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Dabigatran Versus Warfarin

Effects on Ischemic and Hemorrhagic Strokes and Bleeding in Asians and Non-Asians With Atrial Fibrillation

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Background and Purpose—Intracranial hemorrhage rates are higher in Asians than non-Asians, especially in patients receiving warfarin. This randomized evaluation of long-term anticoagulation therapy subgroup analysis assessed dabigatran etexilate (DE) and warfarin effects on stroke and bleeding rates in patients from Asian and non-Asian countries.

Methods—There were 2782 patients (15%) from 10 Asian countries and 15 331 patients from 34 non-Asian countries. A Cox regression model, with terms for treatment, region, and their interaction was used.

Results—Rates of stroke or systemic embolism in Asians were 3.06% per year on warfarin, 2.50% per year on DE 110 mg BID (DE 110), and 1.39% per year on DE 150 mg BID (DE 150); in non-Asians, the rates were 1.48%, 1.37%, and 1.06% per year with no significant treatment-by-region interactions. Hemorrhagic stroke on warfarin occurred more often in Asians than non-Asians (hazard ratio [HR], 2.4; 95% confidence interval [CI], 1.3–4.7; P=0.007), with significant reductions for DE compared with warfarin in both Asian (DE 110 versus warfarin HR, 0.15; 95% CI, 0.03–0.66 and DE 150 versus warfarin HR, 0.22; 95% CI, 0.06–0.77) and non-Asian (DE 110 versus warfarin HR, 0.37; 95% CI, 0.19–0.72 and DE 150 versus warfarin HR, 0.28; 95% CI, 0.13–0.58) patients. Major bleeding rates in Asians were significantly lower on DE (both doses) than warfarin (warfarin 3.82% per year, DE 110 2.22% per year, and DE 150 2.17% per year).

Conclusions—Hemorrhagic stroke rates were higher on warfarin in Asians versus non-Asians, despite similar blood pressure, younger age, and lower international normalized ratio values. Hemorrhagic strokes were significantly reduced by DE in both Asians and non-Asians. DE benefits were consistent across Asian and non-Asian subgroups.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00262600. **(*Stroke*. 2013;44:1891-1896.)**

Key Words: Asia ■ atrial fibrillation ■ bleeding ■ dabigatran ■ intracranial hemorrhage ■ RE-LY ■ warfarin

Patients of Asian ethnicity are at greater risk of hemorrhage while receiving vitamin K antagonist therapy.[1] However, a randomized controlled trial comparing the effects and safety of different anticoagulants has not been reported.

Atrial fibrillation (AF) is responsible for 20% to 30% of ischemic stroke[2] and anticoagulation reduces this risk, but this benefit is off-set by increased hemorrhage, including hemorrhagic stroke. Warfarin is recommended for the prevention of stroke in AF in Asian countries but its use is limited by concerns related to the increased risk of hemorrhage. This is reflected in Japanese guidelines for anticoagulation, where the target range of international normalized ratio (INR) control with warfarin in patients aged ≥70 years is 1.6–2.6.[3] New oral anticoagulants have been shown to be effective against stroke with lower rates of hemorrhage; however, there are no reports on the benefits

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and risk of these agents in Asian patients. The randomized evaluation of long-term anticoagulation therapy (RE-LY) compared the use of dabigatran etexilate (DE), at doses of 110 mg BID and 150 mg BID, with warfarin in patients with AF; and included patients from non-Asian and Asian countries.[4,5] Overall in RE-LY, DE 110 mg BID was associated with rates of stroke and systemic embolism (SE) that were similar to those associated with warfarin, as well as lower rate of major bleeding. DE 150 mg BID, as compared with warfarin, was associated with lower rates of stroke and SE but similar rates of major hemorrhage.

In this analysis, we report the effects of DE versus warfarin among Asians and non-Asians on ischemic and hemorrhagic strokes and on bleeding.

Methods

Trial Design and Participants

RE-LY was an international multicenter study, in which 18 113 patients were recruited from 951 centers in 44 countries.[4,5] Two fixed doses (110 or 150 mg BID) of DE administered in a blinded manner were compared with open-label warfarin (target INR of 2.0–3.0) in patients with AF. Patients were not included if they had a severe heart-valve disorder, recent stroke, increased risk of hemorrhage, a creatinine clearance <30 mL/min, liver disease, or pregnancy. The Asian countries included were China, Hong Kong, Japan, South Korea, Taiwan, India, Malaysia, Philippines, Singapore, and Thailand. All remaining countries were considered to be non-Asian.

Outcomes

The primary outcome was the occurrence of stroke or SE. Strokes were classified as ischemic and hemorrhagic. Major bleeding was defined as a reduction in the hemoglobin level of ≥20 g/L, transfusion of ≥2 U of blood, or symptomatic bleeding in a critical area or organ. Life-threatening bleeding was a subcategory of major bleeding that consisted of fatal bleeding, symptomatic intracranial hemorrhage, bleeding with a decrease in the hemoglobin level of ≥50 g/L, or bleeding requiring transfusion of ≥4 U of blood or inotropic agents or necessitating surgery. All other bleeding was considered as minor bleeding, which was reported by investigators. All major bleeds were adjudicated blindly by ≥2 adjudicators. Net clinical benefit was defined as a composite of stroke, SE, pulmonary embolism, myocardial infarction, death, or major bleeding.

Statistical Analyses

The study outcomes were compared between the randomized treatment groups within 2 regions, Asia and non-Asia, separately for DE 110 mg BID versus warfarin, and DE 150 mg BID versus warfarin. A Cox regression model was used to calculate hazard ratios (HRs), confidence intervals (CIs), and *P* values. The model contained terms for treatment, region, and the interaction. Event rates stratified by treatment and region were calculated. As this was a post hoc subgroup analysis, all *P* values should be viewed cautiously. As differences were observed in age between regions, an age-adjusted Cox regression analysis was also performed. The model additionally included the effects of age and the interaction with treatment. All analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC).

Results

Demographic Characteristics of the Study Patients

There were 2782 patients from the 10 Asian countries (15%), and 15 331 patients from the remaining non-Asian countries. The baseline demographic characteristics of the 3 randomized treatment groups were well balanced within Asian and non-Asian subgroups, but there were some differences in the characteristics between Asian and non-Asian patients (Table 1). Asians were on average 4 years younger than non-Asians and had substantially lower body weight (66 versus 86 kg), with a higher rate of previous stroke (24% versus 10%) but less previous myocardial infarction (9% versus 18%). The values of estimated creatinine clearance were lower in Asians than in non-Asians (65.3±22.1 versus 74.2±28.1 mL/min).

Ethnicity of the subjects corresponded with the analysis by region. There were a total of 2875 Asians in the RE-LY trial and 2782 patients in this Asian regional analysis. The stroke or SE and bleeding rates by ethnic origin were similar to the geographic analysis (data not shown).

INR Control for Warfarin Treatment

Time in therapeutic range was lower in Asian patients (mean, 54.5%) than in non-Asian (66.2%), with less time above (10.1% in Asian versus 14.0% in non-Asian) and more time below the therapeutic range (35.4% versus 19.8%; Table 2).

