Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation

An Analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial

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Background—Dabigatran 150 and 110 mg twice a day and warfarin are effective for stroke prevention in atrial fibrillation. The purpose of this study was to compare their risks of bleeding in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial.

Methods and Results—The RE-LY trial randomized 18 113 patients to receive dabigatran 110 or 150 mg twice a day or warfarin dose adjusted to an international normalized ratio of 2.0 to 3.0 for a median follow-up of 2.0 years. Compared with warfarin, dabigatran 110 mg twice a day was associated with a lower risk of major bleeding (2.87% versus 3.57%; $P=0.002$), whereas dabigatran 150 mg twice a day was associated with a similar risk of major bleeding (3.31% versus 3.57%; $P=0.32$). There was a significant treatment-by-age interaction, such that dabigatran 110 mg twice a day compared with warfarin was associated with a lower risk of major bleeding in patients aged <75 years (1.89% versus 3.04%; $P<0.001$) and a similar risk in those aged ≥75 years (4.43% versus 4.37%; $P=0.89$; P for interaction <0.001), whereas dabigatran 150 mg twice a day compared with warfarin was associated with a lower risk of major bleeding in those aged <75 years (2.12% versus 3.04%; $P<0.001$) and a trend toward higher risk of major bleeding in those aged ≥75 years (5.10% versus 4.37%; $P=0.07$; P for interaction <0.001). The interaction with age was evident for extracranial bleeding, but not for intracranial bleeding, with the risk of the latter being consistently reduced with dabigatran compared with warfarin irrespective of age.

Conclusions—In patients with atrial fibrillation at risk for stroke, both doses of dabigatran compared with warfarin have lower risks of both intracranial and extracranial bleeding in patients aged <75 years. In those aged ≥75 years, intracranial bleeding risk is lower but extracranial bleeding risk is similar or higher with both doses of dabigatran compared with warfarin.

Clinical Trial Registration—http://www.clinicaltrials.gov. Unique identifier: NCT00262600. (***Circulation*. 2011;123:2363-2372.**)

Key Words: anticoagulants ■ atrial fibrillation

The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial in patients with atrial fibrillation (AF) demonstrated that dabigatran 110 mg twice a day compared with warfarin was associated with a similar risk of stroke and a lower risk of major bleeding and that dabigatran 150 mg twice a day was associated with a lower risk of stroke and a similar risk of major bleeding.[1] The effects of both doses of dabigatran in stroke prevention were consistent irrespective of patient baseline characteristics,[1] suggesting that the efficacy results can be applied widely. However, we

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have not reported previously the safety results of both doses of dabigatran compared with warfarin for different types of major bleeding and in key subgroups.

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Methods

RE-LY Trial Design

The RE-LY trial design has been published previously.[2] Briefly, the primary study objective was to establish the noninferiority of 2 doses of dabigatran compared with warfarin for stroke prevention in patients with AF. The RE-LY investigators randomized 18 113 patients with AF, who had at least 1 additional risk factor for stroke, to receive dabigatran 110 mg twice a day, dabigatran 150 mg twice a day, or dose-adjusted warfarin (target international normalized ratio 2.0 to 3.0) for a median of 2 years. The main safety outcome was major bleeding, and the primary efficacy outcome was stroke or systemic embolism.

Outcome Definitions

All primary and secondary outcome events were blindly and doubly adjudicated.

Major bleeding was defined as bleeding associated with a reduction in hemoglobin level of ≥2.0 g/dL, transfusion of ≥2 U of blood, or symptomatic bleeding into a critical area or organ. Major bleeding was separated into intracranial (intracerebral, subdural) and extracranial (gastrointestinal, nongastrointestinal) bleeding. Life-threatening bleeding was a subset of major bleeding that included fatal or symptomatic intracranial bleeding, bleeding associated with a hemoglobin decrease of ≥5.0 g/dL or requiring transfusion of ≥4 U of blood or inotropic agents, or bleeding necessitating surgery.

Statistical Analyses

We examined the effects of dabigatran 110 mg twice a day, dabigatran 150 mg twice a day, and warfarin on risk of major bleeding and performed exploratory analyses of the effect on different types of major bleeding according to severity and site of the bleeding. Cox regression was used to calculate relative risks, confidence intervals, and *P* values. Kaplan-Meier curves were constructed for each of the 3 treatment groups for the outcomes of major bleeding, intracranial bleeding, gastrointestinal bleeding, and total bleeding (major and minor bleeding). The risk of bleeding is reported as percentage per year, which was calculated by dividing the total number of patients with events by the total number of patient-years of follow-up.

We examined the relative risks of major bleeding in prespecified subgroups defined by age (<65, 65 to 74, ≥75 years), sex (male, female), body weight (<50, 50 to 99, ≥100 kg), creatinine clearance (<50, 50 to 79, ≥80 mL/min, as calculated by the Cockcroft-Gault method), and baseline use compared with no baseline use of aspirin, and we calculated *P* values for interaction between treatment and subgroup. We also explored the relative risk of major bleeding in subgroups defined post hoc according to baseline use compared with no baseline use of amiodarone and proton pump inhibitors.

We further explored the interaction between treatment and age for major bleeding by plotting the risk of intracranial and extracranial bleeding in each of the 3 treatment groups by age categories (<55, 55 to 64, 65 to 74, 75 to 84, and ≥85 years) and by examining the relative risks of different types of major bleeding (intracranial, extracranial, gastrointestinal bleeding, extracranial nongastrointestinal bleeding) in subgroups defined by age.

Not all major bleeds were categorized according to site of bleeding on the case report forms, and investigators were not required to report whether gastrointestinal bleeding was from the upper or lower gastrointestinal tract. To provide more detail for this analysis, the adjudication documents for all major bleeding events of unknown site were reviewed by 2 adjudicators, and, when possible, bleeding events were classified according to site of bleeding. Adjudication documents for all major gastrointestinal bleeding events were also reviewed, and, when possible, gastrointestinal bleeding events were classified according to whether they were from the upper or lower gastrointestinal tract.

