Periprocedural Bleeding and Thromboembolic Events With Dabigatran Compared With Warfarin

Results From the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Randomized Trial

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Background—Dabigatran reduces ischemic stroke in comparison with warfarin; however, given the lack of antidote, there is concern that it might increase bleeding when surgery or invasive procedures are required.

Methods and Results—The current analysis was undertaken to compare the periprocedural bleeding risk of patients in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial treated with dabigatran and warfarin. Bleeding rates were evaluated from 7 days before until 30 days after invasive procedures, considering only the first procedure for each patient. A total of 4591 patients underwent at least 1 invasive procedure: 24.7% of patients received dabigatran 110 mg, 25.4% received dabigatran 150 mg, and 25.9% received warfarin, $P=0.34$. Procedures included: pacemaker/defibrillator insertion (10.3%), dental procedures (10.0%), diagnostic procedures (10.0%), cataract removal (9.3%), colonoscopy (8.6%), and joint replacement (6.2%). Among patients assigned to either dabigatran dose, the last dose of study drug was given 49 (35–85) hours before the procedure on comparison with 114 (87–144) hours in patients receiving warfarin, $P<0.001$. There was no significant difference in the rates of periprocedural major bleeding between patients receiving dabigatran 110 mg (3.8%) or dabigatran 150 mg (5.1%) or warfarin (4.6%); dabigatran 110 mg versus warfarin: relative risk, 0.83; 95% CI, 0.59 to 1.17; $P=0.28$; dabigatran 150 mg versus warfarin: relative risk, 1.09; 95% CI, 0.80 to 1.49; $P=0.58$. Among patients having urgent surgery, major bleeding occurred in 17.8% with dabigatran 110 mg, 17.7% with dabigatran 150 mg, and 21.6% with warfarin: dabigatran 110 mg; relative risk, 0.82; 95% CI, 0.48 to 1.41; $P=0.47$; dabigatran 150 mg: relative risk, 0.82; 95% CI, 0.50 to 1.35; $P=0.44$.

Conclusions—Dabigatran and warfarin were associated with similar rates of periprocedural bleeding, including patients having urgent surgery. Dabigatran facilitated a shorter interruption of oral anticoagulation.

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The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial demonstrated that dabigatran is well tolerated and that, compared with warfarin, dabigatran 150 mg BID is more effective at preventing stroke and systemic embolism with a similar risk of major bleeding, whereas dabigatran 110 mg BID is associated with a lower risk of major bleeding and a similar rate of stroke and systemic embolism.[1] However, because the anticoagulant effect of dabigatran is currently difficult to precisely measure, and the drug does not yet have a specific antidote, there is concern that dabigatran may increase the risk of bleeding in patients undergoing invasive procedures, particularly if performed on an emergency basis.[2,3]

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Each year, ≈10% of all patients receiving oral anticoagulants require treatment interruption for surgery or an invasive procedure.[4] Given the long and variable half-life of vitamin K antagonists, guidelines recommend that patients discontinue

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Table 1. Amended Perioperative Guidelines for Management of Dabigatran in the RE-LY Trial for Patients Having Surgery After August 7, 2008[11]

Renal Function Impairment (CrCL mL/min)	Estimated Half-Life, h (Range)	Stopping Dabigatran Before Surgery/Procedure	
		High Risk for Bleeding	Standard Risk for Bleeding
Mild: ≥50 to 80	15 (12–18)	2–3 d*	24 h (2 doses)*
Moderate: ≥30 to <50	18 (18–24)	4 d	At least 2 d (48 h)
Severe: <30	27 (>24)	>5 d	2–4 d

CrCL indicate creatinine clearance.

warfarin 5 days before major procedures, and that those at moderate or high risk of thromboembolic events receive perioperative bridging with low-molecular-weight heparin[4–6]; however, this is associated with additional costs, inconvenience, and risks.[4,7,8] The more predictable anticoagulant effect and shorter half-life of dabigatran has the potential to simplify the perioperative management of anticoagulation, but the risk of perioperative bleeding and thrombotic events with dabigatran has not been reported, and the best strategy for perioperative management of dabigatran is uncertain. The RE-LY trial captured extensive data on anticoagulant discontinuation for surgery or invasive procedure[9] and can help inform both of these issues.

