Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 10, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.05.042

Balancing the Benefits and Risks of 2 Doses of Dabigatran Compared With Warfarin in Atrial Fibrillation

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Objectives This study sought to compare the net clinical benefit of dabigatran 110 mg bid and 150 mg bid with that of warfarin in patients with atrial fibrillation (AF).

Background In patients with AF, dabigatran 110 mg bid and 150 mg bid are associated with similar rates of death. However, the higher dose reduces ischemic stroke and increases bleeding compared with the lower dose. Therefore, there is uncertainty about how to evaluate the overall benefit of the 2 doses.

Methods In 18,113 AF patients in the RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy) trial, we used a previously developed method for integrating ischemic and bleeding events as "ischemic stroke equivalents" in order to compare a weighted benefit of 2 doses of dabigatran with each other, and with that of warfarin.

Results Compared with warfarin, there was a significant decrease in ischemic stroke equivalents with both dabigatran doses: −0.92 per 100 patient years (95% confidence interval [CI]: −1.74 to −0.21, p = 0.02) with dabigatran 110 mg bid and −1.08 (95% CI: −1.86 to −0.34, p = 0.01) with dabigatran 150 mg bid. There was no significant difference in ischemic stroke equivalents between the 2 doses: −0.16 (95% CI: −0.80 to 0.43) comparing dabigatran 150 mg bid with 110 bid. When including death in the weighted benefit calculations, the results were similar.

Conclusions On a group level both doses of dabigatran as compared with warfarin have similar benefits when considering a weighted estimate including both efficacy and safety. The similar overall benefits of the 2 doses of dabigatran versus warfarin support individualizing the dose based on patient characteristics and physician and patient preferences. (Randomized Evaluation of Long Term Anticoagulant Therapy [RE-LY] With Dabigatran Etexilate; NCT00262600) (J Am Coll Cardiol 2013;62:900–8) © 2013 by the American College of Cardiology Foundation

The RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy) trial demonstrated the superiority of dabigatran 150 mg bid and the noninferiority of 110 mg bid compared with warfarin for prevention of stroke or systemic embolism. Both doses of dabigatran significantly reduced hemorrhagic stroke (1,2). The higher dose of dabigatran reduced ischemic stroke and cardiovascular mortality, whereas the lower dose caused less major bleeding. There was no significant difference in cardiovascular and all-cause mortality between the 2 doses of dabigatran.

In the absence of a significant difference between the 2 dabigatran doses on mortality, how to compare the integrated effects of the 2 doses of dabigatran on all events is not clear. One approach is to examine the effects of the 2 doses in patient subgroups. For example, the effects of dabigatran on the primary outcome of stroke or systemic embolism were consistent across subgroups, but the higher dose of dabigatran was associated with a higher rate of extracranial bleeding in the elderly (3). Balanced against this, however,

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Manuscript received January 10, 2013; revised manuscript received May 13, 2013, accepted May 21, 2013.

older patients have a significantly higher risk of stroke than younger patients, indicating a larger absolute benefit of the higher dose for prevention of ischemic stroke in older patients.

The different effects of the 2 doses of dabigatran on stroke and bleeding have led to conflicting recommendations by regulators. The European Medicines Agency, Health Canada, and the Australian Therapeutic Goods Administration approved both doses of dabigatran and recommended the lower dose for elderly patients. The U.S. Food and Drug Administration (FDA) approved the 150 mg bid dose but not 110 mg bid, based on their assessment that "nonfatal and extracranial bleeding episodes are clearly less clinically significant than strokes for most patients" and that they were "unable to find any population for whom the availability of a lower dose would improve dabigatran's benefit–risk profile" (4). The U.S. FDA also approved the 75 mg bid dose for the treatment of patients with estimated glomerular filtration rate 15 to 29 ml/min, although this was based on pharmacokinetic modeling as the 75 mg dose was not tested in the RE-LY trial. The apparent disparity in the decisions of these public agencies has caused considerable uncertainly for clinicians and further highlights the need for methods to integrate the anti-ischemic and hemorrhagic effects of antithrombotic therapy by means of a validated measure of net clinical benefit.

Currently no concept of assessing net clinical benefit has been generally accepted. Simply adding up the number of deaths, ischemic strokes, hemorrhagic strokes, myocardial infarctions and major bleeding events could yield misleading results because the relative importance of thrombotic and bleeding events for patients (in terms of mortality, disability, and costs) is not equivalent. A more useful approach to assess the net clinical benefit of dabigatran and warfarin might be to integrate the overall effects of the drugs including all important clinical events with weighting of events according to their measured clinical importance.

In this report we explore whether the use of a weighted net benefit assessment, first reported in the ACTIVE (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) trial (5) and further developed here, could improve our understanding of the net benefit of each dose of dabigatran and warfarin in the RE-LY trial.