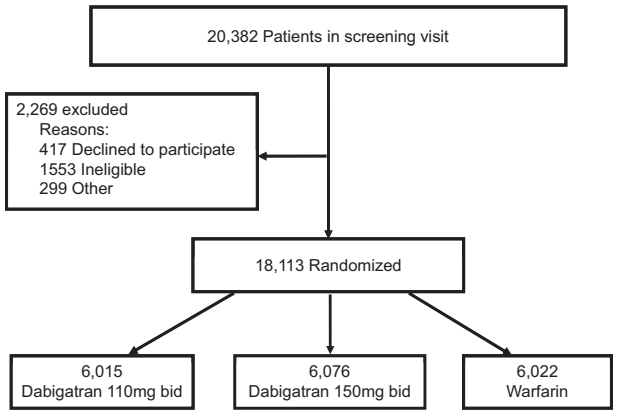


Figure 1. Patient flow diagram.

All analyses were performed with the use of SAS software, version 9.1 (SAS Institute Inc, Cary, NC). A 2-sided *P* value of <0.05 was considered statistically significant. We also calculated a more conservative *P* value threshold of 0.001 on the basis of Bonferroni adjustment for multiple testing, and we cautiously interpreted results associated with *P* values between 0.05 and 0.001.

The study was approved by all appropriate national regulatory authorities and ethics committees. All patients provided written informed consent before study entry. The authors of the manuscript had full access to the data and planned the statistical analyses.

Results

Patient Disposition and Baseline Characteristics

Patient flow is presented in Figure 1. Patient baseline characteristics are summarized in Table 1.

Major Bleeding

Table 2 presents the risk of major bleeding, different types of major bleeding, minor bleeding, and red cell transfusion according to randomized treatment allocation. Figure 2 presents Kaplan-Meier curves for major and gastrointestinal bleeding, and Figure 3 presents Kaplan-Meier curves for intracranial bleeding.

Dabigatran 110 mg twice a day compared with warfarin was associated with a lower risk of major bleeding (risk 2.87% versus 3.57%; $P=0.002$), including intracranial bleeding (0.23% versus 0.76%; $P<0.001$) and life-threatening bleeding (1.24% versus 1.85%; $P<0.001$), with no difference in extracranial bleeding (2.66% versus 2.84%; $P=0.42$).

Dabigatran 150 mg twice a day and warfarin were associated with similar risks of major bleeding (3.31% versus 3.57%; $P=0.32$) and extracranial bleeding (3.02% versus 2.84%; $P=0.36$), but dabigatran 150 mg twice a day was associated with more gastrointestinal bleeding (1.85% versus 1.25%; $P<0.001$) and less intracranial bleeding (0.32% versus 0.76%; $P<0.001$) than warfarin.

Dabigatran 150 mg twice a day compared with dabigatran 110 mg twice a day was associated with a numerically higher risk of major bleeding (3.31% versus 2.87%; $P=0.04$), mainly gastrointestinal bleeding (1.85% versus 1.36%; $P=0.002$).

Table 1. Baseline Characteristics of Patients Enrolled in the Randomized Evaluation of Long-Term Anticoagulant Therapy Trial, According to Treatment Group

Characteristic	Dabigatran, 110 mg BID	Dabigatran, 150 mg BID	Warfarin
Age, y	71.4±8.6	71.5±8.8	71.6±8.6
Weight, kg	82.9±19.9	82.5±19.4	82.7±19.7
Blood pressure, mm Hg			
Systolic	130.8±17.5	131.0±17.6	131.2±17.4
Diastolic	77.0±10.6	77.0±10.6	77.1±10.4
Male sex, No./total No. (%)	3865/6015 (64.3)	3840/6076 (63.2)	3809/6022 (63.3)
Type of atrial fibrillation, No./total No. (%)			
Persistent	1950/6011 (32.4)	1909/6075 (31.4)	1930/6021 (32.0)
Paroxysmal	1929/6011 (32.1)	1978/6075 (32.6)	2036/6021 (33.8)
Permanent	2132/6011 (35.4)	2188/6075 (36.0)	2055/6021 (34.1)
$CHADS_2$ score*	2.1±1.1	2.2±1.2	2.1±1.1
0 or 1, No./total No. (%)	1958/6014 (32.6)	1958/6076 (32.2)	1859/6022 (30.9)
2, No./total No. (%)	2088/6014 (34.7)	2137/6076 (35.2)	2230/6022 (37.0)
3–6, No./total No. (%)	1968/6014 (32.7)	1981/6076 (32.6)	1933/6022 (32.1)
Previous stroke or transient ischemic attack, No./total No. (%)	1195/6015 (19.9)	1233/6076 (20.3)	1195/6022 (19.8)
Prior myocardial infarction, No./total No. (%)	1008/6015 (16.8)	1029/6076 (16.9)	968/6022 (16.1)
Heart failure, No./total No. (%)	1937/6015 (32.2)	1934/6076 (31.8)	1922/6022 (31.9)
Diabetes mellitus, No./total No. (%)	1409/6015 (23.4)	1402/6076 (23.1)	1410/6022 (23.4)
Hypertension, No./total No. (%)	4738/6015 (78.8)	4795/6076 (78.9)	4750/6022 (78.9)
Medications in use at baseline, No./total No. (%)			
Aspirin	2404/6013 (40.0)	2352/6075 (38.7)	2442/6017 (40.6)
Proton pump inhibitor	812/6013 (13.5)	847/6075 (13.9)	832/6017 (13.8)
H_2 receptor antagonist	225/6013 (3.7)	241/6075 (4.0)	256/6017 (4.3)
Long-term vitamin K antagonist therapy†	3011/6015 (50.1)	3049/6076 (50.2)	2929/6022 (48.6)

Values are mean±SD unless indicated otherwise. The table is reproduced with permission from Reference 1.

*The $CHADS_2$ score is a measure of the risk of stroke in which congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus are each assigned 1 point and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient.

†Long-term therapy with a vitamin K antagonist denotes a total lifetime use of a VKA of ≥61 days.

