for patients with intracranial hemorrhage.

hemorrhage. There was no statistically significant difference between dabigatran and warfarin or between the 2 doses of dabigatran for any comparison of the change in score (Table 4).

For 710 (52%) of the bleeding events requiring hospitalization in the RE-LY trial, the discharge destination was specified as one of 3 categories (home, long-term facility, or other hospital). There was no significant difference in the proportion of these destinations according to treatment (Table 4).

Sensitivity Analyses

Results for transfusion of blood or plasma, or for administration vitamin K and for drop in hemoglobin from baseline until admission for bleeding, and for nights in intensive care were similar to the above reported, when analyzed only for events on treatment (Table II in the online-only Data Supplement). The all-cause mortality for bleeding events restricted to the on-treatment period only in the 5 trials was 4.8% in the dabigatran group and 7.7% in the warfarin group (P=0.062) at 7 days and 8.1% and 12.6%, respectively, at 30 days (P=0.018). The adjusted odds ratio for 30-day mortality in the dabigatran group and bleeds on treatment was 0.62 (95% CI, 0.40–0.96; P=0.03).

Hemostatic treatment for all major bleeding events, analyzed with correction for multiple events with the generalized estimating equation method (Table III in the online-only Data Supplement), showed similar results as in the main Table 3.

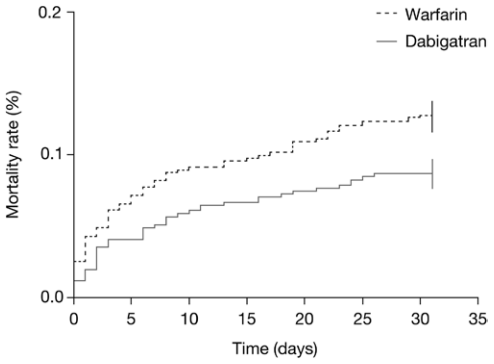

Figure. Thirty-day mortality rate after a major bleeding event.

Discussion

It has previously been reported that the risk of intracranial bleeding (RE-LY) or clinically relevant bleeding (RE-LY, RE-COVER) is lower with dabigatran than with warfarin.[1,2] We are now presenting data on the management and outcome of major bleeding events in 5 phase III trials on long-term treatment with dabigatran. One of the most important findings of our study is that patients who had a major bleeding event on dabigatran treatment were older, had worse renal function, and more often concomitant treatment with aspirin or a nonsteroid anti-inflammatory agent than those with warfarin. This implies that when bleeding occurs with dabigatran, the patient is usually at higher risk compared with patients with major bleeding events on warfarin and raises the possibility that some of these bleeds might be avoidable by using a lower dose of dabigatran, as also recommended in some treatment guidelines.[22] Avoidance of concomitant medication with aspirin and nonsteroid anti-inflammatory agents might also reduce the risk and severity of bleeding.

Most major bleeding events were managed with supportive care only. Coagulation factor concentrates were rarely used, irrespective of the anticoagulant therapy. Patients with bleeding on dabigatran were more often transfused with red cells, whereas patients with bleeding on warfarin more often received plasma. This was primarily explained by greater use of red cell transfusion in dabigatran compared with warfarin-treated patients who experienced major gastrointestinal bleeding (71% versus 54% transfused, respectively). The outcome of major bleeding events in patients on dabigatran was better than in those on warfarin, as evidenced by a shorter stay in the intensive care unit and a trend towards lower adjusted all-cause mortality at 30 days after major bleeding.

The 1121 major bleeding events assessed by our 2 independent reviewers is lower than the total of 1507 events reported from the 5 studies, because we had a strict cut-off of 3 days after the last dose of study drug. Thus we only included events that had a probable temporal relationship to the study drug. In a few cases the use of a blood component or plasma derivative was detected by narrative analysis, which had not been entered into the case report form (=database) and vice versa.

In the 5 trials with a pooled population of 27 419 patients the prevalence of risk factors for bleeding was balanced at baseline but not subsequently at the time of major bleeding for those with an event. RE-LY trial analyses have demonstrated that both age and renal function are independent risk factors for bleeding, and there was also an interaction between age and randomized treatment for major extracranial bleeding. There was no interaction between renal function as assessed by the Cockcroft-Gault formula and treatment, which is a surprising finding because renal function is a determinant of dabigatran exposure.[23] Other analyses have not consistently shown that renal dysfunction is a risk factor for bleeding in patients treated with anticoagulants,[23,24] although low-molecular-weight heparin, which like dabigatran depends on renal elimination, is associated with a higher incidence of bleeding at low glomerular filtration rates.[25] Concomitant antiplatelet therapy has been shown to increase the risk of bleeding in patients on warfarin and dabigatran.[26,27] The higher prevalence of these risk factors in patients treated with dabigatran compared with warfarin who experienced major bleeding suggests that dabigatran is associated with a higher threshold for bleeding.