Methods

The RE-LY trial. The RE-LY trial design has been previously published (6). Briefly, the primary study objective was to establish the non-inferiority of each 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 bid, dabigatran 150 mg bid, or dose-adjusted warfarin (target international normalized ratio 2.0 to 3.0) for a median of 2 years. The main efficacy outcome was stroke or systemic embolism and the main safety outcome was major bleeding. Major efficacy and safety outcomes were defined using objective criteria, as previously described in the RE-LY methods paper (6).

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
CNS = central nervous system
FDA = Food and Drug Administration
MI = myocardial infarction
TIA = transient ischemic attack

Weighting of events according to their impact on death. We generated weights for each outcome (ischemic stroke, non–central nervous system [CNS] systemic embolism, hemorrhagic stroke, subdural bleeding, major extracranial bleeding [major bleeding excluding extracranial bleeding], and myocardial infarction [MI]) in the RE-LY trial database using the methods previously published (5). For the first occurrence of each ischemic and bleeding event, the hazard ratio for death after the event was estimated using a Cox regression model adjusted for all important baseline predictors of death, and including the outcome as a time-dependent covariate. Both unadjusted and adjusted models were explored but yielded similar results and we therefore present only adjusted analyses. Pre-specified variables included in the adjusted models were age, sex, history of stroke or transient ischemic attack (TIA), hypertension, heart failure, diabetes, and MI or coronary artery disease. Randomized treatment was included as a stratification variable. Weights for each event represent the ratio of the adjusted hazard ratios for that event, using the hazard ratio for ischemic stroke as a reference.

We combined the data from the ACTIVE and RE-LY trials in order to increase the number of each type of event and thereby to obtain the most precise estimates of the relative prognostic impact (i.e., weights) of different events. We first assessed whether the weights that we previously computed from patients with AF receiving antiplatelet therapy (in ACTIVE-warfarin [7] and ACTIVE-aspirin [8]) differed from those computed from patients receiving anticoagulant therapy (in RE-LY [1,2] and ACTIVE-warfarin [7]). Having shown that the weights calculated in these 2 patient populations were not statistically different, we then calculated the impact of each type of event on mortality using the combined data from the ACTIVE and RE-LY trial databases.

Calculation of net clinical benefit. We first calculated the crude incidence rate (IR) per 100 patient years for the first occurrence of each outcome for patients receiving dabigatran 110 mg bid, dabigatran 150 mg bid, and warfarin. Net clinical benefit was defined as the weighted sum of these rates in the experimental group minus the weighted sum of these rates in the comparator group according to the following formula: net clinical benefit = $[IR_{ischemic\_treatment\ 1} + w1\ IR_{non\text{-}CNS\ embolism\_treatment\ 1} + w2\ IR_{hemorrhagic\_treatment\ 1} + w3\ IR_{subdural\_treatment\ 1} + w4\ IR_{extracranial\_treatment\ 1} + w5\ IR_{MI\_treatment\ 1}] - [IR_{ischemic\_treatment\ 2} + w1\ IR_{non\text{-}CNS\ embolism\_treatment\ 2} + w2\ IR_{hemorrhagic\_treatment\ 2} + w3$

$IR_{subdural\_treatment\ 2}$ + w4 $IR_{extracranial\_treatment\ 2}$ + w5 $IR_{MI\ treatment\ 2}$] in which w1, w2, w3, w4, and w5 are the weights associated with non-CNS systemic embolism, hemorrhagic stroke, subdural bleeding, major extracranial bleeding, and MI, respectively.

We expressed net clinical benefit as ischemic stroke equivalents prevented per 100 patient years of treatment because ischemic stroke was used as the reference outcome for each weight. Estimates of net clinical benefit were calculated for the overall trial population and for subgroups categorized by age <75 or ≥75 years; the presence or absence of history of heart failure, diabetes and stroke/TIA; $CHADS_2$ score of <3 or ≥3 (calculated by assigning 1 point for each of congestive heart failure, hypertension, age >75 years, and diabetes; and 2 points for history of stroke) (9); CHA_2DS_2VASc score of 0 to 1, 2 to 4, or ≥5 (calculated by assigning 1 point for each of congestive heart failure, hypertension, diabetes, history of vascular disease, age 65 to 74 years, and female sex; and 2 points for age >75 years and history of stroke) and HAS-BLED score (calculated by assigning 1 point for each of blood pressure >160 mm Hg, abnormal renal function, abnormal liver function, history of stroke, history of bleeding, labile international normalized ratio, age >65 years, concomitant use of antiplatelet or nonsteroidal anti-inflammatory drugs, and alcohol abuse) (9); baseline systolic blood pressure above or below the median level; and creatinine clearance <50 or ≥50 ml/min as estimated by the Cockcroft-Gault formula (10).

We obtained confidence intervals for net clinical benefit by using the bias corrected and accelerated bootstrap method. One thousand bootstrap samples were obtained and stratified by treatment, and the incidence rate, weightings and net clinical benefit were estimated from each. We then used a *Z* test or analysis of variance to compare the net clinical benefit of the treatments and to obtain a p value.