Sites of Major Bleeding

Table 3 presents the risks of major bleeding at nongastrointestinal extracranial sites. The relatively small numbers of bleeds at most extracranial sites yielded estimates with wide confidence intervals, but in each case the estimates were consistent with estimates of relative risk for major extracranial bleeding in the overall trial. Despite lacking an antidote, dabigatran did not increase major bleeding at surgical sites compared with warfarin (dabigatran 110 mg twice a day versus warfarin: 0.45% versus 0.59%; $P=0.14$; dabigatran 150 mg twice a day versus warfarin: 0.40% versus 0.59%; $P=0.042$).

Major Bleeding in Subgroups

Figure 4A presents the relative risks of major bleeding in patients randomized to receive dabigatran 110 mg twice a day or dabigatran 150 mg twice a day compared with warfarin in key subgroups according to patient baseline characteristics. The risk of bleeding increased with increasing age, and both doses of dabigatran compared with warfarin were associated with an increasing relative risk of major bleeding with increasing age categories (<65, 65 to 74, ≥75 years) (P for interaction <0.001 for each analysis). The risk of bleeding also increased with decreasing creatinine clearance and with concomitant aspirin use (40.0%, 38.7%, and 40.6% of patients treated with dabigatran 110 mg twice a day, dabigatran 150 mg twice a day, and warfarin, respectively, were taking aspirin at baseline, and 21.1%, 19.6%, and 20.8% of patients in each randomized treatment group took aspirin throughout the study), but there were no significant interactions between creatinine clearance or concomitant aspirin and randomized treatment. Likewise, there were no significant interactions between sex, body weight, or concomitant use of amiodarone or proton pump inhibitors and randomized treatment ($P>0.10$ for each analysis).

Table 2. Risk of Major Bleeding, Minor Bleeding, and Red Cell Transfusion With Dabigatran 110 Twice a Day, Dabigatran 150 mg Twice a Day, and Warfarin

	Warfarin (n=6022)		Dabigatran 110 mg BID (n=6015)		Dabigatran 150 mg BID (n=6076)		Dabigatran 110 mg BID vs Warfarin (n=12 037)		Dabigatran 150 mg BID vs Warfarin (n=12 098)		Dabigatran 150 mg BID vs Dabigatran 110 mg BID (n=12 091)	
	n	%/y	n	%/y	n	%/y	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Major bleeding	421	3.57	342	2.87	399	3.31	0.80 (0.70–0.93)	0.002	0.93 (0.81–1.07)	0.32	1.16 (1.00–1.34)	0.04
Intracranial	90	0.76	27	0.23	39	0.32	0.30 (0.19–0.45)	<0.001	0.42 (0.29–0.62)	<0.001	1.43 (0.88–2.34)	0.15
Intracerebral	48	0.41	15	0.13	16	0.13	0.31 (0.17–0.55)	<0.001	0.33 (0.19–0.57)	<0.001	1.05 (0.52–2.13)	0.88
Subdural	40	0.34	12	0.10	23	0.19	0.30 (0.16–0.57)	<0.001	0.56 (0.34–0.94)	0.028	1.90 (0.94–3.81)	0.07
Extracranial	335	2.84	317	2.66	364	3.02	0.94 (0.81–1.09)	0.42	1.07 (0.92–1.24)	0.36	1.14 (0.98–1.33)	0.09
Gastrointestinal	148	1.25	162	1.36	223	1.85	1.09 (0.87–1.36)	0.44	1.49 (1.21–1.84)	<0.001	1.37 (1.12–1.67)	0.002
Nongastrointestinal	202	1.71	168	1.41	166	1.38	0.82 (0.67–1.01)	0.06	0.80 (0.65–0.99)	0.038	0.98 (0.79–1.21)	0.83
Life-threatening bleeding	218	1.85	147	1.24	179	1.49	0.67 (0.54–0.82)	<0.001	0.80 (0.66–0.98)	0.030	1.21 (0.97–1.50)	0.09
Fatal bleeding	39	0.33	23	0.19	28	0.23	0.58 (0.35–0.97)	0.039	0.70 (0.43–1.14)	0.15	1.20 (0.69–2.09)	0.51
Minor bleeding	1931	16.37	1566	13.16	1787	14.84	0.79 (0.74–0.84)	<0.001	0.91 (0.85–0.97)	0.005	1.16 (1.08–1.24)	<0.001
Total bleeding*	2150	18.23	1745	14.66	1980	16.45	0.78 (0.73–0.83)	<0.001	0.91 (0.85–0.96)	0.002	1.16 (1.08–1.23)	<0.001
Red cell transfusion	228	1.93	207	1.74	253	2.10	0.90 (0.75–1.09)	0.29	1.10 (0.92–1.31)	0.30	1.22 (1.01–1.46)	0.036

n indicates number of patients; RR, relative risk; and CI, confidence interval.
*Includes major and minor bleeding.

Bleeding rates were higher among patients who received treatment with the combination of aspirin and clopidogrel compared with those who did not receive combination antiplatelet therapy during the course of the RE-LY trial. The relative effects of both dabigatran 110 mg twice a day and dabigatran 150 mg twice a day compared with warfarin on major bleeding risk were, however, consistent irrespective of whether patients received dual antiplatelet therapy (Table I in the online-only Data Supplement).

Figure 4B presents the relative risks of major bleeding in patients randomized to receive dabigatran 150 mg twice a day compared with dabigatran 110 mg twice a day in subgroups according to patient baseline characteristics. The effects of dabigatran 150 mg twice a day compared with 110 mg twice a day on major bleeding were consistent in all subgroups examined.

Age-by-Treatment Interaction for Bleeding

Figure 5 presents plots of intracranial bleeding and extracranial bleeding risks according to treatment allocation in patients aged <55, 55 to 64, 65 to 74, 75 to 84, and ≥85 years. The risks of both intracranial and extracranial bleeding were progressively higher with increasing age. Both doses of dabigatran were consistently associated with lower risks of intracranial bleeding than warfarin. In younger patients, both doses of dabigatran were associated with less extracranial bleeding than warfarin, whereas in older patients, both doses of dabigatran were associated with higher risks of extracranial bleeding than warfarin.

