ONLINE FIRST

Dabigatran Association With Higher Risk of Acute Coronary Events

Meta-analysis of Noninferiority Randomized Controlled Trials

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Background: The original RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) trial suggested a small increased risk of myocardial infarction (MI) with the use of dabigatran etexilate vs warfarin in patients with atrial fibrillation. We systematically evaluated the risk of MI or acute coronary syndrome (ACS) with the use of dabigatran.

Methods: We searched PubMed, Scopus, and the Web of Science for randomized controlled trials of dabigatran that reported on MI or ACS as secondary outcomes. The fixed-effects Mantel-Haenszel (M-H) test was used to evaluate the effect of dabigatran on MI or ACS. We expressed the associations as odds ratios (ORs) and their 95% CIs.

Results: Seven trials were selected (N = 30 514), including 2 studies of stroke prophylaxis in atrial fibrillation, 1 in acute venous thromboembolism, 1 in ACS, and 3 of short-term prophylaxis of deep venous thrombosis. Control arms included warfarin, enoxaparin, or placebo administration. Dabigatran was significantly associated with a higher risk of MI or ACS than that seen with agents used in the control group (dabigatran, 237 of 20 000 [1.19%] vs control, 83 of 10 514 [0.79%]; OR_{M-H}, 1.33; 95% CI, 1.03-1.71; $P = .03$). The risk of MI or ACS was similar when using revised RE-LY trial results (OR_{M-H}, 1.27; 95% CI, 1.00-1.61; $P = .05$) or after exclusion of short-term trials (OR_{M-H}, 1.33; 95% CI, 1.03-1.72; $P = .03$). Risks were not heterogeneous for all analyses ($I^2 = 0\%$; $P \geq .30$) and were consistent using different methods and measures of association.

Conclusions: Dabigatran is associated with an increased risk of MI or ACS in a broad spectrum of patients when tested against different controls. Clinicians should consider the potential of these serious harmful cardiovascular effects with use of dabigatran.

Arch Intern Med. 2012;172(5):397-402.
Published online January 9, 2012.
doi:10.1001/archinternmed.2011.1666

DABIGATRAN ETEXILATE WAS approved by the European Medicines Agency in 2008 for prophylaxis of venous thromboembolism (VTE) in adults who have undergone total hip or knee replacement and by the US Food and Drug Administration in 2010 for prevention of stroke and systemic embolism in persons with nonvalvular atrial fibrillation (AF).[1] The largest study of dabigatran, the RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) trial, followed more than 18 000 persons with AF and compared the safety and efficacy of dabigatran with that of warfarin in preventing stroke and systemic embolism for a median observation time of 2 years. In its original publication,[2] the RE-LY trial reported a significant decrease in stroke and systemic embolism of 34% in the group receiving dabigatran etexilate, 150 mg, twice daily compared with adjusted-dose warfarin, but also reported a significant relative increase in myocardial infarction (MI) of 38% (relative risk, 1.38; 95% CI, 1.00-1.91; $P = .048$) in the group receiving dabigatran etexilate, 150 mg, twice daily compared with warfarin. A subsequent review[3] of outcome and safety events revealed additional events of stroke, bleeding, and MI, and the revised results no longer showed a significantly higher risk of MI with the use of dabigatran (increased by 27%; relative risk, 1.27; 95% CI, 0.94-1.71; $P = .12$). Dabigatran has also been studied for acute VTE treatment, VTE prophylaxis after joint replacement, and acute coronary syndrome (ACS) in noninferiority randomized controlled trials (RCTs). We systematically evaluated the risk of MI or ACS with the use of dabigatran for several clini-