Stroke and Other Efficacy Outcomes

The rates of stroke or SE in Asian patients were 3.06% per year on warfarin, 2.50% per year on DE 110 mg BID, and 1.39% per year on DE 150 mg BID (Figure 1; Table 3). In Asian patients, compared with warfarin, the rate was nonsignificantly lower with DE 110 mg BID (HR, 0.81; 95% CI, 0.54–1.21) and the rate was significantly lower with DE 150 mg BID (HR, 0.45; 95% CI, 0.28–0.72). In non-Asians, the rates of stroke or SE were 1.48% per year on warfarin, 1.37% per year on DE 110 mg BID, and 1.06% per year on DE 150 mg BID (Table 3). For DE 110 mg BID versus warfarin, the rates of stroke or SE were nonsignificantly lower (HR, 0.93; 95% CI, 0.74–1.17); for DE 150 mg BID versus warfarin, the rates were significantly lower (HR, 0.72; 95% CI, 0.56–0.92). However, there was no treatment-by-region interaction for either dose of DE showing consistency of the treatments effects across regions for the RE-LY study primary outcome.

There were no treatment-by-region interactions for either dose of DE on stroke, ischemic stroke, hemorrhagic stroke, myocardial infarction, and death from any cause. However, the absolute rates of stroke were numerically higher in Asians than in non-Asians in all treatment groups (2.39 versus 1.27 for DE 110 mg BID, 1.34 versus 0.96 for DE 150 mg BID, 2.78 versus 1.37 for warfarin; Table 3). Furthermore, rates of ischemic stroke in warfarin groups were doubled in Asians (Asians 2.02% per year versus non-Asians 0.98% per year).

Bleeding

The rates of major bleeding in Asian patients were 3.82% per year on warfarin, 2.22% per year on DE 110 mg BID, and 2.17% per year on DE 150 mg BID (Figure 2; Table 4). The corresponding rates in non-Asian patients were 3.53%, 2.99%, and 3.52% per year. In Asian patients, compared with warfarin, the rate was significantly lower with both DE 110 mg BID (HR, 0.57; 95% CI, 0.38–0.85) and DE 150 mg BID

Table 1. Baseline Demographic Characteristics of Asian and Non-Asian Patients

	Asian (n=2782)		Non-Asian (n=15 331)	
Age, y				
Mean, SD	68.0	9.8	72.1	8.3
<65 (n, %)	746	26.8	2235	14.6
65–74 (n, %)	1273	45.8	6621	43.2
≥75 (n, %)	763	27.4	6475	42.2
Weight, kg				
Mean, SD	66.3	12.8	85.6	19.2
Blood pressure, mm Hg				
Systolic (mean, SD)	129.0	17.5	131.3	17.4
Diastolic (mean, SD)	77.6	10.7	76.9	10.5
Sex				
Men (n, %)	1775	63.8	9739	63.5
Type of atrial fibrillation				
Paroxysmal (n, %)	770	27.7	5173	33.7
Persistent (n, %)	1151	41.4	4638	30.3
Permanent (n, %)	861	30.9	5514	36.0
Creatinine clearance, mL/min				
Mean, SD	65.3	22.1	74.2	28.1
<50 (n,%)	740	26.6	2814	18.4
50–79 (n, %)	1427	51.3	7126	46.5
≥80 (n, %)	606	21.8	5238	34.2
$CHADS_2$ score				
Mean, SD	2.2	1.1	2.1	1.1
0–1 (n, %)	841	30.2	4942	32.2
2 (n, %)	917	33.0	5536	36.1
3–6 (n, %)	1024	36.8	4852	31.6
Previous stroke				
Yes (n, %)	672	24.2	1601	10.4
Previous myocardial infarction				
Yes (n, %)	260	9.3	2745	17.9
Heat failure				
Yes (n, %)	1011	36.3	4782	31.2
Diabetes mellitus				
Yes (n, %)	698	25.1	3523	23.0
Hypertension				
Yes (n, %)	1980	71.2	12 303	80.2
Medication in use at the baseline				
Aspirin (n, %)	1309	47.1	5844	38.1
ARB (n, %)	914	32.9	3422	22.3
ACE-I (n, %)	790	28.4	7333	47.8
β-Blocker (n, %)	1286	46.2	10 112	66.0
Amiodarone (n, %)	394	14.2	1582	10.3
Verapamil (n, %)	130	4.7	941	6.1
Proton pump inhibitor (n, %)	222	8.0	2345	15.3
H_2 blocker (n, %)	155	5.6	603	3.9
Long-term VKA therapy				
Experience (n, %)	1015	36.5	7969	52.0

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and VKA, vitamin K antagonist.

(HR, 0.57; 95% CI, 0.38–0.84). There was a statistically significant interaction (P=0.008) between treatment and region when comparing DE 150 mg BID versus warfarin in Asians with that in non-Asians. As there is a previously reported interaction between age and the effect of dabigatran on major bleeding compared with warfarin,[6] we performed an analysis with adjustment for age. In this analysis, this interaction was somewhat attenuated (P=0.06).

The rate of hemorrhagic stroke in warfarin-treated patients was 0.75% per year in Asian patients, whereas 0.32% per year in non-Asian patients (HR, 2.4; 95% CI, 1.3–4.7; P=0.007), despite the younger age, the greater time below therapeutic range and the comparable baseline systolic and diastolic blood pressure in Asians (Table 3). In DE-treated patients, the rates of hemorrhagic stroke in both subgroups were much lower than for warfarin, ranging from 0.09 to 0.17% (Table 3). Regarding gastrointestinal major bleeding, there was a significant interaction (P=0.009) between treatment and region when comparing DE 150 mg BID versus warfarin (Table 4). This interaction was still present after adjustment for age (P=0.04). Compared with warfarin, both DE 110 mg BID and DE 150 mg BID significantly reduced total bleeding in Asians (DE 110 mg BID versus warfarin HR, 0.48; 95% CI, 0.40–0.56/DE 150 mg BID versus warfarin HR, 0.60; 95% CI, 0.51–0.70). For both DE doses compared with warfarin, there was a highly significant treatment-by-region interaction for total bleeding (P<0.0001 with or without age adjustment).

For warfarin, the rates of all bleeding outcomes (major, gastrointestinal major, life-threatening major, minor, total, intracranial, and hemorrhagic stroke) were numerically higher in Asians than non-Asians, despite comparable blood pressure, younger age, and lower INR values, whereas those on DE tended to be lower in Asians than non-Asians (Tables 3 and 4).

The rates of stroke and SE and major bleeding, and the number of patients in each country in RE-LY are given in an Appendix in the online-only Data Supplement.

Net Clinical Benefit

Net clinical benefit was consistently in favor of DE for both doses compared with warfarin, in both Asians and non-Asians (Table 4). However, only the DE 150 mg BID versus warfarin in Asians was clearly superior (HR, 0.66; 95% CI, 0.52–0.83). The treatment-by-region interaction was significant (P=0.004) for this comparison.

Adverse Events

In both Asians and non-Asians, the most common adverse event on DE was dyspepsia-like symptoms (DE 110 mg BID: Asian 16.1%, non-Asian 12.1%; DE 150 mg BID: Asian 15.9%, non-Asian 11.5%; warfarin: Asian 8.7%, non-Asian; 5.4%).

Table 2. Time Ratios of INR for Warfarin Treatment Groups

	Asian (n=880)			Non-Asian (n=4909)		
INR	<2	2–3	>3	<2	2–3	>3
Mean, %	35.4	54.5	10.1	19.8	66.2	14.0
Median, %	30.8	56.5	8.1	15.4	68.9	11.6

INR indicates international normalized ratio.