Table 4 presents a breakdown of the data on the relative risks of major, intracranial, extracranial, gastrointestinal, and nongastrointestinal extracranial bleeding in patients aged <75 and ≥75 years. Data for stroke or systemic embolism in patients aged <75 and ≥75 years are provided for comparison. When 75 years is used as a cutoff to define age subgroups, interactions between age and treatment were evident for major and extracranial bleeding, including gastrointestinal and nongastrointestinal extracranial bleeding, but not for intracranial bleeding or for the outcome of stroke or systemic embolism.

Site of Major Gastrointestinal Bleeding

Among patients randomized to receive dabigatran for whom information on the site of major gastrointestinal bleeding was available, 53% (103/194) had bleeding from the upper gastrointestinal tract, and 47% (91/194) had bleeding from the lower gastrointestinal tract. Among patients who received warfarin for whom this information was available, 75% (54/72) had bleeding from the upper gastrointestinal tract, and 25% (18/72) had bleeding from the lower gastrointestinal tract (Table II in the online-only Data Supplement).

Discussion

Both doses of dabigatran were associated with lower risks of intracranial, life-threatening, and minor bleeding than warfarin, but the higher dose of dabigatran was associated with more gastrointestinal bleeding than warfarin. There was a highly significant interaction between treatment and age for major bleeding, such that both doses of dabigatran compared with warfarin were associated with lower risks of major bleeding in patients aged <75 years and similar risks or higher risks of major bleeding in those aged ≥75 years. The marked interaction between treatment and age was evident for extracranial bleeding but not for intracranial bleeding; the risk of intracranial bleeding was lower with both doses of dabigatran compared with warfarin irrespective of age.

Our finding of a >2-fold higher risk of major bleeding with dabigatran or warfarin in patients with a creatinine clearance <50 mL/min compared with those who had a clearance ≥80 mL/min is consistent with published reports that renal function is a powerful predictor of bleeding risk in patients who are treated with warfarin.[3] Dabigatran is 80%

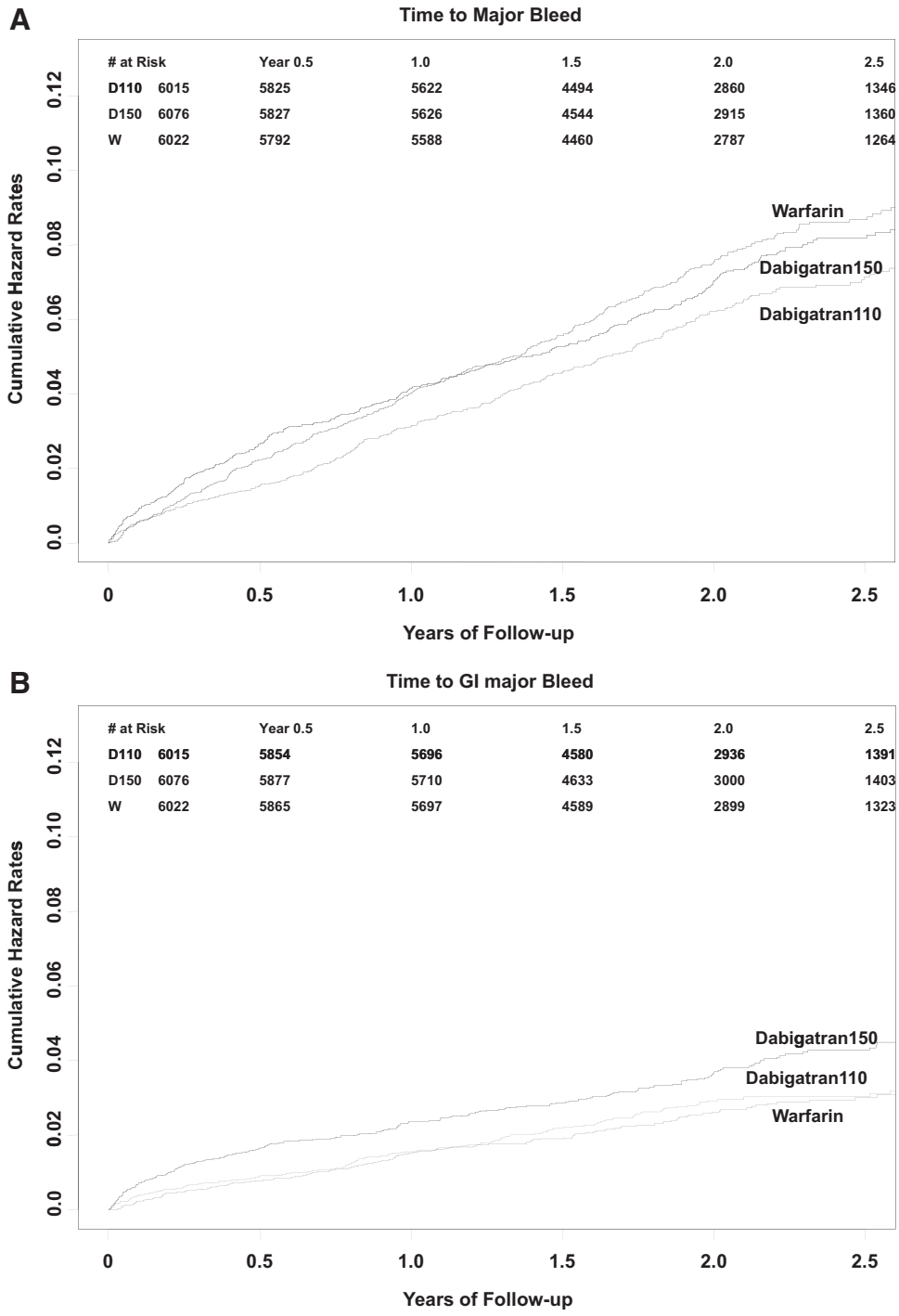


Figure 2. Kaplan-Meier curves for each of the 3 treatment groups for the outcomes of major bleeding **(A)** and gastrointestinal (GI) bleeding **(B)**. D110 indicates dabigatran 110 mg; D150, dabigatran 150 mg; and W, warfarin.