Methods

The main results of the RE-LY trial have previously been published.[1] During the course of the study, all patients who required surgery, dental procedures, cardiac catheterization, or invasive diagnostic procedures (including percutaneous biopsy, peripheral angiography, and similar procedures) had details of the perioperative management of their anticoagulation prospectively recorded. Local investigators indicated if surgery was elective or urgent. Procedures were classified as major if they were documented to last >1 hour. The perioperative management of warfarin was according to local practice. From December 22, 2005 until August 7, 2008, the RE-LY protocol recommended discontinuation of dabigatran 24 hours before a procedure or surgery in all patients. Based on an improved understanding of the anticoagulant effect of dabigatran,[10–12] from August 7, 2008 until the end of the study on March 31, 2009, a protocol amendment recommended that dabigatran be discontinued 24 hours before surgery or procedures deemed to be associated with a low risk of bleeding, such as coronary angiography or pacemaker implantation. For surgery or procedures deemed to be associated with a high risk of bleeding (such as cardiac, abdominal, and neurosurgery or procedures requiring spinal anesthesia), dabigatran was to be discontinued 2 to 5 days before surgery, depending on renal function (Table 1). In all cases, dabigatran was restarted postprocedure once adequate hemostasis had been achieved.

For this analysis, the periprocedural period was defined as lasting from 7 days before the procedure until 30 days after. All outcomes were defined with the use of the same criteria that were used in the main RE-LY trial.[9] Bleeding outcomes of interest included major bleeding, fatal bleeding, bleeding requiring surgery, and all-cause bleeding. Major bleeding was the primary bleeding outcome for all analyses and was defined as a reduction in hemoglobin of at least 20 g/L, transfusion of at least 2 U of blood, or symptomatic bleeding into a critical area or organ.[1] Thromboembolic complications included ischemic stroke, systemic embolism, myocardial infarction, pulmonary embolism, and death. The primary analysis was limited to the first surgery or procedure for each patient during the course of the study to avoid the influence of intrapatient correlation for subsequent events; however, data are also presented for all surgeries performed during the trial. All cases of periprocedural stroke, systemic embolism, and myocardial infarction were reviewed to exclude outcomes in which the procedure or surgery was performed secondary to a clinical event (eg, embolectomy to treat systemic embolism).

The rate of bleeding and thrombotic complications in patients receiving warfarin in comparison with the rate in patients receiving dabigatran 110 mg BID or dabigatran 150 mg BID was presented by using the relative risk and a χ^2 test. Subgroup analyses were prespecified in the analysis plan to evaluate the outcome of major bleeding in patients having elective versus urgent surgery, in patients having major versus minor surgery, and for patients whose dabigatran was managed by use of the original versus amended protocol. The effect of these subgroups was evaluated using an interaction probability value. The effect of the timing of anticoagulant interruption on major bleeding was a post hoc analysis and was evaluated using the Cochran-Armitage test for trend. A secondary analysis of major bleeding was done using data from all procedures performed during the study, including subsequent procedures for patients who had >1. This analysis involved fitting a marginal logistic regression model with generalized estimating equation method, and the treatment effect was presented using the odds ratio.

Results

During a mean follow-up of 2 years, 4591 patients in the RE-LY trial had oral anticoagulant therapy interrupted at least once to have surgery or another invasive procedure. This represented 24.7% of patients assigned to dabigatran 110 mg, 25.4% assigned to dabigatran 150 mg, and 25.9% assigned to warfarin, $P=0.34$. The baseline characteristics of patients having interruption of oral anticoagulant therapy for surgery or procedures were similar between the 3 treatment groups (Table 2). The most common surgeries and procedures were pacemaker or defibrillator insertion (10.3%), dental procedures (10.0%), diagnostic procedures (10.0%), cataract removal (9.3%), colonoscopy (8.6%), and joint replacement (6.2%), with other types of surgery each accounting for a smaller proportion of cases (Table 2). Periprocedural bridging with intravenous heparin or low-molecular-weight heparin was used in 15.3% of patients assigned to dabigatran 110 mg BID, 17.0% of patients assigned to dabigatran 150 mg BID, and 28.5% of patients assigned to warfarin ($P<0.001$). Vitamin K was given perioperatively in 99 patients (2.2%): 9 of 1487 on dabigatran 110 mg BID, 18 of 1546 on dabigatran 150 mg BID, and 72 of 1558 on warfarin. Fresh-frozen plasma was given to 1.5% of patients: 20 of 1487 on dabigatran 110 mg BID, 17 of 1546 on dabigatran 150 mg BID, and 32 of 1558 on warfarin.