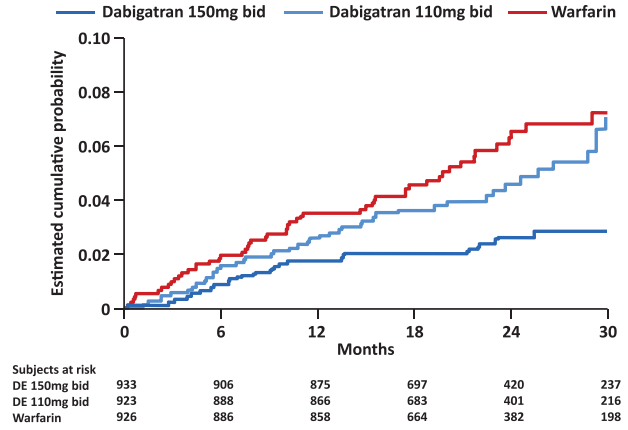

Figure 1. Cumulative hazard rates for the primary outcome of stroke or systemic embolism, according to treatment group in Asian population. DE indicates dabigatran etexilate.

Discussion

The key findings of this analysis of RE-LY are that the effects of dabigatran against stroke and SE are similar in Asian and non-Asian patients for both doses of dabigatran compared with warfarin. The second key finding is that although Asian patients on warfarin had considerably more time below therapeutic range and were younger, there was a trend for more bleeding in Asian than in non-Asian patients. For total bleeding and for hemorrhagic stroke, the rates in Asian patients on warfarin were significantly higher than in non-Asians. Finally, for total bleeding there was a statistically significant interaction between treatment and region (Asian versus non-Asian) indicating that dabigatran reduced the risk of bleeding outcomes more in Asians than in non-Asians.

The rates of all bleeding outcomes (major, gastrointestinal major, life-threatening major, minor, total, intracranial, and hemorrhagic stroke) on warfarin were numerically higher in Asians than non-Asians (Tables 3 and 4). This may be because of the genetic differences in blood coagulation between Asians and non-Asians. Indeed, differences in warfarin sensitivity genotyping were reported between Asians and non-Asian,[7] and no factor V-Leiden mutations were found in Asians.[8] However, these genetic differences may minimally contribute to the ethnic difference in bleeding on warfarin because adjustment of warfarin dose with INR values was commonly performed both in Asians and in non-Asians in this controlled trial. In the present study, bleeding outcomes on warfarin showed a higher rate in Asians compared with non-Asians, despite younger age, warfarin control with more time below therapeutic range, and comparable blood pressures in Asians. This strongly suggests Asian propensity to bleed on warfarin. In particular, a 2.4-fold higher risk of hemorrhagic stroke is consistent with previous reports. A previous report on patients with AF treated with warfarin demonstrated a 4-fold higher HR for intracranial hemorrhage in Asians compared with whites.[1] Furthermore in the recent report of meta-analysis on the incidence of intracerebral hemorrhage, the incidence was ≈2-fold higher in Asians compared with whites.[9] The underlying cause of this higher rate may be associated with Asian sensitivity to warfarin which might be explained by ethnic differences in terms of hemostatic state or vascular properties. Cerebral microbleeds were reported to be more frequent in warfarin users with intracerebral hemorrhage compared with nonantithrombotic users (odds ratio, 2.7), and in pooled follow-up data for warfarin users, presence of microbleeds at baseline was associated with an increased risk of subsequent intracerebral hemorrhage (odds ratio, 3.0).[10] The other report showed higher prevalence of microbleeds in Asian patients with intracerebral hemorrhage compared with those of non-Asians (68.4% versus 56.2%).[11] These reports may suggest

Table 3. Efficacy Outcomes With Dabigatran Versus Warfarin Among Asians and Non-Asians

	Dabigatran 110 mg BID					Dabigatran 150 mg BID					Warfarin	
	Asian (n=923)		Non-Asian (n=5092)			Asian (n=933)		Non-Asian (n=5143)			Asian (n=926)	Non-Asian (n=5096)
	Event Number (%/y)	HR (95% CI)	Event Number (%/y)	HR (95% CI)	Interaction *P* Value	Event Number (%/y)	HR (95% CI)	Event Number (%/y)	HR (95% CI)	Interaction *P* Value	Event Number (%/y)	
Stroke or systemic embolism	44 (2.50)	0.81 (0.54–1.21)	139 (1.37)	0.93 (0.74–1.17)	0.56	25 (1.39)	0.45 (0.28–0.72)	109 (1.06)	0.72 (0.56–0.92)	0.09	53 (3.06)	149 (1.48)
Stroke	42 (2.39)	0.85 (0.56–1.29)	129 (1.27)	0.93 (0.73–1.18)	0.73	24 (1.34)	0.48 (0.29–0.78)	98 (0.96)	0.70 (0.54–0.90)	0.18	48 (2.78)	138 (1.37)
Ischemic stroke	36 (2.05)	1.01 (0.63–1.61)	116 (1.14)	1.17 (0.89–1.53)	0.60	20 (1.12)	0.55 (0.32–0.95)	83 (0.81)	0.82 (0.61–1.10)	0.20	35 (2.02)	99 (0.98)
Hemorrhagic stroke	2 (0.11)	0.15 (0.03–0.66)	12 (0.12)	0.37 (0.19–0.72)	0.27	3 (0.17)	0.22 (0.06–0.77)	9 (0.09)	0.28 (0.13–0.58)	0.76	13 (0.75)	32 (0.32)
MI*	9 (0.51)	0.88 (0.36–2.17)	89 (0.88)	1.36 (0.99–1.87)	0.38	9 (0.50)	0.87 (0.35–2.13)	88 (0.86)	1.33 (0.97–1.83)	0.38	10 (0.58)	65 (0.65)
Death from any cause	88 (5.01)	0.98 (0.73–1.32)	358 (3.53)	0.89 (0.77–1.02)	0.59	72 (4.01)	0.78 (0.57–1.07)	366 (3.57)	0.90 (0.78–1.04)	0.42	88 (5.09)	399 (3.96)

P values for treatment-by-region interaction are calculated using Cox regression model with the terms for treatment, region and treatment-by-region interaction. CI indicates confidence interval; HR, hazard ratio; and MI, myocardial infarction.

*MI includes silent MI.

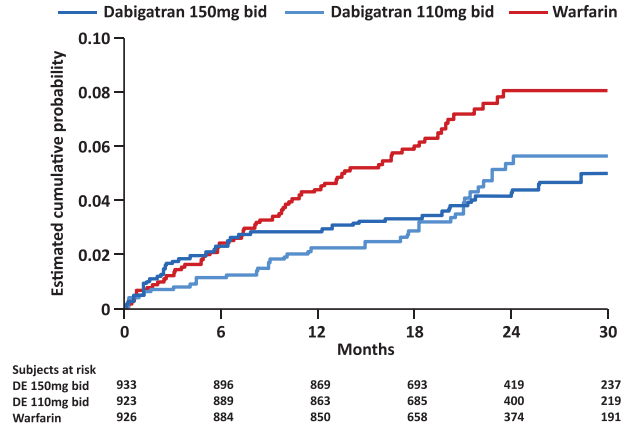

Figure 2. Cumulative hazard rates for major bleeding, according to treatment group in Asian population. DE indicates dabigatran etexilate.

ethnic difference of prevalence of microbleeds and susceptibility to intracranial hemorrhage. Ethnic difference in salt sensitivity to intracranial hemorrhage may also be involved.[12]

The rates of stroke or SE or ischemic stroke in patients on warfarin were ≈2-fold higher in Asians compared with non-Asians. The lower time in therapeutic range in warfarin control in Asians and higher proportion of patients with previous stroke in Asians (Asian 24% versus non-Asian 10%) may contribute to the higher rates of stroke or SE in Asians. A similar finding was also observed in the previous subgroup analysis of the RE-LY trial in which rates of stroke are ≈2-fold higher in patients with previous stroke or transient ischemic attack than those without in all treatment groups.[13] The consistency of the treatment effect of dabigatran against stroke (in comparison to warfarin) observed in this analysis is not surprising. In many different subgroup analyses of RE-LY, there has been no evidence of any subgroup responding differently to dabigatran.[5] The present analysis comparing Asians to non-Asians is in line with the previous findings.