Sensitivity analyses. We explored the robustness of our results by examining the effects of dabigatran 110 mg bid, dabigatran 150 mg bid, and warfarin on net clinical benefit expressed as death equivalents, in which we weighted hemorrhagic stroke as being equivalent to 0.25, 0.5, or 0.75 deaths. All other events were then weighted relative to hemorrhagic stroke using previously calculated weights. For this analysis, net clinical benefit was defined as the weighted sum of these rates in the experimental group minus the weighted sum of these rates in the comparator group, in the same way as described previously, except that we gave patients who died a score of 1 and we gave those who did not die a score that represents the sum of nonfatal events expressed as death equivalents.

In secondary analyses we also explored the effects of dabigatran 110 mg bid, dabigatran 150 mg bid, and warfarin on various composites of serious thrombotic and bleeding events, including stroke or major bleeding, disabling stroke or life-threatening bleeding, disabling stroke or life-threatening bleeding or death, disabling stroke or life-threatening

Table 1 Adjusted Hazard Ratios for Death and Weights for Ischemic and Bleeding Events in the RE-LY and ACTIVE Trials

	Oral Anticoagulant Therapy (RE-LY and ACTIVE-Warfarin Trials)			Antiplatelet Therapy (ACTIVE Trial)			Oral Anticoagulant or Antiplatelet Therapy		
	Events/Deaths	HR (95% CI)	Weight*	Events/Deaths	HR (95% CI)	Weight*	Events/Deaths	HR (95% CI)	Weight*
Ischemic stroke	516/170	8.33 (7.09–9.79)	1.00§	785/362	5.74 (5.10–6.47)	1.00§	1301/532	6.46 (5.87–7.12)	1.00§
Systemic embolism	65/17	5.10 (3.16–8.24)	0.61	138/68	6.08 (4.76–7.77)	1.07	203/85	5.84 (4.70–7.26)	0.90 (w1)
Hemorrhagic stroke	105/70	26.92 (21.08–34.39)	3.23	59/48	17.67 (13.15–23.75)	3.08	164/118	21.29 (17.65–25.67)	3.29 (w2)
Subdural bleeding	90/27	6.89 (4.70–10.09)	0.83	42/15	3.44 (2.06–5.74)	0.60	132/42	5.08 (3.75–6.90)	0.79 (w3)
Extracranial Bleeding	1164/291	5.23 (4.60–5.95)	0.63	435/162	3.82 (3.24–4.51)	0.67	1599/453	4.60 (4.16–5.09)	0.71 (w4)
Myocardial infarction	301/107	7.40 (6.06–9.04)	0.89	260/120	5.44 (4.51–6.56)	0.95	561/227	6.19 (5.40–7.10)	0.96 (w5)

Hazard ratios (HR) are adjusted for age; sex; history of stroke or transient ischemic attack, hypertension, heart failure, diabetes, myocardial infarction or coronary artery disease; and study group. Data for the ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) trials are from Connolly et al. (5). *Weights (w1, w2, w3, w4, and w5) are the ratio of the adjusted HR, using the HR for ischemic stroke as a reference. There were no significant differences in weights derived from patients treated with anticoagulants and those treated with antiplatelet therapy (non–central nervous system embolism, p = 0.14; hemorrhagic stroke, p = 0.92; subdural bleeding, p = 0.55; major extracranial bleeding, p = 0.73; myocardial infarction, p = 0.77). †Reference category

CI = confidence interval; RE-LY = Randomized Evaluation of Long-Term Anticoagulant Therapy.

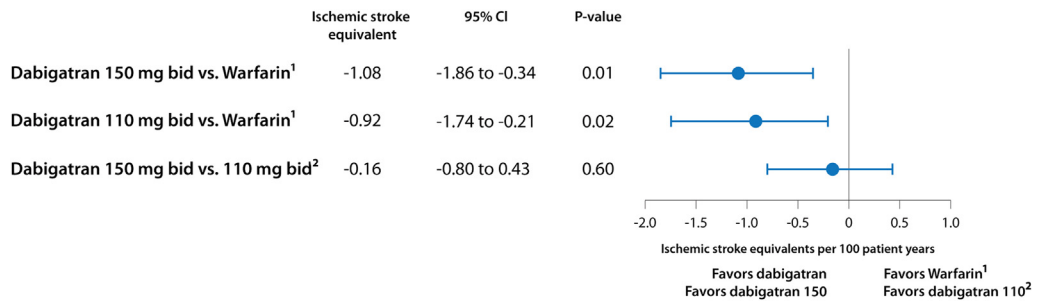


Figure 1 Weighted Net Clinical Benefit of Dabigatran 110 mg bid Compared With Warfarin, Dabigatran 150 mg bid Compared With Warfarin, and Dabigatran 150 mg bid Compared With Dabigatran 110 mg bid

Results are expressed as ischemic stroke equivalents. CI = confidence interval.

bleeding or cardiovascular death, stroke or myocardial infarction or major bleeding, and stroke or systemic embolism or myocardial infarction or pulmonary embolism or death or major bleeding (unweighted net clinical benefit).