There was no significant difference in the incidence of perioperative major bleeding between patients receiving warfarin (4.6%) in comparison with dabigatran 110 mg BID (3.8%) and dabigatran 150 mg BID (5.1%) (Table 3). The results for all other bleeding outcomes, including fatal bleeding, bleeding requiring reoperation, bleeding requiring transfusion of red blood cells, and minor bleeding were consistent with the primary outcome of major bleeding (Table 3). The incidences of stroke and all other thromboembolic complications, including cardiovascular death, systemic embolism, myocardial infarction, or pulmonary embolism, were low and not significantly different between randomized treatment arms (Table 3).

Table 2. Baseline Characteristics of Patients and Types of Surgery or Intervention

Characteristics	Dabigatran 110 mg BID (N=1487)	Dabigatran 150 mg BID (N=1546)	Warfarin (N=1558)
Age, y	72.3±7.7	72.5±7.7	72.6±7.4
Male sex	69.9	66.6	68.2
Prior OAC	58.6	56.9	56.7
BMI	29.6±6.0	29.3±5.7	29.2±5.8
CrCL (SD) mL/min	71.9 (35.0)	69.9 (35.7)	69.8 (33.7)
Prior history of bleeding on OAC	1.0	0.8	0.8
CHADS-2 score	2.1±1.1	2.1±1.1	2.1±1.1
Coronary artery disease	35.8	34.3	35.4
Prior stroke	10.8	10.4	10.5
Peripheral vascular disease	4.4	6.3	5.5
Medications			
ASA	41.0	40.8	40.6
Clopidogrel	5.2	7.1	6.6
β-blocker	65.1	65.9	64.1
Type of surgery			
Pacemaker or ICD	11.6	9.5	9.8
Dental procedure	9.5	9.2	11.4
Other diagnostic procedure*	9.7	10.1	10.1
Cataract removal	8.3	10.1	9.6
Colonoscopy	9.6	8.9	7.4
Total hip or knee replacement	5.9	6.1	6.7
Coronary angiography	7.0	5.3	6.4
Cystoscopic procedure	5.2	4.7	5.0
Inguinal hernia repair	3.0	2.4	3.3
Laparoscopic cholecystectomy	2.2	2.7	2.6
CABG or valve	2.0	1.6	2.4
Colectomy (partial or total)	1.3	2.8	1.7
Peripheral angioplasty	1.4	1.4	0.8
Prostate biopsy	0.7	0.9	0.7
Carotid endarterectomy	0.4	0.7	0.7
Limb amputation	0.5	0.7	0.4

Values are given as percentages, unless stated otherwise. OAC indicates oral anticoagulant therapy; BMI, body mass index; CrCL, creatinine clearance; ICD, implantable cardioverter defibrillator; CABG, coronary artery bypass grafting; and ASA, acetylsalicylic acid.

*Percutaneous biopsy, catheter placement, diagnostic angiography, bronchoscopy, etc.

Repeating this analysis, including initial and all subsequent procedures performed during the RE-LY trial, there were 2485 procedures performed in patients receiving dabigatran 110 mg BID, 2635 in those receiving dabigatran 150 BID, and 2517 in patients receiving warfarin. After adjusting for correlated outcomes, the results for major bleeding remained similar to the analysis examining only first procedures, both for dabigatran 110 mg BID (odds ratio, 0.88; 95% CI, 0.63–1.12; $P=0.23$) and dabigatran 150 mg BID (odds ratio, 0.92; 95% CI, 0.70–1.22; $P=0.57$) compared with warfarin.