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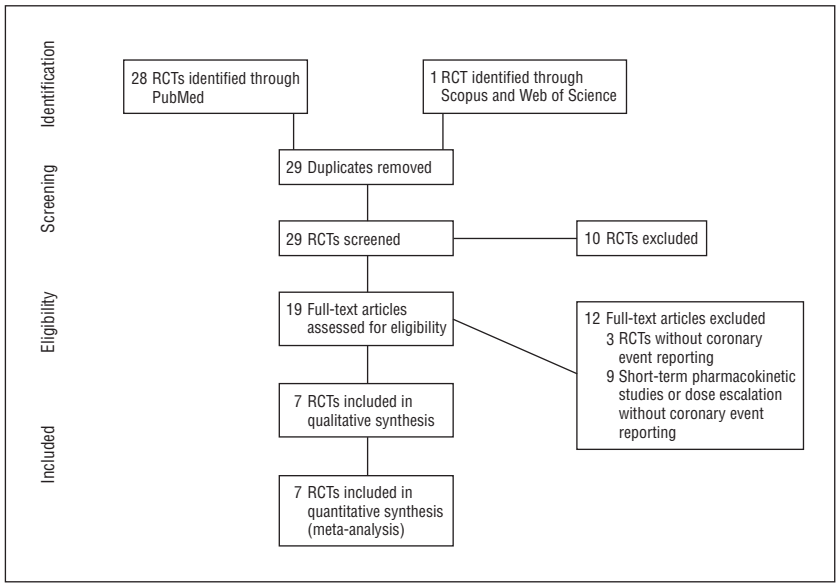

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram of study selection. RCTs indicates randomized controlled trials.

cal indications and against different control arms.

METHODS

SELECTION OF STUDIES

We searched PubMed, Scopus, and the Web of Science in May 2011 for RCTs evaluating the safety and efficacy of dabigatran that reported on MI or ACS as secondary outcomes. The search terms *dabigatran* or *dabigatran etexilate* or *BIBR 1048* (name given by the company for dabigatran in development) and *randomized clinical trial* or *randomized trial* or *randomized controlled trial* were used. The full search strategy for PubMed is shown in the eAppendix (http://www.archinternmed.com). We did not create a formal review protocol.

OUTCOMES

The primary outcomes were acute coronary events: MI or ACS (confirmed unstable angina, MI, and cardiac death) if the study did not report MI as an adverse event. Overall mortality was the secondary outcome. The different dosages of dabigatran evaluated were grouped in the dabigatran arm, and different control treatments were grouped as the control arm.

EXTRACTION OF INFORMATION

One author (K.U.) extracted general characteristics of the trials (acronym, year of publication, type of blinding, study population, original efficacy outcome, dabigatran dosages, treatment duration, and type of control), the number of patients per trial arm, and the number of patients with the composite primary outcome. This information was reviewed by the second author (A.V.H.), and any discrepancy was solved by agreement.

STUDY QUALITY

The Jadad scale assesses the quality of RCTs; it allows up to 2 points for reported randomization, up to 2 points for double-blinding, and up to 1 point for description of withdrawals and dropouts.[4] A Jadad score of 3 or more was considered high quality.

META-ANALYSIS

Our meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (see eTable 1 for PRISMA Checklist).[5] Because of the small number of trials, imbalance between arms, and paucity of outcomes, we performed a meta-analysis with the fixed-effects model and the Mantel-Haenszel (M-H) test for the primary analysis.[6] We corrected for zero events in all studies by adding 0.5 to the arms with zero events. Our main measure of association was the odds ratio and its 95% CI. Heterogeneity was evaluated using the Q test and quantified with the I^2 statistic.[7] Publication bias was evaluated with the funnel plot and the Egger regression test.[8]

SENSITIVITY ANALYSIS

To evaluate the strength of the association of the primary analysis, we used the Peto and inverse variance methods, as well as the random-effects models. We calculated relative risks and risk differences as alternative measures of association. Finally, we used the revised results of the RE-LY trial instead of its main results and removed the short-term ($\leq$1 month) trials or a low-quality trial (Jadad score $<$3) to explore the strength of the association of the main analysis. Random-effects meta-regression analysis using a linear mixed-effects model was used to evaluate the association between the risk of acute coronary events in the control groups (baseline risk) and the odds ratio for acute coronary events with the use of dabigatran. However, the results must be considered carefully, since the associations derived from meta-regressions are observational and have a weaker interpretation than causal relationships derived from randomized comparisons.[9] Commercial software (metafor package of R [http://www.metafor-project.org/] and RevMan 5.1; Cochrane Collaboration) was used for all statistical analyses.