renally excreted, and fixed-dose unmonitored dabigatran therapy can thus be expected to produce higher blood concentrations of the drug in patients with renal dysfunction.[4] Unlike dabigatran, warfarin is not excreted renally, and is dose adjusted according to the results of routine coagulation monitoring. Because renal function also declines with increasing age, it seems logical to attribute the RE-LY trial interaction between age and randomized treatment for major bleeding to the accumulation of dabigatran (but not warfarin) in elderly patients with renal dysfunction. However, we did not find a significant interaction between treatment and creatinine clearance for major bleeding, suggesting that other age-related factors are more important than renal function as determinants of bleeding risk in elderly patients treated with dabigatran. The quality of international normalized ratio control was an important determinant of the relative risk of major bleeding with warfarin compared with dabigatran in the RE-LY trial,[5] but we did not find any differences in the quality of international normalized ratio control according to age category (data not shown). The lack of an interaction

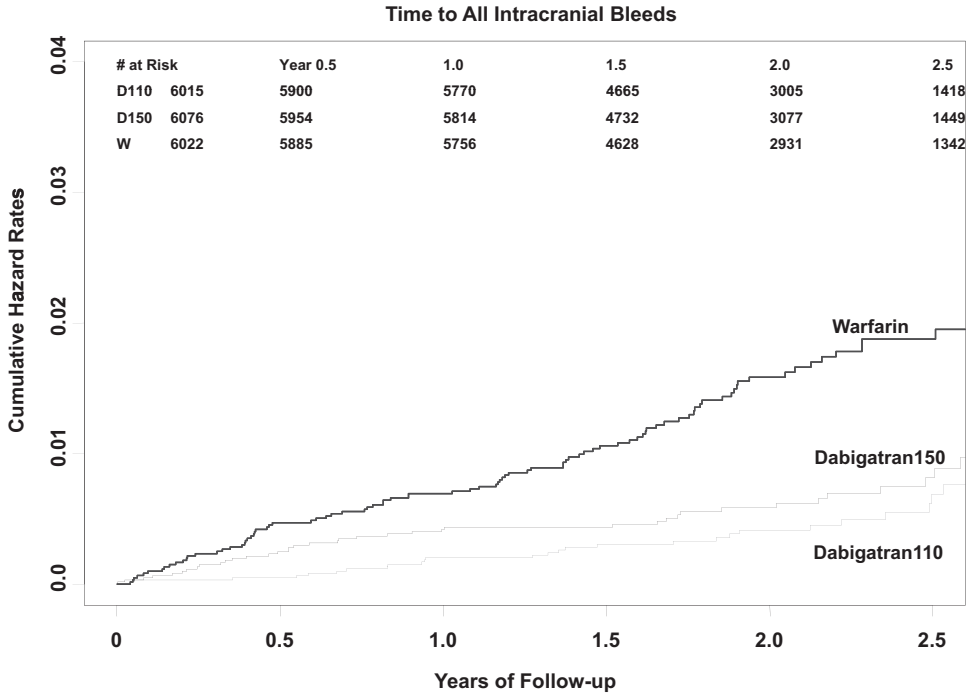


Figure 3. Kaplan-Meier curves for each of the 3 treatment groups for the outcome of intracranial bleeding. D110 indicates dabigatran 110 mg; D150, dabigatran 150 mg; and W, warfarin.

between age and treatment for intracranial bleeding suggests that the interaction between age and treatment is not simply a pharmacokinetic interaction.

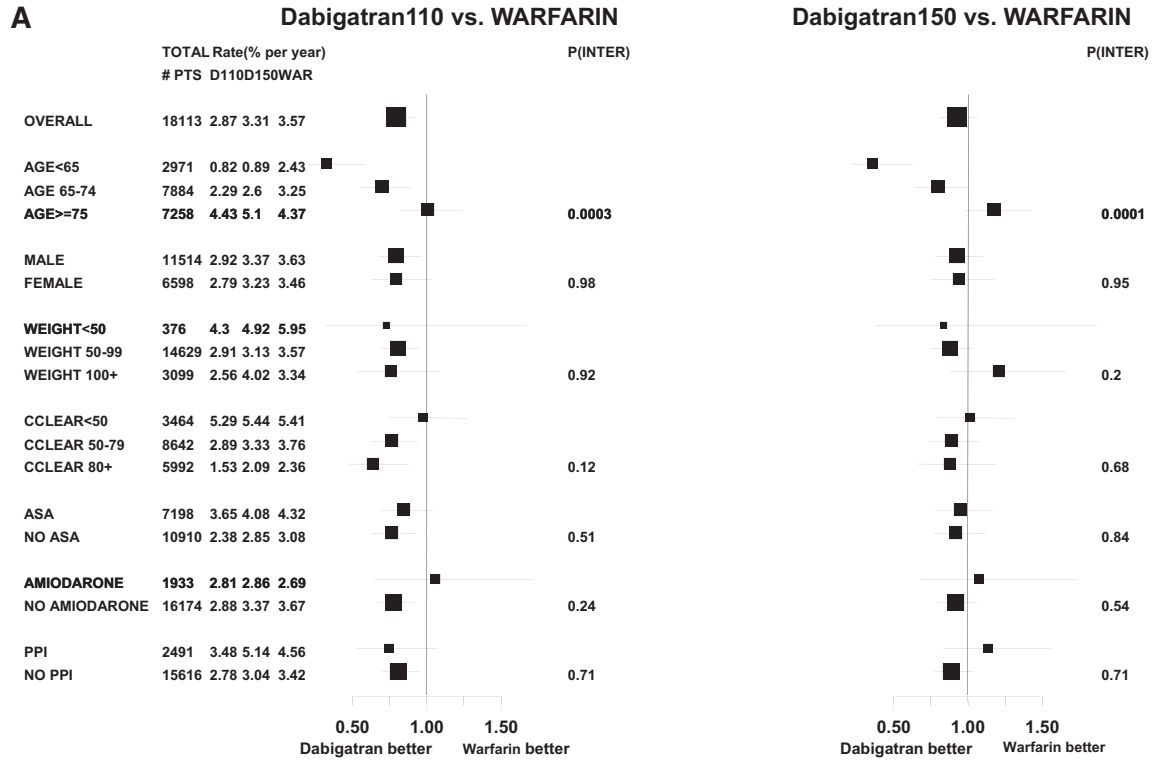
Intracranial bleeding remains one of the most feared complications of anticoagulant therapy.[6,7] The much lower risk of intracranial bleeding with dabigatran compared with warfarin in the RE-LY trial irrespective of age might be related to different effects of 2 drugs on blood coagulation. Tissue factor (TF) is a transmembrane receptor for factor VIIa that is found in high concentrations in the brain, where it is believed to provide additional hemostatic protection in the case of injury.[8,9] TF-VIIa complexes that are formed when activated coagulation factor VII binds to TF are the primary cellular initiators of coagulation. Warfarin blocks vitamin K–dependent γ-carboxylation of coagulation factors II, VII, IX, and X,[10] thereby suppressing production of factor VIIa and formation of TF-VIIa complexes. We hypothesize that by selectively targeting thrombin and not interfering with the formation of TF-VIIa complexes, dabigatran preserves hemostatic mechanisms in the brain that could protect elderly patients against the risk of spontaneous intracranial bleeding. TF is also expressed in high concentrations at the site of atherosclerotic plaque rupture,[11] and more effective inhibition by warfarin compared with dabigatran of TF-VIIa complex