We used SAS version 9.1 (SAS Institute, Cary, North Carolina) for all analyses.

Results

The most common clinical events, which occurred in patients in the RE-LY trial were deaths (1,371 events), extracranial major bleeding (956 patients with at least 1 event), and ischemic strokes (413 patients with at least 1 event). MI (clinical and silent; 270 patients with at least 1 event), systemic embolism (35 patients with at least 1 event), hemorrhagic stroke (71 patients with at least 1 event), and subdural bleeding (79 patients with at least 1 event) were less common.

Weighting of thrombotic and bleeding events. Table 1 shows the number of ischemic strokes, non-CNS systemic emboli, hemorrhagic strokes, subdural bleeds, extracranial major bleeds, and MIs; the number of deaths that occurred in these patients, and the adjusted hazard ratio for death following each of these outcomes for patients on oral

Table 2 Weighted Net Clinical Benefit of Dabigatran 110 mg bid Compared With Warfarin, Dabigatran 150 mg Compared With Warfarin, and Dabigatran 150 mg bid Compared With Dabigatran 110 mg bid

	Net Clinical Benefit	95% CI	p Value
Dabigatran 110 mg bid versus warfarin (n = 12,037)			
Ischemic stroke equivalents	−0.92	−1.74 to −0.21	0.02
Death equivalents*			
Hemorrhagic stroke = 0.25 deaths	−0.41	−0.92 to 0.08	0.12
Hemorrhagic stroke = 0.50 deaths	−0.44	−0.96 to 0.05	0.10
Hemorrhagic stroke = 0.75 deaths	−0.48	−1.00 to 0.02	0.07
Dabigatran 150 mg bid versus warfarin (n = 12,098)			
Ischemic stroke equivalents	−1.08	−1.86 to −0.34	0.01
Death equivalents*			
Hemorrhagic stroke = 0.25 deaths	−0.54	−1.07 to −0.05	0.03
Hemorrhagic stroke = 0.50 deaths	−0.59	−1.12 to −0.09	0.02
Hemorrhagic stroke = 0.75 deaths	−0.64	−1.17 to −0.14	0.01
Dabigatran 150 mg bid versus dabigatran 110 mg bid (n = 12,091)			
Ischemic stroke equivalents	−0.16	−0.80 to 0.43	0.60
Death equivalents*			
Hemorrhagic stroke = 0.25 deaths	−0.13	−0.62 to 0.34	0.60
Hemorrhagic stroke = 0.50 deaths	−0.15	−0.64 to 0.32	0.55
Hemorrhagic stroke = 0.75 deaths	−0.16	−0.66 to 0.30	0.53

*In these analyses hemorrhagic stroke was assigned a weight of 0.25, 0.5, or 0.75 deaths. All other events were then weighted relative to hemorrhagic stroke using previously calculated weights. Weights were used to calculate net clinical benefit according to the formula: net clinical benefit = [incidence ratio (IR) $_{ischemic\_treatment\ 1}$ + w1 IR $_{non\text{-}CNS\ embolism\_treatment\ 1}$ + w2 IR $_{hemorrhagic\_treatment\ 1}$ + w3 IR $_{subdural\_treatment\ 1}$ + w4 IR $_{extracranial\_treatment\ 1}$ + w5 IR $_{MI\_treatment\ 1}$] − [IR $_{ischemic\_treatment\ 2}$ + w1 IR $_{non\text{-}CNS\ embolism\_treatment\ 2}$ + w2 IR $_{hemorrhagic\_treatment\ 2}$ + w3 IR $_{subdural\_treatment\ 2}$ + w4 IR $_{extracranial\_treatment\ 2}$ + w5 IR MI $_{treatment\ 2}$], in which IR is per 100 patient years of each outcome for patients receiving dabigatran 110 mg bid, dabigatran 150 mg bid, and warfarin and w1, w2, w3, w4, and w5 are the weights associated with non–central nervous system systemic embolism, hemorrhagic stroke, subdural bleeding, major extracranial bleeding, and myocardial infarction, respectively.

CI = confidence interval.