Among patients assigned to warfarin, 7.1% of surgery was classified as urgent in comparison with 4.2% of patients assigned to dabigatran 110 mg BID and 9.1% of patients assigned to dabigatran 150 mg BID (Table 4). In comparison with those having elective surgery, the incidence of major bleeding for patients in each treatment arm who had urgent surgery were 5- to 6-fold higher (Table 4, $P<0.001$ for all treatment arms). Similarly, the incidence of ischemic stroke or systemic embolism was >4 times greater among patients in all treatment groups who underwent urgent surgery: dabigatran 110 mg BID (2.8% versus 0.3%); dabigatran 150 mg BID (1.4% versus 0.4%), and warfarin (1.8% versus 0.4%). However, there were no significant differences in these outcomes between treatment groups when separately considering elective or urgent surgery (Table 4).

Accurate procedural durations were available for 28% of all surgery or procedures, which were classified as major in 53% of cases. In all 3 treatment arms, major bleeding was more common with major than with minor surgery: dabigatran 110 mg BID, 6.1% versus 1.9%; dabigatran 150 mg BID, 6.5% versus 3.2%; and warfarin, 7.8% versus 1.8%; $P<0.01$ for all (Table 4). However, there were no significant differences between treatment arms for either major surgery (dabigatran 110 mg BID versus warfarin: relative risk, 0.78 [95% CI, 0.49–1.24; $P=0.30$]; dabigatran 150 mg BID versus warfarin: relative risk, 0.82 [95% CI, 0.53–1.29; $P=0.40$]) or minor surgery (dabigatran 110 mg BID versus warfarin: relative risk, 1.03 [95% CI, 0.39–2.71; $P=0.96$]; dabigatran 150 mg BID versus warfarin: relative risk, 1.75 [95% CI, 0.74–4.14; $P=0.19$]).

During the course of the RE-LY trial, the suggested approach for the preprocedural management of dabigatran was changed from discontinuation 24 hours preprocedurally in all cases, to an algorithm based on renal function for patients having surgery with an anticipated high risk of bleeding, which recommended discontinuation of dabigatran 5 days or more before the procedure for those with a creatinine clearance of <30 mL/min (Table 1). The majority of surgeries and procedures in this analysis were characterized as having a low risk of bleeding (Table 2). For patients treated with each dabigatran dose, there was no significant difference in the rate of major bleeding before the amended perioperative recommendations and after (P-interaction is 0.81 for dabigatran 110 mg BID versus warfarin and 0.81 for dabigatran 150 mg BID versus warfarin; Table 4).

A separate analysis was done to determine the impact of the timing of preoperative study medication interruption on the rate of major bleeding and the influence of baseline renal function on this risk (Table 5). Among patients assigned to dabigatran 110 mg BID, the last dose of study drug was given 49 (interquartile range, 35–85) hours before the procedure; 49 (interquartile range, 34–84.5) hours among patients receiving dabigatran 150 mg BID and 114 (interquartile range, 87–144) hours in patients receiving warfarin, $P<0.001$. Study drug was discontinued within 48 hours before the surgery or procedure in 46% of patients receiving dabigatran 110 mg BID, 46% of patients receiving dabigatran 150 mg BID, and 11% of patients receiving warfarin, $P<0.001$. Among surgeries or procedures that were completed within 48 hours of study drug discontinuation, they were classified as urgent in 7.9% of patients receiving dabigatran 110 mg BID, 10.5% of