Table 3. Risks of Bleeding at Nongastrointestinal Extracranial Sites With Dabigatran 110 Twice a Day, Dabigatran 150 mg Twice a Day, and Warfarin*

	Warfarin (n=6022)		Dabigatran 110 mg BID (n=6015)		Dabigatran 150 mg BID (n=6076)		Dabigatran 110 mg BID vs Warfarin (n=12 037)		Dabigatran 150 mg BID vs Warfarin (n=12 098)		Dabigatran 150 mg BID vs Dabigatran 110 mg BID (n=12 091)	
	n	%/y	n	%/y	n	%/y	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Ear, nose, throat	18	0.15	7	0.06	9	0.07	0.39 (0.16–0.93)	0.033	0.49 (0.22–1.09)	0.08	1.27 (0.47–3.41)	0.64
Genitourinary	15	0.13	22	0.18	16	0.13	1.46 (0.76–2.81)	0.26	1.05 (0.52–2.12)	0.90	0.72 (0.38–1.37)	0.31
Intra-articular	7	0.06	5	0.04	2	0.02	0.71 (0.22–2.23)	0.55	0.28 (0.06–1.35)	0.11	0.39 (0.08–2.03)	0.26
Intraocular	14	0.12	15	0.13	11	0.09	1.07 (0.52–2.21)	0.86	0.77(0.35–1.70)	0.52	0.72 (0.33–1.58)	0.42
Intrathoracic	8	0.07	10	0.08	9	0.07	1.24 (0.49–3.14)	0.65	1.10 (0.42–2.85)	0.84	0.89 (0.36–2.19)	0.80
Pericardial	4	0.03	2	0.02	3	0.02	0.50 (0.09–2.71)	0.42	0.74 (0.17–3.32)	0.70	1.48 (0.25–8.88)	0.67
Retroperitoneal	13	0.11	2	0.02	9	0.07	0.15 (0.03–0.67)	0.013	0.67 (0.29–1.58)	0.36	4.46 (0.96–20.6)	0.06
Intramuscular/intraspinal	23	0.19	11	0.09	11	0.09	0.48 (0.23–0.98)	0.043	0.47 (0.23–0.96)	0.039	0.99 (0.43–2.28)	0.98
Surgical bleeding	69	0.59	53	0.45	48	0.40	0.76 (0.53–1.09)	0.14	0.68 (0.47–0.99)	0.042	0.90 (0.61–1.32)	0.58
No site reported	37	0.31	39	0.33	48	0.40	1.04 (0.66–1.63)	0.86	1.27 (0.83–1.96)	0.27	1.22 (0.80–1.86)	0.36

n indicates number of patients; RR, relative risk; and CI, confidence interval.

*Gastrointestinal bleeding is reported in Table 2.