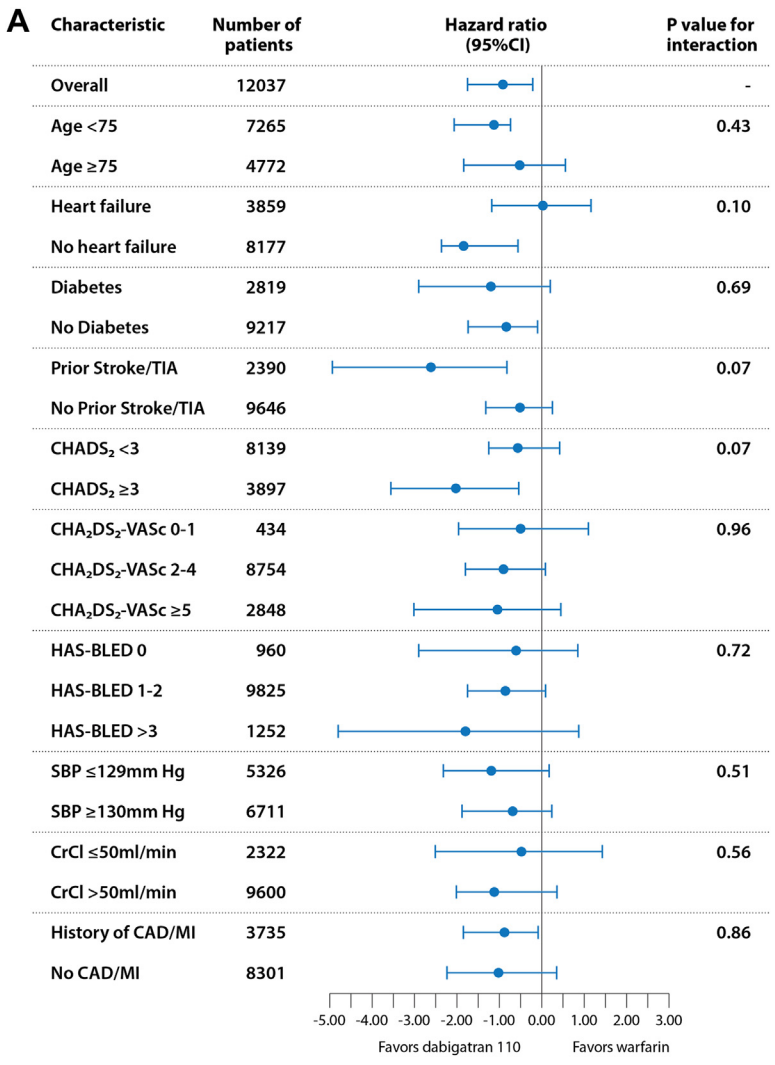
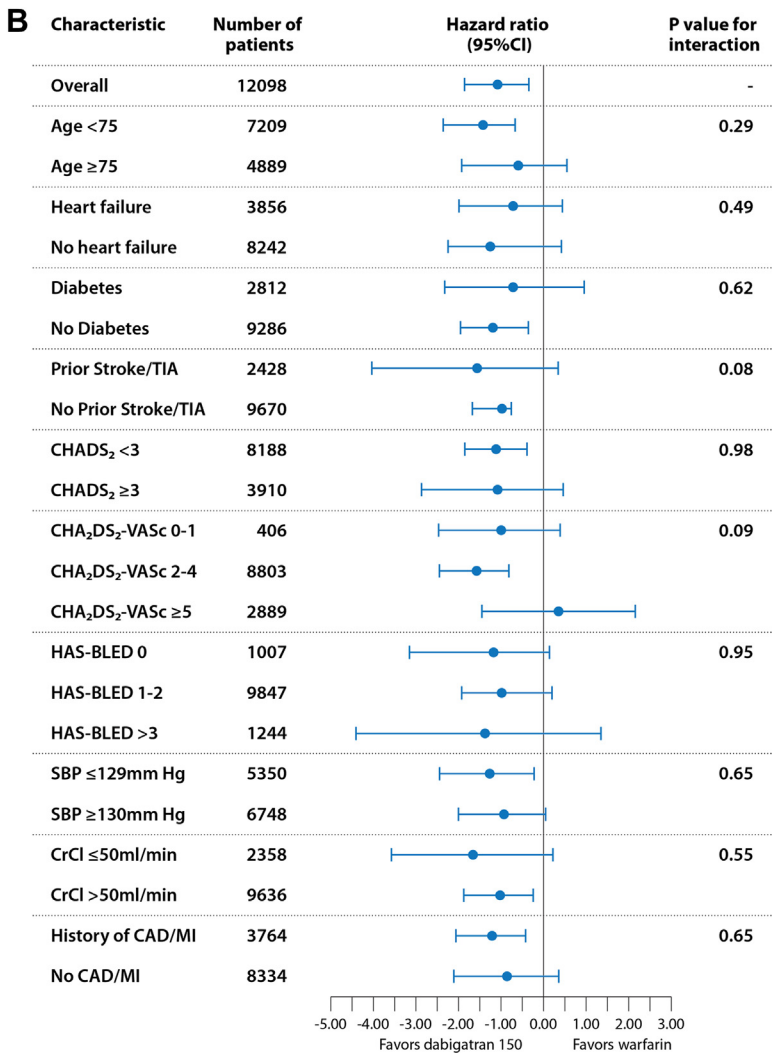