The greater reduction in hemoglobin in the dabigatran group from baseline to the time of admission for the bleed is most likely explained by the higher incidence of gastrointestinal bleeding and lower incidence of intracranial bleeding with dabigatran. It is, however, reassuring that there was no difference between the treatments for the additional reduction of hemoglobin until the lowest level recorded. The drop in hemoglobin seen in patients treated with warfarin or dabigatran who did not experience any bleeding event might be related to occult gastro-intestinal blood loss. Even though the decrease in hemoglobin was greater in the dabigatran groups than in the warfarin group, the mean difference between the two anticoagulants was modest (1.1 g/L per 12 months for the dabigatran 150 mg group).

Dialysis to eliminate dabigatran was only used in a single case, refractory to treatment with a variety of blood products, and the response was recorded in the narrative as good.[7] This is supported by experimental data and some clinical data.[6,8] There were not sufficient data to identify any coagulation factor product that would be useful to reverse the effect of dabigatran. Perhaps surprisingly, of 418 bleeds on warfarin only 12 were managed with rapidly acting reversal agents (n=10 with PCC, n=2 with rFVIIa). This probably reflects clinical practice, because major bleeds were at least initially managed by staff in the emergency department; not necessarily at the site of the investigator but at the nearest hospital. The median amount of plasma transfused (4 units) is about half of what has been calculated as necessary to normalize the prothrombin time.[28]

This analysis presents all-cause mortality within 30 days after a major bleed as opposed to the data from RE-LY published by Eikelboom et al,[23] showing fatal bleeding (ie, bleeding leading to death) without a specified time frame. In a recent analysis of intracranial hemorrhages in RE-LY, mortality after intracranial hemorrhage was similar for dabigatran and warfarin, whereas the number of fatal intracranial bleeds was higher in the warfarin arm than in either of the dabigatran arms.[29] Warfarin treatment increases the risk of hematoma expansion in patients with warfarin related intracranial hemorrhage.[30] Early reversal of the anticoagulant effect of warfarin seems to limit hematoma expansion,[31,32] the size of which is related to the functional outcome and mortality after ICH.[30,33] It appears that management of warfarin-associated

bleeding is suboptimal,[32] probably requiring more education and implementation of guidelines that have been developed to support the use of PCC for rapid reversal.[4] Vitamin K was only given to 31% of patients with warfarin treatment at the time of a major bleed without any preference to a particular type of bleed. Appropriate use of these reversal agents could have improved the outcomes for the warfarin patients.

A strength of this study is that we have used all the data available in the RE-LY database and in addition the serious adverse event- and major bleeding narratives from all 5 trials to assess the treatment of bleeding. One of the limitations is that the treatment with dabigatran versus warfarin in the RE-LY trial was open, although the data reported on use of blood products, length of stay, and mortality are unlikely to be biased. Another limitation is that management of bleeding was not determined by random allocation. We also acknowledge that our study is a retrospective analysis, with the potential for biased data acquisition and outcome ascertainment. However, all data for these analyses were collected prospectively in the 5 clinical trials, using detailed and specific data acquisition forms, and all major bleeding events were classified as such by an independent adjudication committee. Finally, the data presented have been derived from clinical trials with selected patients and the resources required or the outcomes of major bleeding might be different in real world.

In conclusion, the overall resources required to manage bleeding were not greater and the prognosis after a major bleeding was not worse than after a warfarin-associated bleed. More frequent transfusion with red cells was counterbalanced by shorter stay by ≈1 day in the intensive care unit and less frequent transfusion of plasma. Our results point at the need for protocols to evaluate coagulation factor concentrates for the management of dabigatran-associated bleeding and for improved knowledge translation to manage warfarin-associated bleeding.

The main clinical implication of this study is that dabigatran offers an alternative to warfarin with similar or superior efficacy, carrying similar or lower risk for major bleeding events (especially intracranial hemorrhage), that can be managed satisfactorily with simple measures (drug discontinuation, transfusion of red cell concentrates) with a trend to lower mortality after such bleeding events compared to warfarin. The overall safety profile of dabigatran is favorable. Whether the management of bleeding on dabigatran can be further improved by a specific antidote remains to be evaluated.[14]

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CLINICAL PERSPECTIVE

The oral thrombin inhibitor dabigatran is approved for stroke prophylaxis in atrial fibrillation and has also been studied in the prophylaxis and treatment of venous thromboembolism. There is no available reversal agent for dabigatran, but it has a shorter half-life than warfarin. The major bleeding events that occurred during the clinical trials with dabigatran versus warfarin were generally managed by physicians in the nearest Emergency Department, but data on the management and outcomes were collected in the case report forms and summarized in the event narratives. We reviewed all available documentation to compare the resources used and the outcomes of major bleeding associated with dabigatran or warfarin in the 5 phase III long-term treatment trials, altogether 1121 events. The majority of cases were managed with supportive care, and coagulation factor concentrates were rarely used. Patients treated with dabigatran more frequently received red cell transfusion, whereas patients treated with warfarin received more often plasma with similar absolute differences. Those treated with dabigatran spent fewer nights in intensive care units, and for other resources there was similar use in the 2 groups. The 30-day all-cause mortality after major bleeding tended to be lower in the dabigatran group, and for the Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate (RE-LY) study population the adjusted risk estimate for 30-day mortality was significantly lower in the dabigatran group. Thus, patients with major bleeding on dabigatran should be managed with supportive care, including red cell transfusions as needed, and outcomes do not appear worse than for warfarin.