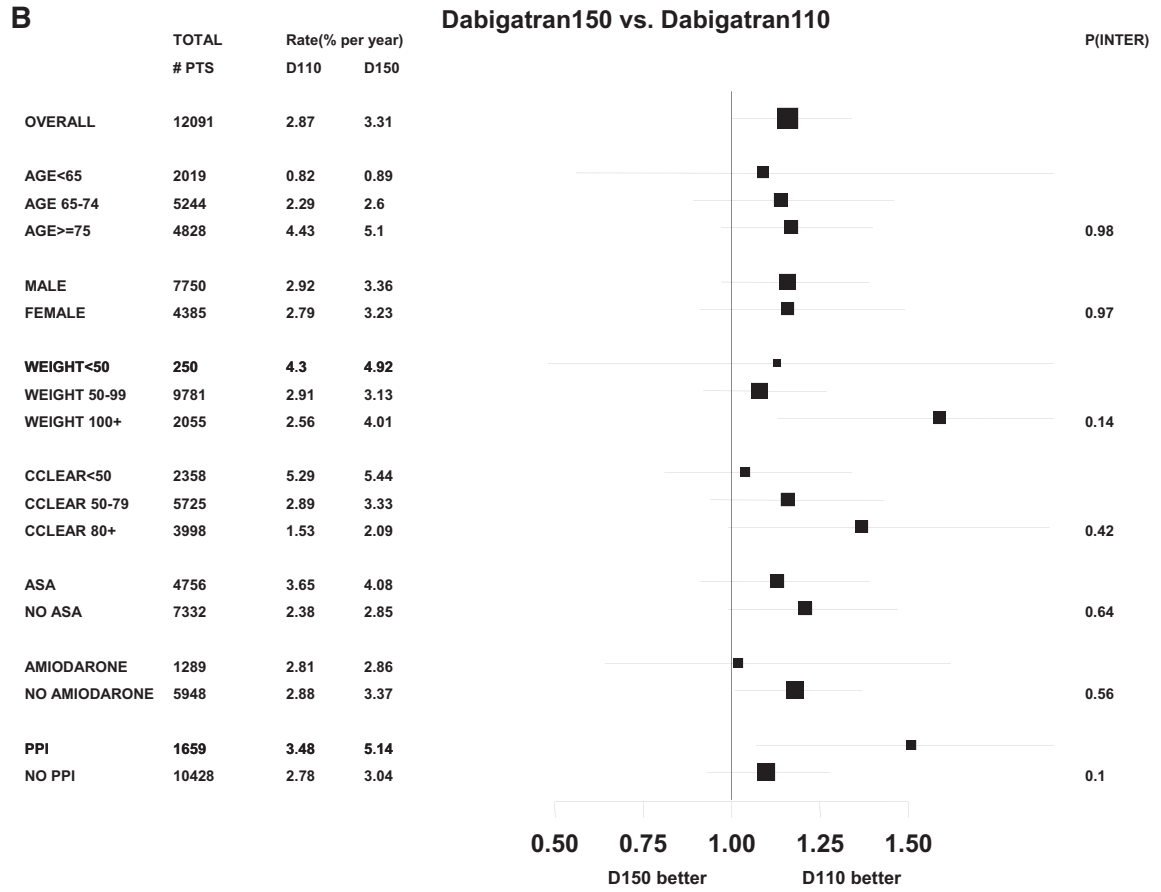


Figure 4. Risk of major bleeding with dabigatran versus warfarin **(A)** and with dabigatran 150 mg twice a day vs dabigatran 110 mg twice a day **(B)** in key subgroups according to baseline characteristics. The squares with horizontal lines are hazard ratios and corresponding 95% confidence intervals; the sizes of the squares are proportional to the sizes of the subgroups. Creatinine clearance was calculated according to the Cockcroft-Gault method. D110 indicates dabigatran 110 mg; D150, dabigatran 150 mg; W, warfarin; PTS, patients; ASA, aspirin; BMI, body mass index; CCLEAR, creatinine clearance; and PPI, proton pump inhibitor.

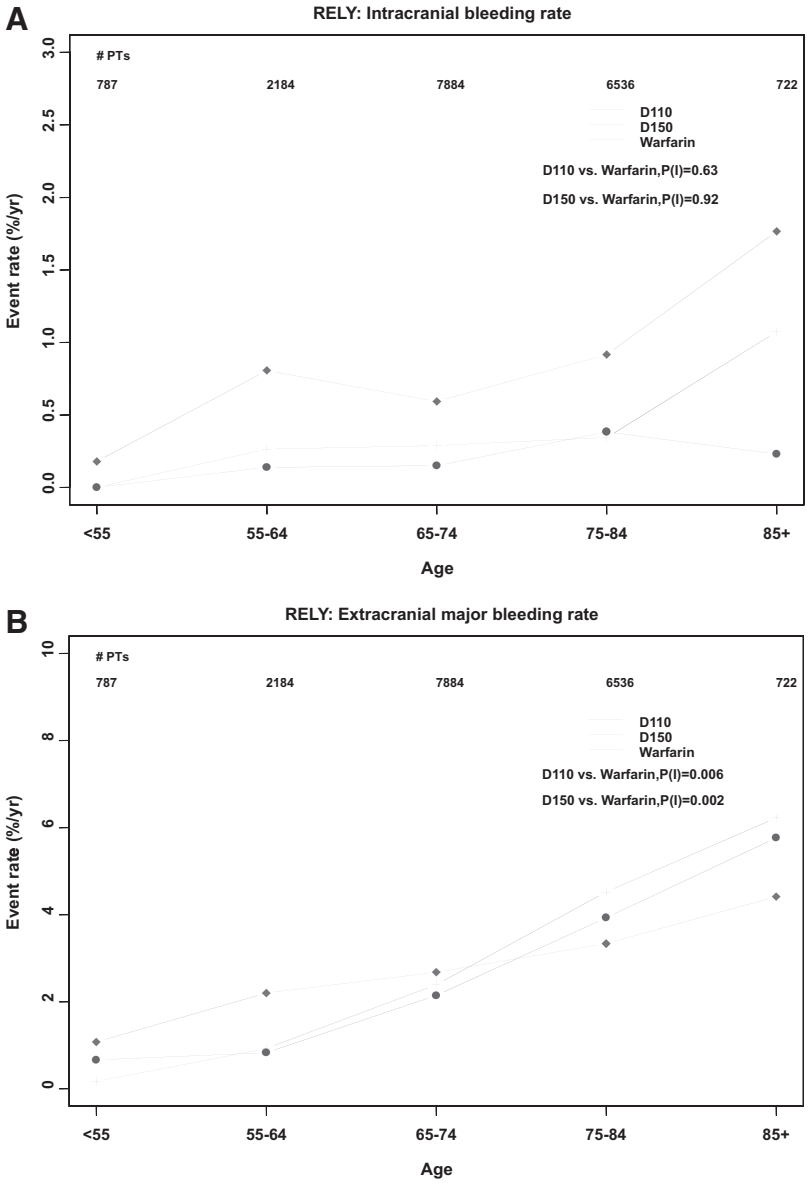


Figure 5. Plots of risks of intracranial **(A)** and extracranial **(B)** bleeding by treatment allocation according to age categories (<55, 55 to 64, 65 to 74, 75 to 84, and ≥85 years). D110 indicates dabigatran 110 mg; D150, dabigatran 150 mg; PTs, patients; and RELY, Randomized Evaluation of Long-Term Anticoagulant Therapy trial.

formation might also explain why warfarin appeared to be more effective than dabigatran in preventing myocardial infarction in the RE-LY trial.