Figure 2 **Weighted Net Clinical Benefit in Subgroups**

(A) Dabigatran 110 mg bid compared with warfarin, **(B)** dabigatran 150 mg compared with warfarin, and **(C)** dabigatran 150 mg bid compared with dabigatran 110 mg bid. Results are expressed as ischemic stroke equivalents. CAD = coronary artery disease; CI = confidence interval; MI = myocardial infarction; SBP = systolic blood pressure; TIA = transient ischemic attack

anticoagulant therapy (from both the RE-LY and ACTIVE trials), on antiplatelet therapy (from ACTIVE) and for all patients (from both the RE-LY and ACTIVE trials). Although there were differences in the hazard ratio for death, there were no significant differences in the relative weights for death after a specific event in patients receiving antiplatelet therapy or receiving anticoagulant therapy. Therefore, the weights derived from the entire dataset provide the most precise estimates of the relative importance of each event. The adjusted hazard ratio for death after hemorrhagic stroke was 26.92 (95% confidence interval [CI]: 21.08 to 34.39) whereas that for ischemic stroke was 8.33 (95% CI: 7.09 to 9.79). Therefore, a hemorrhagic stroke increased the hazard ratio for death by 3.29-fold compared with the increase in risk of death after an ischemic stroke. The adjusted hazard ratio for non-CNS systemic embolism was 0.90 compared with an ischemic stroke; the corresponding numbers for subdural hemorrhage, major extracranial bleeding and myocardial infarction were 0.79, 0.71, and 0.96, respectively (Table 1).

Weighted benefit as ischemic stroke equivalents. Both doses of dabigatran resulted in a significant reduction in ischemic stroke equivalents, compared with warfarin (Fig. 1, Table 2). With dabigatran 110 mg bid the reduction in ischemic stroke equivalents per 100 patient years was −0.92 (95% CI −1.74 to −0.21, p = 0.02); and



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with dabigatran 150 mg bid the reduction was −1.08 (95% CI −1.86 to −0.34, p = 0.01). These results were consistent in all subgroups examined (Figs. 2A and 2B, Online Table 1).

There was no significant difference in ischemic stroke equivalents of dabigatran 150 mg bid compared with dabigatran 110 mg bid (Fig. 1, Table 2); a difference of −0.16 ischemic stroke equivalents with dabigatran 150 mg bid (95% CI: −0.80 to 0.43). Exploratory subgroup analyses provided no evidence of any difference in ischemic stroke equivalents for either dose of dabigatran according to age, heart failure, diabetes, prior stroke/TIA, categories of HAS-BLED score, systolic blood pressure above and below the median, creatinine clearance <50 versus ≥50 ml/min, or history of coronary artery disease/MI. There was a nominally significant interaction between categories of $CHADS_2$ score (p = 0.03) and dabigatran dose; the lower compared with higher dose of dabigatran appeared to be associated with increased benefit in patients with a $CHADS_2$ score of ≥3, whereas the higher compared with lower dose of dabigatran appeared to be associated with increased benefit in patients with a $CHADS_2$ score of <3 (Fig. 2C, Online Table 2). A similar interaction was evident for CHA_2DS_2VASc score of 0 to 1, 2 to 4, or ≥5 (p = 0.01).

Sensitivity analyses. The net clinical benefit of dabigatran 150 mg bid compared with 110 mg bid was similar when we included deaths in the weighted benefit analysis irrespective of whether we weighted hemorrhagic stroke as being equivalent to 0.25, 0.5, or 0.75 deaths (Table 2).

The effects of dabigatran 110 mg bid, dabigatran 150 mg bid, and warfarin on various composites of serious thrombotic and bleeding events were consistent with the results of the