Table 3. Perioperative Bleeding and Thrombotic Events by Treatment Allocation

	D110 (N=1487) % (n)	D150 (N=1546) % (n)	Warfarin (N=1558) % (n)	D110 vs Warfarin RR (95% CI, *P* Value)	D150 vs Warfarin RR (95% CI, *P* Value)
Bleeding events					
Minor bleed	8.1 (120)	9.0 (139)	7.8 (122)	1.03 (0.81–1.31, 0.81)	1.15 (0.91–1.45, 0.24)
Major bleed	3.8 (57)	5.1 (78)	4.6 (72)	0.83 (0.59–1.17, 0.28)	1.09 (0.80–1.49, 0.58)
Fatal bleed	0.2 (3)	0.1 (2)	0.1 (2)	1.57 (0.26–9.39, 0.62)	1.01 (0.14–7.15, 0.99)
Requiring reoperation	0.6 (9)	1.4 (22)	1.0 (16)	0.59 (0.26–1.33, 0.20)	1.39 (0.73–2.63, 0.32)
Requiring RBC transfusion	3.3 (49)	3.5 (54)	4.0 (64)	0.81 (0.56–1.18, 0.27)	0.86 (0.60–1.23, 0.42)
Thrombotic events					
CV death	0.6 (9)	0.5 (7)	0.5 (7)	1.35 (0.50–3.61, 0.55)	1.01 (0.35–2.96, 0.99)
Stroke (all-cause)	0.5 (7)	0.5 (7)	0.6 (10)	0.73 (0.28–1.92, 0.53)	0.71 (0.27–1.85, 0.48)
Ischemic stroke	0.40 (6)	0.39 (6)	0.39 (6)	1.05 (0.34–3.24, 0.94)	1.01 (0.33–3.12, 0.99)
Hemorrhagic stroke	0.00 (0)	0.00 (0)	0.26 (4)	0.00 (0.04)	0.00 (0.046)
Systemic embolism	0.1 (1)	0.1 (1)	0.1 (1)	1.05 (0.07–16.7, 0.97)	1.01 (0.06–16.1, 1.0)
Ischemic stroke or systemic embolism	0.5 (7)	0.5 (7)	0.5 (7)	1.05 (0.55–2.01, 0.89)	1.01 (0.35–2.87, 0.99)
Myocardial infarction	0.1 (2)	0.5 (8)	0.3 (5)	0.42 (0.08–2.16, 0.28)	1.61 (0.53–4.92, 0.40)
Pulmonary embolism	0.1 (1)	0.1 (2)	0.2 (3)	0.35 (0.04–3.35, 0.34)	0.67 (0.11–4.02, 0.66)
Composite of CV death, ischemic stroke, non-CNS and pulmonary embolism	1.2 (18)	1.5 (23)	1.2 (18)	1.05 (0.55–2.01, 0.89)	1.29 (0.70–2.38, 0.42)

D110 indicates dabigatran 110 mg BID; D150, dabigatran 150 mg BID; RR, relative risk; RBC, red blood cell; CV, cardiovascular; and CNS, central nervous system.

patients receiving dabigatran 150 mg BID, and 28.7% of patients receiving warfarin, $P<0.0001$. In comparison with warfarin, both doses of dabigatran were associated with a lower risk of perioperative bleeding when study medication was discontinued within 48 hours before surgery (Table 5).

Discussion

This study compared the periprocedural use of dabigatran with warfarin and includes data from 7637 procedures in 4591 people who underwent at least 1 surgical procedure. It demonstrates that both dabigatran doses and warfarin are associated with similar rates of perioperative bleeding and thrombotic complications, even among patients having urgent or major surgery. This is reassuring, given the lack of a widely available test to precisely measure the anticoagulant effect of dabigatran and the lack of a direct reversing agent[2] and the concern that dabigatran may increase the risk of bleeding complications related to surgery or procedures, especially those that are urgent.[3] This analysis also highlights how commonly anticoagulated patients with atrial fibrillation require invasive procedures or surgery, because this occurred in approximately one-fourth of patients in RE-LY[1] over a 2-year period.

The RE-LY trial was not specifically designed to evaluate periprocedural bleeding, and no formal statistical power was calculated a priori for this outcome. However, the randomized design of RE-LY and the large number of patients included in this analysis should reliably exclude large differences in periprocedural bleeding outcomes between the anticoagulant strategies that were evaluated. Using the confidence interval approach and examining only outcomes for first procedures, we can conclude with 95% confidence that, compared with warfarin, the use of dabigatran 110 mg BID does not increase the rate of periprocedural major bleeding by