Higher blood concentrations of dabigatran with increasing age might have contributed to the higher risk of extracranial bleeding with dabigatran compared with warfarin in patients aged >75 years, but cannot explain the apparent selectivity of the increase in major gastrointestinal bleeding with dabigatran for the lower gastrointestinal tract. Dabigatran has a low bioavailability after oral ingestion, and it is possible that metabolism of dabigatran etexilate by esterases leads to progressively higher concentrations of the active drug during transit of the gastrointestinal tract. The prevalence of gastrointestinal tract pathology, such as diverticulosis and angiodysplasia, increases with age,[12] and the risk of bleeding from affected areas might be increased by direct exposure to dabigatran. Unlike dabigatran, warfarin has a high bioavailability, and any unabsorbed warfarin cannot cause bleeding because warfarin requires metabolism by hepatic enzymes before it can exert an anticoagulant effect. Thus, local effects of dabigatran on diseased mucosa could account for the relative increase in lower gastrointestinal bleeding seen with dabigatran compared with warfarin in elderly patients in the RE-LY trial.

Patients in the RE-LY trial who were taking concomitant aspirin had a higher risk of bleeding than those not taking aspirin, but there is no convincing evidence from subgroup analyses in the RE-LY trial[1] or from small randomized trials directly comparing the combination of aspirin and an anticoagulant compared with anticoagulant alone[13–15] that the addition of aspirin improves antithrombotic efficacy in patients with AF. Our bleeding data highlight that the combination of aspirin and anticoagulant therapy should be used with caution in these patients.[16]

In conclusion, our analyses of bleeding from the RE-LY trial indicate that both doses of dabigatran compared with warfarin provide substantial safety benefits in patients with AF and at least 1 additional risk factor for stroke. At ages

Table 4. Risks of Major, Intracranial, and Extracranial Bleeding With Dabigatran 110 Twice a Day, Dabigatran 150 mg Twice a Day, and Warfarin in Patients Aged <75 (n=10 855) and ≥75 (n=7258) Years

	Warfarin		Dabigatran 110 mg BID		Dabigatran 150 mg BID		Dabigatran 110 mg BID vs Warfarin (n=12 037)		Dabigatran 150 mg BID vs Warfarin (n=12 098)		Dabigatran 150 mg BID vs Dabigatran 110 mg BID (n=12 091)	
	n	%/y	n	%/y	n	%/y	RR	*P**	RR	*P**	RR	*P**
Stroke/systemic embolism												
Age <75 y	101	1.43	96	1.32	65	0.90	0.93 (0.70–1.22)		0.63 (0.46–0.86)		0.68 (0.50–0.94)	
Age ≥75 y	101	2.14	87	1.89	69	1.43	0.88 (0.66–1.17)	0.81	0.67 (0.49–0.90)	0.81	0.76 (0.55–1.04)	0.65
Major bleeding												
Age <75 y	215	3.04	138	1.89	153	2.12	0.62 (0.50–0.77)		0.70 (0.57–0.86)		1.12 (0.89–1.41)	
Age ≥75 y	206	4.37	204	4.43	246	5.10	1.01 (0.83–1.23)	<0.001	1.18 (0.98–1.42)	<0.001	1.17 (0.97–1.40)	0.80
Intracranial bleeding												
Age <75 y	43	0.61	10	0.14	19	0.26	0.22 (0.11–0.45)		0.43 (0.25–0.74)		1.92 (0.89–4.13)	
Age≥75 y	47	1.00	17	0.37	20	0.41	0.37 (0.21–0.64)	0.28	0.42 (0.25–0.70)	0.91	1.13 (0.59–2.15)	0.29
Extracranial bleeding												
Age <75 y	173	2.44	128	1.76	138	1.91	0.72 (0.57–0.90)		0.78 (0.63–0.98)		1.09 (0.86–1.39)	
Age≥75 y	162	3.44	189	4.10	226	4.68	1.20 (0.97–1.48)	0.001	1.39 (1.13–1.70)	<0.001	1.15 (0.95–1.40)	0.72
Gastrointestinal bleeding												
Age <75 y	73	1.03	61	0.84	88	1.22	0.82 (0.58–1.15)		1.19 (0.87–1.63)		1.46 (1.06–2.03)	
Age≥75 y	75	1.59	101	2.19	135	2.80	1.39 (1.03–1.98)	0.02	1.79 (1.35–2.37)	0.06	1.29 (0.99–1.66)	0.54
Nongastrointestinal extracranial bleeding												
Age <75 y	110	1.55	76	1.04	57	0.79	0.67 (0.50–0.90)		0.51 (0.37–0.70)		0.76 (0.54–1.07)	
Age ≥75 y	92	1.95	92	2.00	109	2.26	1.02 (0.76–1.36)	0.04	1.16 (0.88–1.53)	<0.001	1.14 (0.86–1.50)	0.07

n indicates number of patients; RR, relative risk.
**P* for interaction.

<75 years, the higher dabigatran dose seems preferable because of the lower risk of stroke without any increase risk of bleeding, whereas at higher ages, the lower dabigatran dose might be considered a means to reduce the risk of bleeding in selected patients who are at high risk of bleeding.

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CLINICAL PERSPECTIVE

The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial in patients with atrial fibrillation and at least 1 additional risk factor for stroke demonstrated that dabigatran 110 mg twice a day compared with warfarin was associated with a similar risk of stroke or systemic embolism and a lower risk of major bleeding, and that dabigatran 150 mg twice a day compared with warfarin was associated with a lower risk of stroke or systemic embolism and a similar risk of major bleeding. The effects of dabigatran compared with warfarin on stroke or systemic embolism were consistent in all subgroups examined, but there was a significant treatment-by-age interaction for major bleeding such that dabigatran 110 mg twice a day compared with warfarin was associated with a lower risk of major bleeding in patients aged $<$75 years and a similar risk in those aged $\geq$75 years, whereas dabigatran 150 mg twice a day compared with warfarin was associated with a lower risk of major bleeding in those aged $<$75 years and a trend toward higher risk of major bleeding in those aged $\geq$75 years. The interaction between treatment and age was evident for extracranial bleeding but not for intracranial bleeding, which was consistently reduced with dabigatran compared with warfarin irrespective of age. These results suggest that in patients with atrial fibrillation and at least 1 additional risk factor for stroke who are aged $<$75 years, the higher dabigatran dose might be preferable, whereas in older patients, the lower dabigatran dose might be considered a means to reduce the risk of bleeding.