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Supplemental Material

Supplemental Tables

Table 1. Number of bleeding events according to bleeding site

Bleeding site	D 110mg	D 150mg	Dabigatran	Warfarin	Total	P value D 110 vs D 150	P value D 110 vs W	P value D 150 vs W	P value D vs W
Intracranial	23	29	52	90	142	0.72	<0.001†	<0.001†	<0.001†
Gastrointestinal	143	218	361	151	512	0.18	<0.001‡	<0.001‡	<0.001‡
Respiratory	7	9	16	16	32	0.90	0.34	0.19	0.17
Urinary	14	12	26	17	43	0.19	0.65	0.40	0.81
Genital	1	4	5	1	6	0.29	0.76	0.13	0.31
Intra-articular	3	6	9	10	19	0.62	0.21	0.39	0.19
Intra-muscular	5	6	11	20	32	0.88	0.03†	0.007†	0.002†
Other*	77	89	166	93	259	0.19	0.17	0.97	0.44
Post-operative	20	30	50	27	77	0.83	0.82	0.54	0.59
Total	293	403	696	425	1121				

D – dabigatran; W - Warfarin

* Including patients with bleeding at following sites: intraarticular, retroperitoneal, fracture bleeding, visceral bleeding, subcutaneous hematoma, hemopericardium, hemothorax, and unclear bleeding site.

† Favoring dabigatran

‡ Favoring warfarin

Table 2. Short-term consequences of first major bleeding event, sensitivity analyis of on treatment period only

	D 110 mg	D 150 mg	Dabigatran	Warfarin	P-value D 110 vs D 150	P-value D vs Warfarin	P-value D110 vs Warfarin	P-value D 150 vs Warfarin
All 5 trials – first major bleed, N	217	318	535	376	.	.	.	.
Blood transfusion, n (%)	124 (57)	189 (59)	311 (58)	148 (39)	0.62	<0.001	<0.001	<0.001
Plasma transfusion, n (%)	29 (13)	68 (21)	97 (18)	105 (28)	0.019	0.001	<0.001	0.048
Vitamin K, n (%)	15 (7)	26 (8)	41(8)	115 (31)	0.57	<0.001	<0.001	<0.001
RE-LY – first major bleed, N	217	281	498	305				
Blood transfusion, n (%)	124 (57)	172 (61)	296 (59)	123 (40)	0.38	<0.001	<0.001	<0.001
Plasma transfusion, n (%)	29 (13)	61 (22)	90 (18)	88 (29)	0.016	0.052	<0.001	<0.001
Vitamin K, n (%)	15 (7)	23 (8)	38 (8)	93 (30)	0.57	<0.001	<0.001	<0.001
Decrease in Hgb (g/L) from baseline to time of bleeding, mean (SD)	41.1(30.8)	36.1(27.0)	38.5(28.9)	27.6(23.9)	0.30	<0.001	<0.001	0.04
Nights in ICU/CCU, mean (SD)	1.2(3.5)	2.2(5.4)	1.7(4.7)	3.0(6.1)	0.05	0.02	<0.001	0.20

D – dabigatran; ICU – intensive care unit; CCU – coronary care unit; SD – standard deviation

Table 3. Hemostatic treatment for all major bleeding events in the RE-LY trial, GEE method[*]

	D 110 mg	D 150 mg	Dabigatran	Warfarin	P-value D 110 vs D 150	P-value D vs Warfarin	P-value D110 vs Warfarin	P-value D 150 vs Warfarin
Fresh frozen plasma, %	18	22	20	30	0.12	<0.001	<0.001	0.01
Cryoprecipitate, %	0.7	1.0	0.9	1.4	0.65	0.36	0.30	0.55
Platelets, %	3.2	3.7	3.5	5.0	0.69	0.17	0.17	0.31
Vitamin K, %	9.1	11	10.2	26	0.34	<0.001	<0.001	<0.001
Prothrombin complex concentrate, %	0.7	0.4	0.6	1.0	0.52	0.36	0.64	0.25
Recombinant factor VIIa, %	0.2	1.4	0.9	0.6	0.05	0.96	0.39	0.21
Coagulation factor replacement, %	0.2	0.6	0.4	1.0	0.39	0.21	0.13	0.47

[*]The generalized estimating equation for estimation of the parameters of a generalized linear model with a possible unknown correlation between outcomes. Includes events on treatment and up to 3 days after last dose.