Table 4. Risk of Major Bleeding in Key Subgroups

	D110 % (n/N)	D150 % (n/N)	Warfarin % (n/N)	D110 vs Warfarin RR (95% CI, *P* Value)	*P*-Inter	D150 vs Warfarin RR (95% CI, *P* Value)	*P*-Inter
Urgent surgery	17.8 (19/107)	17.7 (25/141)	21.6 (24/111)	0.82 (0.48–1.41, 0.47)		0.82 (0.50–1.35, 0.43)	
Elective surgery	2.8 (38/1380)	3.8 (53/1405)	3.3 (48/1447)	0.83 (0.55–1.26, 0.38)	0.90	1.14 (0.77–1.67, 0.51)	0.31
Major surgery	6.1 (29/473)	6.5 (33/511)	7.8 (39/498)	0.78 (0.49–1.24, 0.30)		0.82 (0.53–1.29, 0.40)	
Minor surgery	1.9 (8/424)	3.2 (14/435)	1.8 (8/436)	1.03 (0.39–2.71, 0.96)	0.61	1.75 (0.74–4.14, 0.19)	0.13
Original dabigatran protocol	3.8 (47/1234)	4.9 (66/1346)	4.6 (60/1319)	0.84 (0.58–1.22, 0.35)		1.08 (0.77–1.52, 0.67)	
Amended dabigatran protocol	4.0 (10/253)	6.0 (12/200)	5.0 (12/239)	0.79 (0.35–1.79, 0.57)	0.81	1.20 (0.55–2.60, 0.65)	0.81

D110 indicates dabigatran 110 mg BID; D150, dabigatran 150 mg BID; RR, relative risk; and *P*-inter, *P*-interaction.

Table 5. Risk of Major Bleeding by Timing of Preoperative Study Medication Discontinuation

Overall	D110 % (n/N)	D150 % (n/N)	Warfarin % (n/N)	D110 vs Warfarin RR (95% CI, *P* Value)	D150 vs Warfarin RR (95% CI, *P* Value)
<24 h	2.8 (5/180)	6.8 (13/192)	15.4 (12/78)	0.18 (0.07–0.50, <0.001)	0.44 (0.21–0.92, 0.027)
24–48 h	3.2 (16/505)	3.3 (17/520)	9.0 (8/89)	0.35 (0.16–0.80, 0.01)	0.36 (0.16–0.82, 0.01)
48–72 h	4.5 (14/310)	4.5 (14/309)	5.7 (7/122)	0.79 (0.33–1.90, 0.60)	0.79 (0.33–1.91, 0.60)
>72 h	4.7 (21/451)	6.2 (29/468)	3.6 (45/1237)	1.28 (0.77–2.12, 0.34)	1.70 (1.08–2.68, 0.02)
				P Trend=0.002	*P* Trend=0.001

D110 indicates dabigatran 110 mg BID; D150, dabigatran 150 mg BID; and RR, relative risk.

>17% and dabigatran 150 mg BID does not increase major bleeding by >49%. When one considers all 7637 treatment interruptions for procedures in RE-LY, we have 95% confidence to conclude that the rate of periprocedural major bleeding is not increased by >12% with dabigatran 110 mg BID and 22% with dabigatran 150 mg BID. Furthermore, our results in those patients undergoing procedures is consistent with the overall results of the RE-LY trial,[1] and this provides additional confidence that our findings of similar rates of major bleeding between treatment groups is accurate.

One of the key advantages of dabigatran in comparison with warfarin in patients undergoing invasive procedures is its short half-life, which enables dabigatran to be continued in many patients until 24 to 48 hours before the procedure, thereby minimizing the risk of thromboembolic complications, the costs and complications of heparin bridging, but still ensuring adequate hemostasis at the time of surgery.[2,7,8] In RE-LY, nearly half of all patients treated with dabigatran had surgery within 48 hours of stopping oral anticoagulation, a rate >4 times higher than among patients receiving warfarin. When surgery or a procedure was performed during this short period, dabigatran-treated patients had a substantially lower rate of major bleeding in comparison with those receiving warfarin, although this is likely explained by the higher proportion of nonurgent surgery that was completed in dabigatran-treated patients. There was very likely a greater tendency among dabigatran-treated patients than among warfarin-treated patients to perform surgery within 24 to 48 hours among patients perceived to be at lower risk of bleeding and to wait >72 hours among patients with a higher risk. There was rather limited use of vitamin K and fresh-frozen plasma among warfarin-treated patients. Although physicians express a desire for specific reversing agents, <5% of warfarin-treated patients in the RE-LY trial received vitamin K and 2% received fresh-frozen plasma before undergoing an invasive procedure. By contrast, the short half-life of dabigatran facilitated rapid restoration of normal hemostasis, obviating the need for an antidote in the majority of patients.