In contrast, we have previously reported that there is an interaction between age and the bleeding effects of both doses of dabigatran compared with warfarin, which indicates that the benefits of dabigatran compared with warfarin seen in younger patients are attenuated significantly in older patients.[6] This age interaction would seem to at least in part explain the results of the present study related to a greater reduction in bleeding with dabigatran compared with warfarin in Asians. In general, Asians were younger than non-Asians in RE-LY and they would, therefore, be expected to have a greater benefit from dabigatran over warfarin. Indeed the highly significant interaction related to dabigatran effect on major bleeding in the unadjusted analysis is somewhat attenuated (P=0.06) when the analysis is adjusted for age. For total bleeding, however, the interaction is highly significant for both dabigatran doses in both adjusted and unadjusted for age (P<0.0001). The large differential in major bleeding also contributes to the significant net clinical benefit of DE 150 mg BID in Asians and the strong treatment-by-region interaction. Poorer INR control on warfarin could also explain a greater benefit from dabigatran in Asian patients as the time in range in Asians was lower than in non-Asians. Undercontrol of INR below therapeutic range may cause greater risk of ischemic stroke, but Nieuwlaat et al[14] have reported that time below range can also predict a greater risk of bleeding possibly reflecting greater variability in INR control.

The present study has some limitations. The number of Asians (2782) is relatively small compared with that of non-Asians (15 331), and the presented results are an exploratory subgroup analysis; all the P values are, therefore, nominal.

Table 4. Risk of Bleeding With Dabigatran Versus Warfarin Among Asians and Non-Asians

	Dabigatran 110 mg BID					Dabigatran 150 mg BID					Warfarin	
	Asian (n=923)		Non-Asian (n=5092)			Asian (n=933)		Non-Asian (n=5143)			Asian (n=926)	Non-Asian (n=5096)
	Event Number (%/y)	HR (95% CI)	Event Number (%/y)	HR (95% CI)	Interaction P Value	Event Number (%/y)	HR (95% CI)	Event Number (%/y)	HR (95% CI)	Interaction P Value	Event Number (%/y)	
Major bleeding	39 (2.22)	0.57 (0.39–0.85)	303 (2.99)	0.85 (0.73–0.99)	0.07	39 (2.17)	0.57 (0.38–0.84)	360 (3.52)	1.00 (0.87–1.16)	0.008	66 (3.82)	355 (3.53)
Gastrointestinal major bleeding	20 (1.15)	0.82 (0.45–1.49)	114 (1.14)	1.13 (0.86–1.47)	0.34	17 (0.96)	0.69 (0.37–1.27)	170 (1.69)	1.67 (1.31- 2.14)	0.009	24 (1.41)	101 (1.01)
Life-threatening major bleeding	16 (0.91)	0.41 (0.23–0.73)	131 (1.29)	0.72 (0.58–0.90)	0.07	23 (1.28)	0.58 (0.34–0.97)	156 (1.52)	0.85 (0.69 -1.06)	0.17	38 (2.20)	180 (1.79)
Minor bleeding	178 (10.12)	0.47 (0.39–0.56)	1388 (13.69)	0.86 (0.80–0.92)	<0.0001	223 (12.43)	0.60 (0.51–0.71)	1564 (15.27)	0.98 (0.92–1.05)	<0.0001	340 (19.66)	1591 (15.81)
Total bleeding	206 (11.72)	0.48 (0.40–0.56)	1549 (15.27)	0.85 (0.79–0.91)	<0.0001	251 (13.99)	0.60 (0.51–0.70)	1743 (17.02)	0.98 (0.91–1.04)	<0.0001	381 (22.03)	1785 (17.74)
Intracranial hemorrhage	4 (0.23)	0.20 (0.07–0.60)	23 (0.23)	0.32 (0.20–0.51)	0.46	8 (0.45)	0.40 (0.18–0.92)	30 (0.29)	0.41 (0.27- 0.63)	0.95	19 (1.10)	71 (0.71)
Net clinical benefit	147 (8.36)	0.85 (0.68–1.06)	726 (7.16)	0.94 (0.85–1.04)	0.39	116 (6.47)	0.66 (0.52–0.83)	739 (7.22)	0.95 (0.86–1.05)	0.004	167 (9.65)	766 (7.61)

P values for treatment-by-region interaction are calculated by using Cox regression model with the terms for treatment, region and treatment-by-region interaction. Major and intracranial hemorrhages are adjudicated. The net clinical benefit outcome is the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction including silent myocardial infarction, death, or major bleeding. CI indicates confidence interval; and HR, hazard ratio.

Moreover, patient demographics in Asians and non-Asians were not comparable; INR control is poorer and age is younger in Asians than in non-Asians. There was also a higher frequency of previous stroke, a lower frequency of myocardial infarction, and less frequent previous exposure to vitamin K antagonist therapy in Asians, similar to what was seen in the subanalysis of Japanese patients in RE-LY.[15] Patients' ethnicity and lifestyle, including dietary differences, are heterogeneous in both Asians and non-Asians. It should also be noted that minor bleeding, a component of total bleeding, is not adjudicated. However, rates of bleeding outcomes on warfarin, including hemorrhagic stroke, were higher in Asians than in non-Asians, and the rates are compatible with previous epidemiological studies.[1,9] In contrast, the efficacy and safety in DE arms were comparable between Asians and non-Asians.

In summary, the present study shows consistency of efficacy profiles of DE in both Asians and non-Asians. The safety profile of DE was also confirmed in Asians and overall. The rates of all bleeding outcomes, including hemorrhagic stroke on warfarin, were higher in Asians than in non-Asians.

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Disclosures

Dr. M. Hori has received consultancy fees from Boehringer Ingelheim, Bayer, Bristol Myers-Squibb and Pfizer. Dr. M. Watanabe and Mr. M. Koyanagi are employees of Nippon Boehringer Ingelheim. Dr. P.A. Reilly is an employee of Boehringer Ingelheim. The other authors have no conflicts to report.