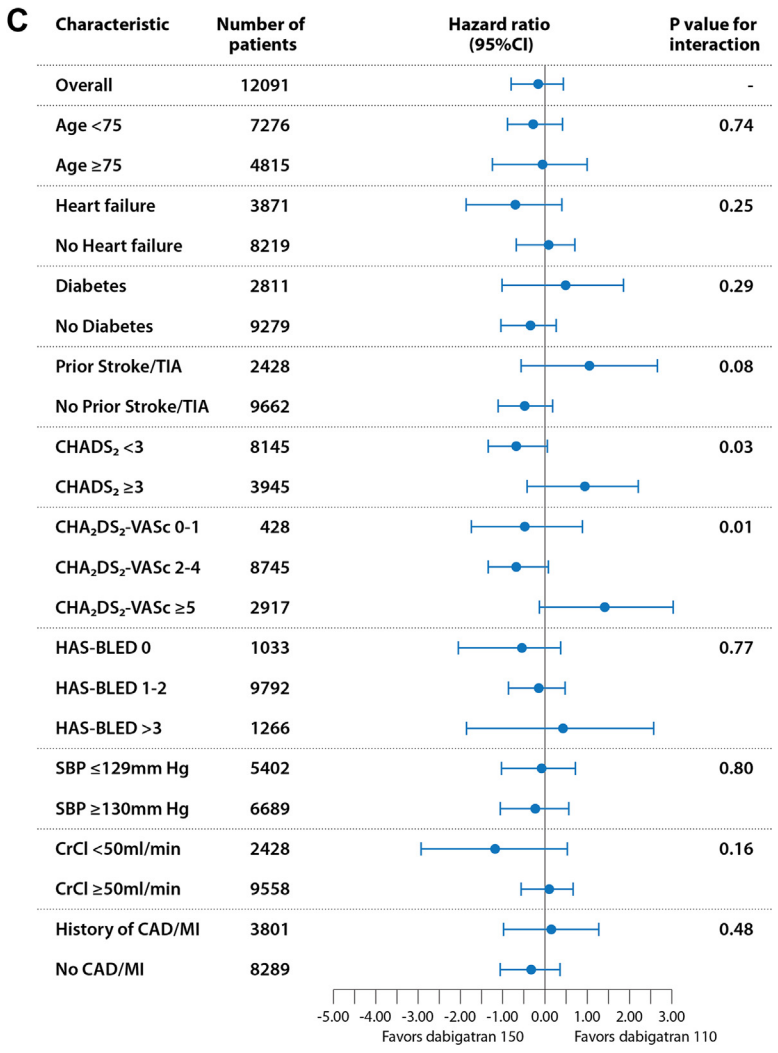

Figure 2 Continued

primary weighted net clinical benefit analyses as well as with the previously reported unweighted net clinical benefit (1), a composite outcome that included stroke, systemic embolism, MI, pulmonary embolism, death, or major bleeding (Table 3). Thus, there was no significant difference between dabigatran 150 mg bid and dabigatran 110 mg bid in their effects on various composites of serious thrombotic and bleeding events.

Discussion

The analysis integrating the information on efficacy and safety outcomes estimated by the weighted ischemic stroke equivalents in the RE-LY trial indicate that both dabigatran 110 mg bid and dabigatran 150 mg bid are superior to warfarin when considering their integrated effects on major ischemic and bleeding events. At a group level, each dabigatran dose prevents about 1 more ischemic stroke equivalent (compared with warfarin) for every 100 patients treated for a year. When comparing the 2 doses of dabigatran, their net clinical benefit is similar irrespective of whether death is included in the calculation of net benefit. The results are also similar when net benefit is examined using unweighted composite outcomes that include various combinations of major efficacy and safety events.

The largest difference between the 2 dabigatran doses was in their effects on major bleeding and on ischemic stroke, with similar effects on the other events. The relative reduction in ischemic stroke with dabigatran 150 mg bid compared with 110 mg bid was large (31%; 95% CI: 12% to 46%) (1,2). Similarly the reduction in major extracranial bleeding with dabigatran 110 mg compared with 150 mg was substantial (12%; 95% CI: −2% to 25%) (3). Although the weight of ischemic stroke in using ischemic stroke equivalents was 1.40 times that of major extracranial

Table 3 Effect of Dabigatran 150 mg bid Compared With Dabigatran 110 mg bid on Mortality, Different Composites of Serious Thrombotic and Bleeding Events, and Unweighted Net Clinical Benefit

	Dabigatran 110 mg bid, n (Rate/100 Patient-Yrs)	Dabigatran 150 mg bid, n (Rate/100 Patient-Yrs)	Warfarin, n (Rate/100 Patient-Yrs)	Dabigatran 110 mg Versus Warfarin, HR (95% CI)	Dabigatran 150 mg Versus Warfarin, HR (95% CI)	Dabigatran 150 mg Versus 110 mg bid, HR (95% CI)
All-cause mortality	446 (3.75)	438 (3.64)	487 (4.13)	0.91 (0.80 to 1.03)	0.88 (0.77 to 1.00)	0.97 (0.85 to 1.11)
Cardiovascular mortality	289 (2.43)	274 (2.28)	317 (2.69)	0.90 (0.77 to 1.06)	0.85 (0.72 to 0.99)	0.94 (0.79 to 1.11)
Stroke or major bleed	474 (3.98)	486 (4.04)	536 (4.54)	0.87 (0.77 to 0.99)	0.89 (0.79 to 1.01)	1.02 (0.90 to 1.15)
Disabling stroke or life-threatening bleed	220 (1.85)	220 (1.83)	268 (2.27)	0.81 (0.68 to 0.97)	0.80 (0.67 to 0.96)	0.88 (0.82 to 1.19)
Disabling stroke or life-threatening bleed or death	598 (5.03)	579 (4.810)	656 (5.56)	0.90 (0.81 to 1.01)	0.86 (0.77 to 0.96)	0.96 (0.85 to 1.07)
Disabling stroke or life-threatening bleed or cardiovascular death	460 (3.87)	442 (3.67)	516 (4.38)	0.88 (0.78 to 1.00)	0.84 (0.74 to 0.95)	0.95 (0.83 to 1.08)
Stroke or myocardial infarction or major bleed	548 (4.61)	548 (4.55)	594 (5.04)	0.91 (0.81 to 1.03)	0.91 (0.81 to 1.02)	0.99 (0.88 to 1.12)
Unweighted net clinical benefit*	873 (7.34)	855 (7.11)	933 (7.91)	0.92 (0.84 to 1.01)	0.90 (0.82 to 0.99)	0.97 (0.88 to 1.07)

*Defined as the composite outcome, stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding.
CI = confidence interval; HR = hazard ratio.

bleeding, the more than twice as many major bleeds as ischemic strokes in RELY explains the similar effects of the 2 doses of dabigatran on ischemic stroke equivalents.