The optimal timing of discontinuation of dabigatran before surgery is influenced by renal function and the bleeding risk of the surgery.[10,11] Dabigatran is 80% renally excreted; in patients with a creatinine clearance >80 mL/min, it has an estimated half-life of 13 hours (range, 11–22 hours); in those with a clearance of 51 to 80 mL/min, the half-life is 15 hours[12–34]; and in those with a clearance of 31 to 50 mL/min, the half-life is 18 hours.[12–23] For patients undergoing procedures that are associated with a standard risk of bleeding (eg, hernia repair), dabigatran should be stopped for 2 to 3 half-lives before the procedure, because this will allow drug levels to fall to 25% or lower of steady-state trough levels.[10,11] For procedures that are associated with a high risk of bleeding (eg, cardiac surgery) or procedures for which normal hemostasis is critical (eg, neurosurgery), dabigatran is recommended to be stopped for 4 to 5 half-lives before surgery, and an activated partial thromboplastin time or thrombin time should ideally be performed before surgery to ensure that the level has returned to normal.[10,11] The Hemoclot test, calibrated for dabigatran, is available outside the United States and will be useful once it becomes more widely available, because it provides a highly accurate estimation of dabigatran concentration.[11] Although this analysis from RE-LY did not demonstrate a reduction in major perioperative bleeding with introduction of the more conservative protocol for the preoperative management of dabigatran (Table 1) in comparison with simply withholding for 24 hours in all patients, the majority of patients included in these analyses underwent surgery with a "standard" risk of bleeding so the comparative analysis is underpowered (Table 2). Furthermore, the amended protocol was introduced relatively late in the course of the trial and was tested in relatively small numbers of patients. Nevertheless, the amended protocol recommendations take into account what we know about the pharmacology of dabigatran,[11–14] and we support their adoption for the management of dabigatran-treated patients undergoing an invasive procedure (Table 1).

Conclusions

Compared with warfarin, dabigatran is associated with similar rates of perioperative bleeding and thrombotic complications, even among patients having major or urgent surgery. Patients receiving dabigatran were 4 times more likely to have their procedure or surgery within 48 hours of withholding anticoagulation.

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Disclosures

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CLINICAL PERSPECTIVE

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial demonstrated that dabigatran is well-tolerated and that, compared with warfarin, dabigatran 150 mg BID is more effective at preventing stroke and systemic embolism, whereas dabigatran 110 mg BID is associated with a lower risk of major bleeding. However, because dabigatran does not yet have a specific antidote, and its anticoagulant effect is currently difficult to precisely measure, there is concern that dabigatran may increase the risk of bleeding in patients undergoing invasive procedures, particularly if performed on an emergency basis. The RE-LY trial highlights the importance of this scenario, because 25% of patients underwent at least 1 surgery or invasive procedure within 2 years. This analysis of periprocedural outcomes from RE-LY includes data on >7500 surgeries and procedures, making it the largest evaluation of any anticoagulant strategy in the periprocedural setting. The open-label design of RE-LY allowed a real-world evaluation of the periprocedural management or anticoagulation and demonstrated that dabigatran-treated patients were 4 times more likely to have their procedure completed within 48 hours of the discontinuation of anticoagulation than patients treated with warfarin. Overall, there was no detectable difference in the rate of minor, major, or fatal bleeding between patients treated with warfarin in comparison with either dose of dabigatran, nor was there any difference in the risk of thromboembolic events. In comparison with patients receiving warfarin, the rates of major bleeding with both doses of dabigatran were also similar in the subgroups of patients having major surgery and those having surgery on an emergency basis.

Periprocedural Bleeding and Thromboembolic Events With Dabigatran Compared With Warfarin: Results From the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Randomized Trial

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Correction

In the article by Healey et al, "Periprocedural Bleeding and Thromboembolic Events With Dabigatran Compared With Warfarin: Results From the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Randomized Trial," which was published in the July 17, 2012 issue of the journal (*Circulation*. 2012;126:343–348), an author's name was spelled incorrectly. The correct spelling of Hein Heidbuchle is Hein Heidbuchel.

The error has been corrected in the current online version of the article. The authors regret the error.

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