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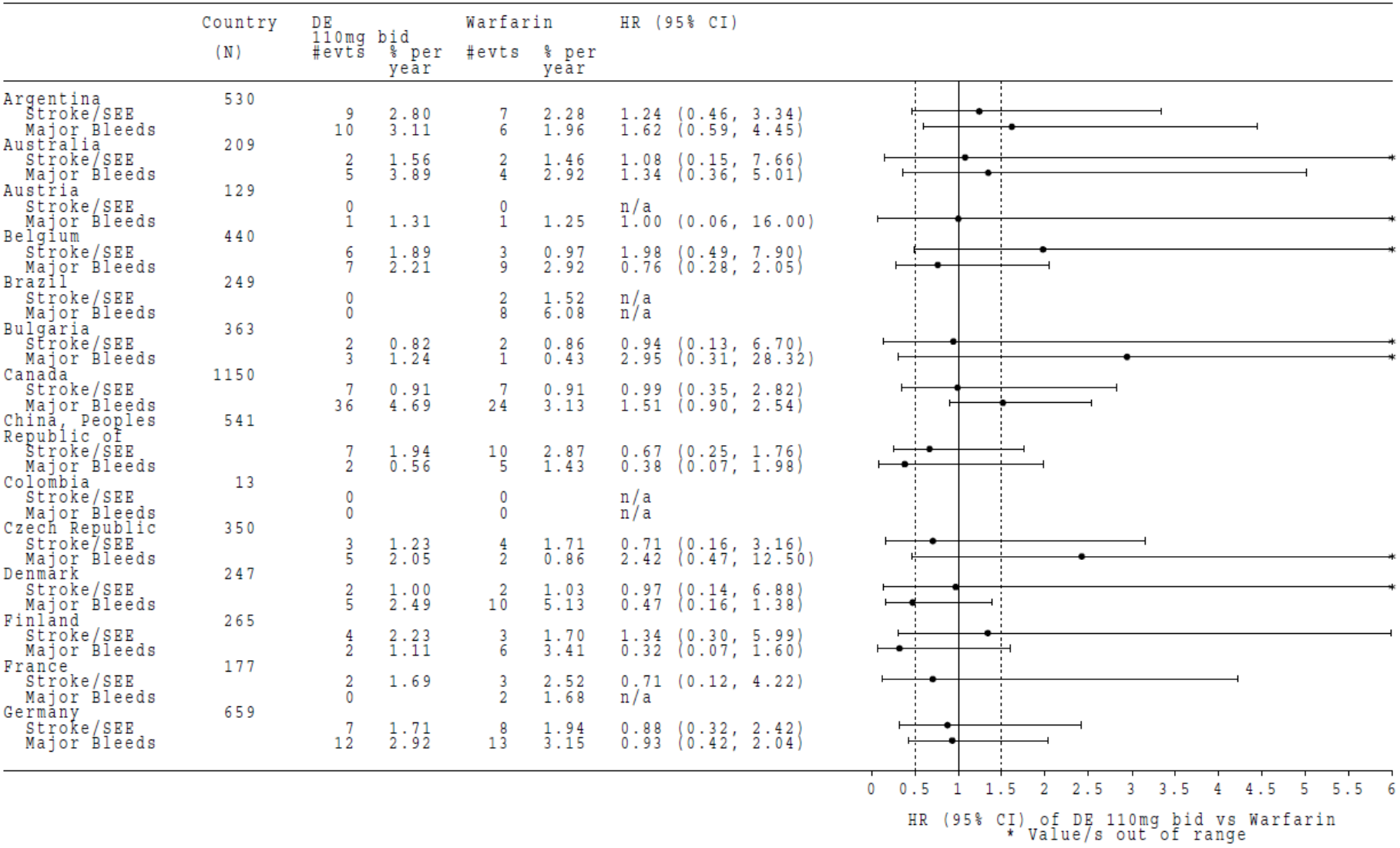
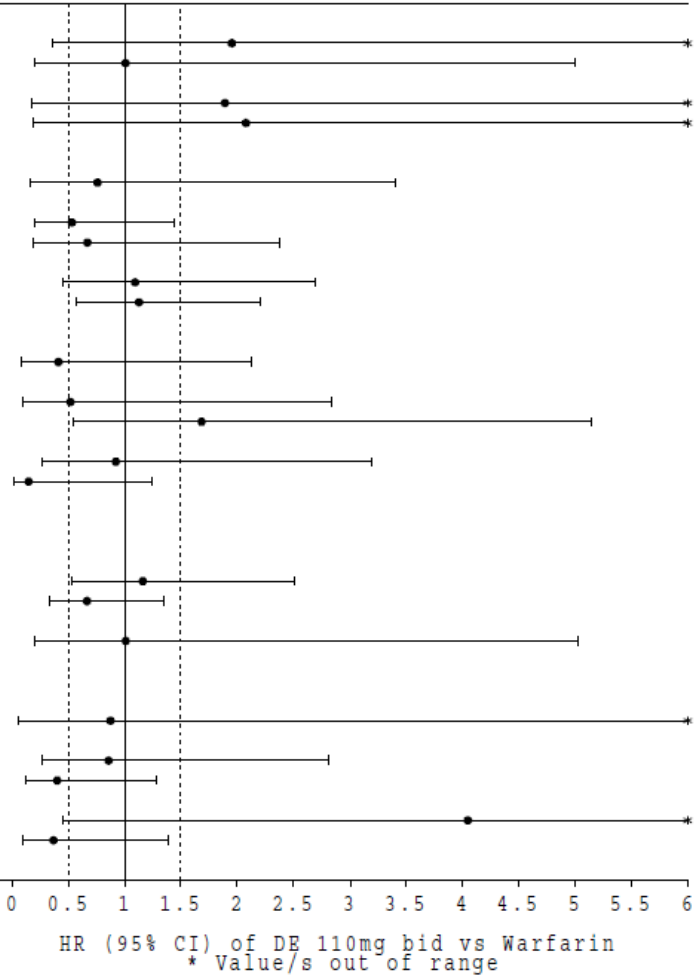
Supplementary Figure 1. The rates of stroke/systemic embolism and major bleeding in each country in RE-LY.



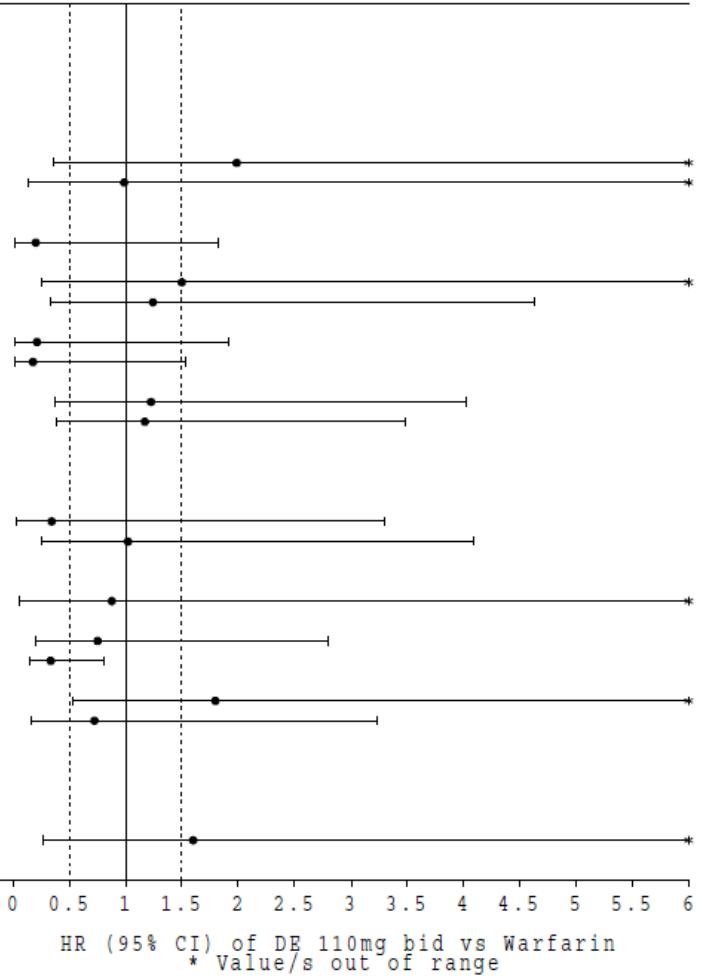
Supplementary Figure 1. The rates of stroke/systemic embolism and major bleeding in each country in RE-LY.