Various approaches have been used to assess the net clinical benefit of antithrombotic therapy. Hong and colleagues weighted individual vascular outcomes according to their impact on disability-adjusted life years using World Health Organization Global Burden of Disease Project methodology (11). Singer et al. (12) calculated the weighted net clinical benefit of warfarin compared with placebo or no warfarin for stroke prevention in AF by assigning intracranial hemorrhage a weight of 1.5 or 2.0 relative to ischemic stroke. The latter approach reflects the greater importance of hemorrhagic compared with ischemic stroke for patients, but is limited by arbitrary assignment of weights and does not take into account other events that are also important for patients (e.g., extracranial bleeding, MI). Both Olesen et al. (13) and Banerjee et al. (14) arbitrarily assigned hemorrhagic stroke a weight of 1.5 relative to ischemic stroke when calculating the net clinical benefit of various antithrombotic therapies for stroke prevention in atrial fibrillation. By disregarding extracranial bleeding, both studies may have overestimated the benefits of dabigatran compared with warfarin in patients at high risk of stroke who are also at high risk of bleeding. Building on the methods by Singer et al. (12) and others (1,13,14), we have taken into account all major cardiovascular events and have used the adjusted hazard of death after each type of important ischemic and bleeding events to determine their weight. We believe that this novel approach has wider applicability to evaluate the net benefit of other treatments that require physicians and patients to consider the tradeoff between benefits and harms.

The decision by the U.S. FDA to approve only the 150 mg bid dose of dabigatran was based on their assessment that extracranial bleeding was relatively unimportant, especially compared with stroke (4). This view is also present in the work of Singer et al. (12), who in their weighting of events for net benefit analysis in AF patients assigned a weight of zero to extracranial bleeding. Challenging this view, a large number of studies of patients receiving either antiplatelet or anticoagulant therapy have found that patients with bleeding have a significant increase in major cardiovascular events and mortality compared with those who do not experience an outcome event (15,16). Furthermore, lower antithrombotic drug doses that are associated with reduced bleeding have demonstrated improved efficacy and a reduction in mortality (17). We observed that the impact on mortality of an extracranial bleed was equivalent to about three-quarters of that of ischemic stroke. Adverse outcomes after bleeding may be a direct effect of bleeding (e.g., shock, exsanguination), an indirect effect related to hazard of blood transfusion and risk of antithrombotic drug discontinuation, or may be confounded by factors that are associated with both bleeding and death (e.g., comorbidities, frailty).

The finding of a similar overall benefit of dabigatran 110 mg bid and 150 mg bid over warfarin might be interpreted as providing support for using any of the 2 dabigatran doses for stroke prevention in AF. However, these results are based on group comparisons and randomly assigned doses and do not take into account individual patient characteristics or preferences. The 2 dabigatran doses achieved their benefits relative to warfarin somewhat differently, the higher dose of dabigatran by reducing ischemic stroke and the lower dose by reducing bleeding. Although many patients appear to place greater value on avoidance of stroke compared with bleeding, and thus may be expected to prefer the higher dose of dabigatran, this is not universal (18). Our subgroup analyses also suggest that higher-risk patients, based on higher $CHADS_2$ or CHA_2DS_2VASc scores, had a larger net benefit with the lower dose of dabigatran and lower-risk patients had a larger overall benefit with the higher dose. This supports the concept that the best balance between

benefit and risk for individual patients may be obtained by tailoring the dabigatran dose according to a patient's risk of stroke and bleeding.

Study limitations. First, we did not consider the impact of outcomes on morbidity or quality-of-life measures in the RE-LY trial because these data were not collected. In the ACTIVE trial, estimates of net clinical benefit of the combination of aspirin and clopidogrel compared with aspirin alone were similar irrespective of whether events were weighted according to their impact on death alone or their impact on disability and death (5), but we do not know whether the results based on disability and death would also be similar to those based on death in RE-LY. Second, we weighted events according to their impact on death but did not incorporate death in our primary analysis. We used this approach because the 2 doses of dabigatran had a similar effect on mortality and there is not a straightforward way to quantitatively weight death relative to any of the other outcomes. We do, however, also report the results that were obtained after incorporating death in our estimates of net clinical benefit, which produced similar results when comparing the net benefit of the 2 doses of dabigatran. Third, these are post hoc analyses; before the start of the RE-LY trial we did not anticipate formally evaluating the net clinical benefit of the 2 doses of dabigatran.

Conclusions

On a group level both doses of dabigatran as compared with warfarin have similar benefits when considering a weighted estimate including both efficacy and safety. These data support a role for both the 110 mg and the 150 mg dose of dabigatran in clinical practice and the approach of tailoring the dose based on individual patient characteristics.

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Key Words: atrial fibrillation ■ dabigatran ■ net benefit ■ warfarin.

APPENDIX

For supplementary tables, please see the online version of this article.