Country (N)	DE 110mg bid #evts	DE 110mg bid % per year	Warfarin #evts	Warfarin % per year	HR (95% CI)
Greece 249					
Stroke/SEE	4	2.54	2	1.30	1.95 (0.36, 10.67)
Major Bleeds	3	1.90	3	1.95	1.01 (0.20, 5.00)
Hong Kong 90					
Stroke/SEE	2	3.17	1	1.58	1.89 (0.17, 20.86)
Major Bleeds	2	3.17	1	1.58	2.08 (0.19, 22.91)
Hungary 172					
Stroke/SEE	0		1	0.90	n/a
Major Bleeds	3	2.67	4	3.59	0.76 (0.17, 3.40)
India 578					
Stroke/SEE	6	1.81	11	3.37	0.53 (0.20, 1.44)
Major Bleeds	4	1.21	6	1.84	0.67 (0.19, 2.37)
Israel 689					
Stroke/SEE	10	2.33	9	2.12	1.09 (0.44, 2.69)
Major Bleeds	18	4.20	16	3.76	1.13 (0.58, 2.21)
Italy 237					
Stroke/SEE	0		2	1.34	n/a
Major Bleeds	2	1.40	5	3.34	0.41 (0.08, 2.13)
Japan 326					
Stroke/SEE	2	1.38	4	2.65	0.52 (0.10, 2.84)
Major Bleeds	8	5.53	5	3.31	1.68 (0.55, 5.15)
Malaysia 185					
Stroke/SEE	5	4.09	5	4.24	0.92 (0.27, 3.19)
Major Bleeds	1	0.82	6	5.09	0.15 (0.02, 1.24)
Mexico 84					
Stroke/SEE	0		0		n/a
Major Bleeds	0		2	3.86	n/a
Netherlands 1266					
Stroke/SEE	14	1.62	12	1.41	1.16 (0.54, 2.51)
Major Bleeds	13	1.51	19	2.23	0.67 (0.33, 1.35)
Norway 115					
Stroke/SEE	3	3.38	3	3.28	1.01 (0.20, 5.02)
Major Bleeds	0		4	4.37	n/a
Peru 80					
Stroke/SEE	1	2.38	0		n/a
Major Bleeds	1	2.38	1	2.67	0.87 (0.05, 13.99)
Philippines 157					
Stroke/SEE	5	5.15	6	6.15	0.86 (0.26, 2.81)
Major Bleeds	4	4.12	10	10.24	0.40 (0.13, 1.28)
Poland 485					
Stroke/SEE	4	1.27	1	0.32	4.05 (0.45, 36.22)
Major Bleeds	3	0.95	8	2.56	0.37 (0.10, 1.39)

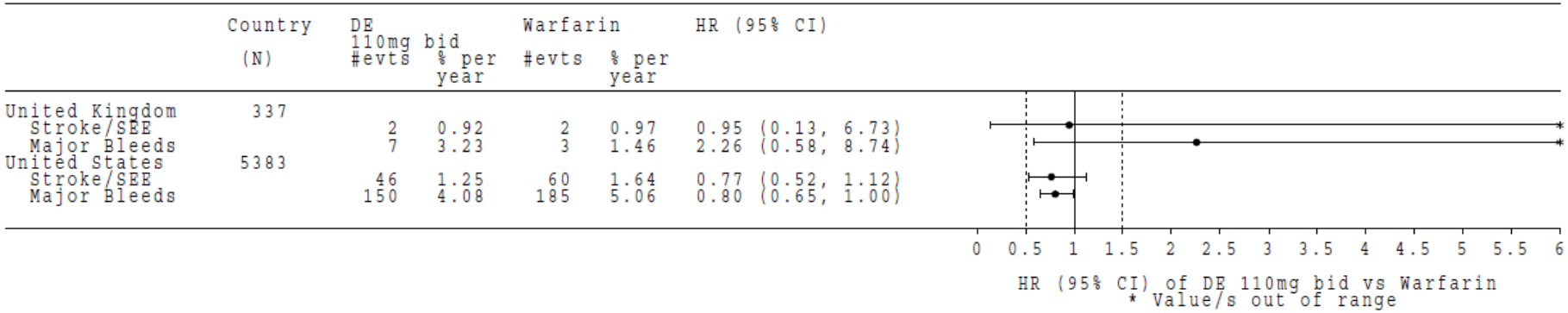


Supplementary Figure 1. The rates of stroke/systemic embolism and major bleeding in each country in RE-LY.

Country (N)	DE 110mg bid #evts	DE 110mg bid % per year	Warfarin #evts	Warfarin % per year	HR (95% CI)
Portugal 117					
Stroke/SEE	0		2	3.47	n/a
Major Bleeds	0		0		n/a
Romania 44					
Stroke/SEE	0		1	5.01	n/a
Major Bleeds	0		0		n/a
Russia 300					
Stroke/SEE	4	2.12	2	1.08	1.99 (0.36, 10.85)
Major Bleeds	2	1.06	2	1.08	0.99 (0.14, 7.02)
Singapore 59					
Stroke/SEE	0		2	5.42	n/a
Major Bleeds	1	2.50	4	10.85	0.20 (0.02, 1.82)
Slovakia 156					
Stroke/SEE	3	2.60	2	1.78	1.50 (0.25, 8.98)
Major Bleeds	5	4.34	4	3.55	1.24 (0.33, 4.63)
South Africa 174					
Stroke/SEE	1	0.91	4	4.09	0.21 (0.02, 1.91)
Major Bleeds	1	0.91	5	5.11	0.18 (0.02, 1.53)
South Korea 336					
Stroke/SEE	6	2.57	5	2.13	1.23 (0.37, 4.02)
Major Bleeds	7	3.00	6	2.56	1.17 (0.39, 3.48)
Spain 107					
Stroke/SEE	0		0		n/a
Major Bleeds	1	1.62	0		n/a
Sweden 277					
Stroke/SEE	1	0.52	3	1.51	0.34 (0.04, 3.30)
Major Bleeds	4	2.09	4	2.02	1.02 (0.26, 4.09)
Switzerland 29					
Stroke/SEE	0		0		n/a
Major Bleeds	1	5.35	1	6.14	0.88 (0.05, 14.04)
Taiwan 355					
Stroke/SEE	4	1.48	5	1.94	0.75 (0.20, 2.80)
Major Bleeds	7	2.59	19	7.38	0.34 (0.14, 0.80)
Thailand 155					
Stroke/SEE	7	7.27	4	4.14	1.80 (0.53, 6.14)
Major Bleeds	3	3.11	4	4.14	0.72 (0.16, 3.24)
Turkey 21					
Stroke/SEE	1	7.39	0		n/a
Major Bleeds	0		1	6.47	n/a
Ukraine 228					
Stroke/SEE	1	0.78	0		n/a
Major Bleeds	3	2.33	2	1.53	1.60 (0.27, 9.58)

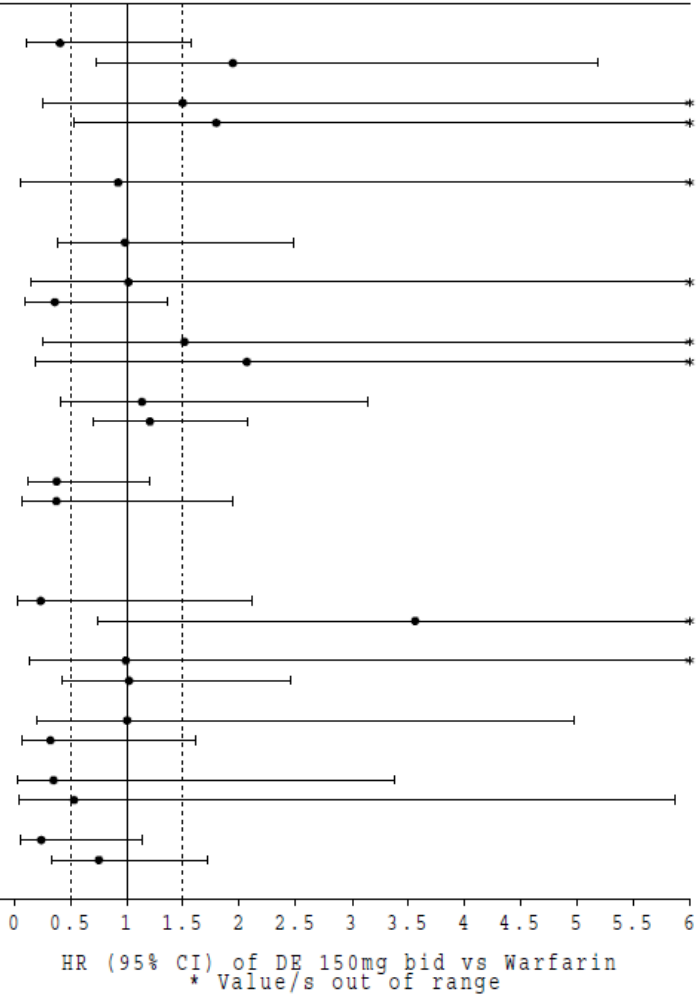


Supplementary Figure 1. The rates of stroke/systemic embolism and major bleeding in each country in RE-LY.



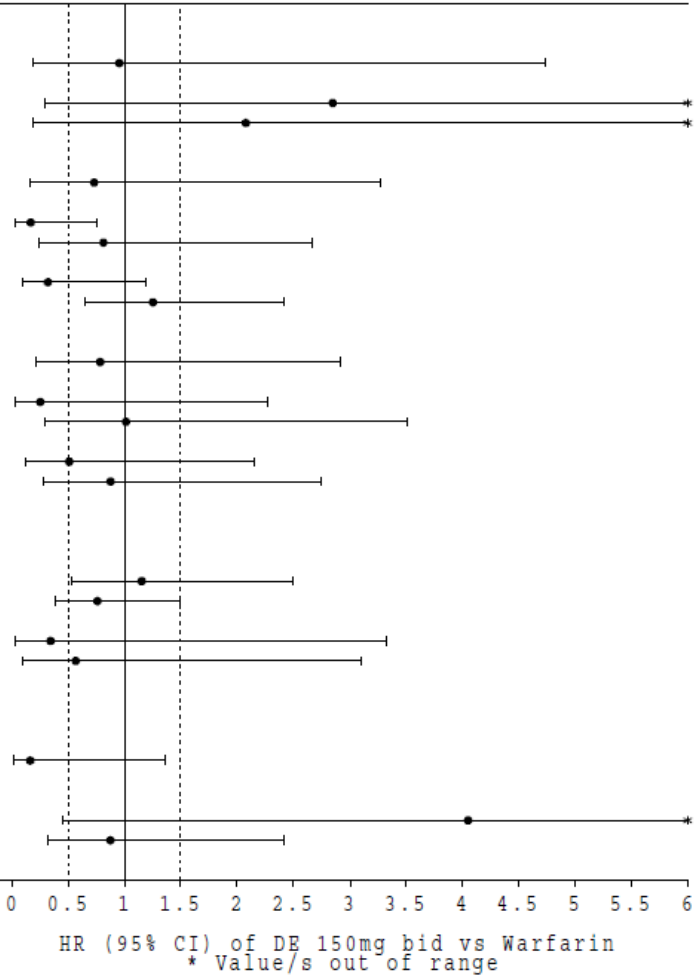
Supplementary Figure 1. The rates of stroke/systemic embolism and major bleeding in each country in RE-LY.

Country (N)	DE 150mg bid #evts	DE 150mg bid % per year	Warfarin #evts	Warfarin % per year	HR (95% CI)
Argentina 530					
Stroke/SEE	3	0.92	7	2.28	0.41 (0.11, 1.58)
Major Bleeds	12	3.69	6	1.96	1.94 (0.73, 5.18)
Australia 209					
Stroke/SEE	3	2.22	2	1.46	1.50 (0.25, 8.97)
Major Bleeds	7	5.19	4	2.92	1.80 (0.53, 6.14)
Austria 129					
Stroke/SEE	2	2.48	0		n/a
Major Bleeds	1	1.24	1	1.25	0.92 (0.06, 14.77)
Belgium 440					
Stroke/SEE	0		3	0.97	n/a
Major Bleeds	9	2.88	9	2.92	0.99 (0.39, 2.48)
Brazil 249					
Stroke/SEE	2	1.50	2	1.52	1.02 (0.14, 7.22)
Major Bleeds	3	2.25	8	6.08	0.36 (0.10, 1.37)
Bulgaria 363					
Stroke/SEE	3	1.31	2	0.86	1.51 (0.25, 9.06)
Major Bleeds	2	0.88	1	0.43	2.07 (0.19, 22.81)
Canada 1150					
Stroke/SEE	8	1.04	7	0.91	1.14 (0.41, 3.13)
Major Bleeds	29	3.76	24	3.13	1.21 (0.70, 2.07)
China, Peoples Republic of 541					
Stroke/SEE	4	1.10	10	2.87	0.38 (0.12, 1.21)
Major Bleeds	2	0.55	5	1.43	0.38 (0.07, 1.94)
Colombia 13					
Stroke/SEE	0		0		n/a
Major Bleeds	0		0		n/a
Czech Republic 350					
Stroke/SEE	1	0.42	4	1.71	0.24 (0.03, 2.11)
Major Bleeds	7	2.95	2	0.86	3.56 (0.74, 17.15)
Denmark 247					
Stroke/SEE	2	1.02	2	1.03	0.99 (0.14, 7.05)
Major Bleeds	10	5.09	10	5.13	1.02 (0.42, 2.45)
Finland 265					
Stroke/SEE	3	1.67	3	1.70	1.00 (0.20, 4.98)
Major Bleeds	2	1.12	6	3.41	0.32 (0.07, 1.61)
France 177					
Stroke/SEE	1	0.88	3	2.52	0.35 (0.04, 3.38)
Major Bleeds	1	0.88	2	1.68	0.53 (0.05, 5.87)
Germany 659					
Stroke/SEE	2	0.47	8	1.94	0.24 (0.05, 1.14)
Major Bleeds	10	2.36	13	3.15	0.75 (0.33, 1.72)



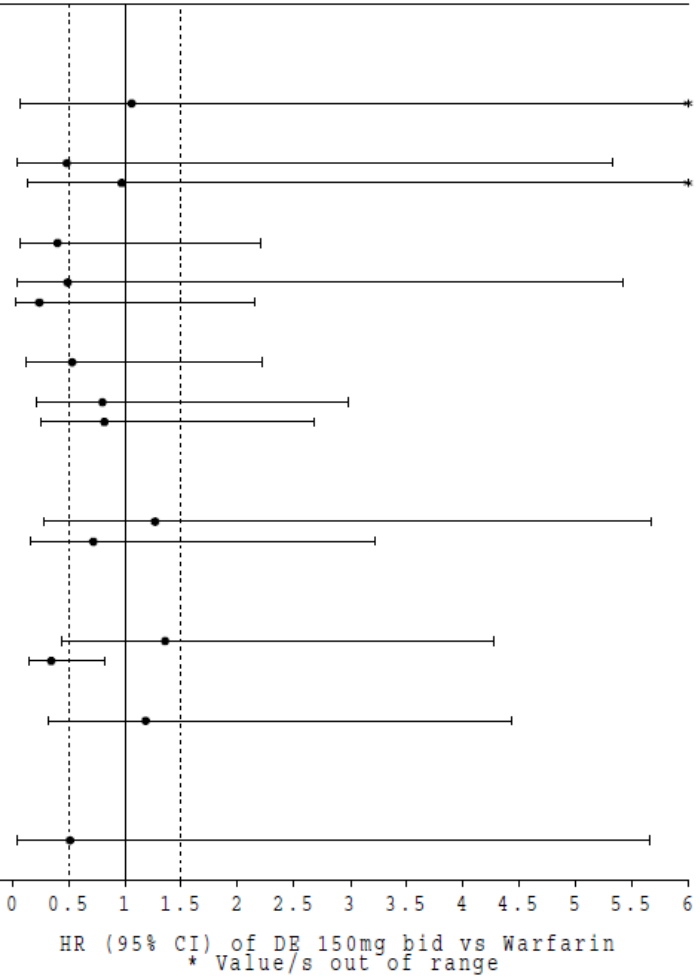
Supplementary Figure 1. The rates of stroke/systemic embolism and major bleeding in each country in RE-LY.

Country (N)	DE 150mg bid #evts	DE 150mg bid % per year	Warfarin #evts	Warfarin % per year	HR (95% CI)
Greece 249					
Stroke/SEE	0		2	1.30	n/a
Major Bleeds	3	1.79	3	1.95	0.96 (0.19, 4.74)
Hong Kong 90					
Stroke/SEE	3	4.91	1	1.58	2.85 (0.30, 27.39)
Major Bleeds	2	3.27	1	1.58	2.08 (0.19, 22.92)
Hungary 172					
Stroke/SEE	0		1	0.90	n/a
Major Bleeds	3	2.72	4	3.59	0.73 (0.16, 3.27)
India 578					
Stroke/SEE	2	0.58	11	3.37	0.17 (0.04, 0.76)
Major Bleeds	5	1.44	6	1.84	0.81 (0.25, 2.67)
Israel 689					
Stroke/SEE	3	0.70	9	2.12	0.32 (0.09, 1.19)
Major Bleeds	20	4.64	16	3.76	1.25 (0.65, 2.42)
Italy 237					
Stroke/SEE	0		2	1.34	n/a
Major Bleeds	4	2.61	5	3.34	0.78 (0.21, 2.92)
Japan 326					
Stroke/SEE	1	0.67	4	2.65	0.25 (0.03, 2.27)
Major Bleeds	5	3.33	5	3.31	1.02 (0.29, 3.51)
Malaysia 185					
Stroke/SEE	3	2.32	5	4.24	0.51 (0.12, 2.15)
Major Bleeds	6	4.64	6	5.09	0.88 (0.28, 2.74)
Mexico 84					
Stroke/SEE	0		0		n/a
Major Bleeds	0		2	3.86	n/a
Netherlands 1266					
Stroke/SEE	14	1.61	12	1.41	1.16 (0.53, 2.50)
Major Bleeds	15	1.73	19	2.23	0.76 (0.39, 1.50)
Norway 115					
Stroke/SEE	1	1.17	3	3.28	0.35 (0.04, 3.33)
Major Bleeds	2	2.35	4	4.37	0.57 (0.10, 3.10)
Peru 80					
Stroke/SEE	0		0		n/a
Major Bleeds	0		1	2.67	n/a
Philippines 157					
Stroke/SEE	1	1.01	6	6.15	0.16 (0.02, 1.37)
Major Bleeds	0		10	10.24	n/a
Poland 485					
Stroke/SEE	4	1.29	1	0.32	4.05 (0.45, 36.25)
Major Bleeds	7	2.26	8	2.56	0.88 (0.32, 2.42)



Supplementary Figure 1. The rates of stroke/systemic embolism and major bleeding in each country in RE-LY.

Country (N)	DE 150mg bid #evts	DE 150mg bid % per year	Warfarin #evts	Warfarin % per year	HR (95% CI)
Portugal 117					
Stroke/SEE	0		2	3.47	n/a
Major Bleeds	0		0		n/a
Romania 44					
Stroke/SEE	1	4.79	1	5.01	1.06 (0.07, 17.05)
Major Bleeds	2	9.58	0		n/a
Russia 300					
Stroke/SEE	1	0.52	2	1.08	0.48 (0.04, 5.34)
Major Bleeds	2	1.04	2	1.08	0.97 (0.14, 6.90)
Singapore 59					
Stroke/SEE	0		2	5.42	n/a
Major Bleeds	2	4.83	4	10.85	0.40 (0.07, 2.21)
Slovakia 156					
Stroke/SEE	1	0.87	2	1.78	0.49 (0.04, 5.42)
Major Bleeds	1	0.87	4	3.55	0.24 (0.03, 2.15)
South Africa 174					
Stroke/SEE	0		4	4.09	n/a
Major Bleeds	3	2.66	5	5.11	0.53 (0.13, 2.22)
South Korea 336					
Stroke/SEE	4	1.71	5	2.13	0.80 (0.22, 2.99)
Major Bleeds	5	2.14	6	2.56	0.82 (0.25, 2.68)
Spain 107					
Stroke/SEE	1	1.46	0		n/a
Major Bleeds	1	1.46	0		n/a
Sweden 277					
Stroke/SEE	4	1.93	3	1.51	1.27 (0.28, 5.67)
Major Bleeds	3	1.45	4	2.02	0.72 (0.16, 3.22)
Switzerland 29					
Stroke/SEE	0		0		n/a
Major Bleeds	0		1	6.14	n/a
Taiwan 355					
Stroke/SEE	7	2.63	5	1.94	1.36 (0.43, 4.28)
Major Bleeds	7	2.63	19	7.38	0.35 (0.15, 0.83)
Thailand 155					
Stroke/SEE	0		4	4.14	n/a
Major Bleeds	5	4.93	4	4.14	1.18 (0.32, 4.43)
Turkey 21					
Stroke/SEE	0		0		n/a
Major Bleeds	0		1	6.47	n/a
Ukraine 228					
Stroke/SEE	2	1.51	0		n/a
Major Bleeds	1	0.76	2	1.53	0.51 (0.05, 5.65)



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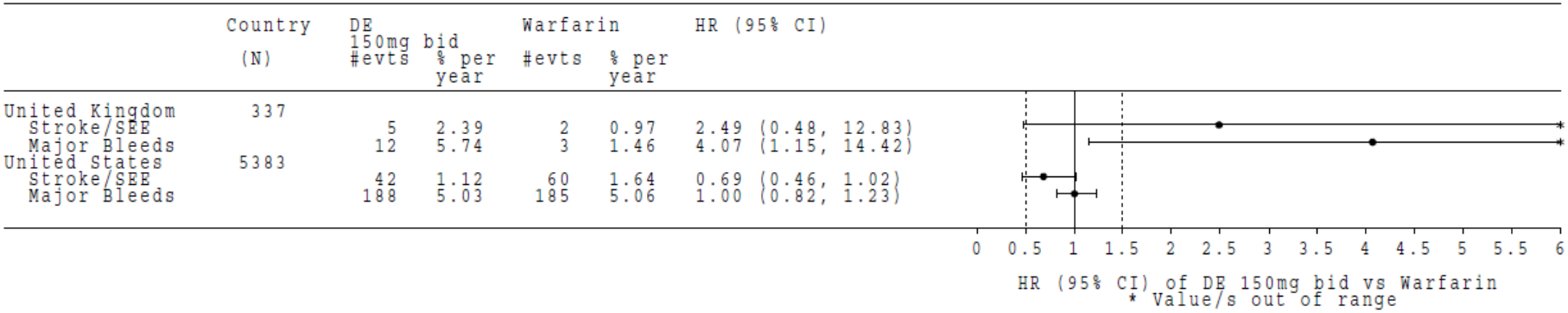

List of Asian Investigators

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