RESULTS

SELECTED TRIALS

We identified 29 abstracts and reviewed 19 full-text articles. Seven RCTs were selected (**Figure 1**), involving 30 514 participants. The characteristics of the trials[2,3,10-15] are provided in **Table 1**. Two studies were of stroke prophylaxis in AF with adjusted-dose warfarin as the comparator (Prevention of Embolic and Thrombotic Events in Patients With Persistent AF Study [PETRO][12] and RE-LY[2,3]), 1 study evaluated acute VTE (RE-COVER)[13] compared with warfarin, 1 study of patients with ACS (RE-DEEM)[14] was placebo-controlled, and 3 short-term trials on the prophylaxis of deep venous thrombosis in joint replacement, with median follow-ups of 1 month or less (RE-NOVATE,[10] RE-MODEL,[11] and RE-NOVATE II[15]), used enoxaparin as the comparator. In none of the studies was MI or ACS the primary outcome. All trials evaluated the noninferiority of dabigatran in bleeding events or other non-ACS vascular events. All studies were sponsored by the manufacturer of dabigatran (Boehringer Ingelheim International GmbH). Six studies[2,3,10,11,13-15] were considered to be high quality (Table 1).

Table 1. Characteristics of Reviewed Noninferiority Randomized Controlled Trials

Source	Design and Population	Primary Outcome of Study and Cardiac Outcome in This Analysis	Dabigatran Regimen	Control Regimen	Treatment Duration	Jadad Score
RE-NOVATE,[10] 2007	DB, DVT prophylaxis in hip replacement	Primary: DVT and death Analysis: ACS adjudicated acute coronary events ("confirmed unstable angina, MI, and cardiac death")	Dabigatran etexilate, 150 mg (n = 1163), or 220 mg (n = 1146), PO once daily	Enoxaparin sodium, 40 mg, SC once daily (n = 1154)	Design: 28-35 d Result: median, 33 d	5
RE-MODEL,[11] 2007	DB, DVT prophylaxis in knee replacement	Primary: DVT and death Analysis: ACS adjudicated acute coronary events ("confirmed unstable angina, MI, and cardiac death")	Dabigatran etexilate, 150 mg (n = 703), or 220 mg (n = 679), PO once daily	Enoxaparin sodium, 40 mg, SC once daily (n = 694)	Design: 6-10 d Result: median, 8 d	5
PETRO,[12] 2007	OL for dabigatran or warfarin, DB for dabigatran dose, AF	Primary: bleeding Analysis: ACS (undefined)	Dabigatran etexilate, 50 mg (n = 107), 150 mg (n = 169), or 300 mg (n = 169), PO twice daily	Adjusted-dose warfarin (n = 70)	Design: 12 wk[a]	2
RE-LY,[2,3] 2009	OL for dabigatran or warfarin, DB for dabigatran dose, AF	Primary: stroke or systemic embolism Analysis: MI (definition described)[16]	Dabigatran etexilate, 110 mg (n = 6015), or 150 mg (n = 6076), PO twice daily	Adjusted-dose warfarin (n = 6022)	Design: duration of recruitment, with ≥1 y for all participants Result: median, 2.0 y	3
RE-COVER,[13] 2009	DB, acute DVT	Primary: DVT and related death Analysis: MI (undefined)	Dabigatran etexilate, 150 mg, PO twice daily (n = 1274)	Adjusted-dose warfarin (n = 1265)	Design: 6 mo Result: 164 d	5
RE-DEEM,[14] 2011	DB, ACS	Primary: major or clinically relevant minor bleeding Analysis: nonfatal MI (defined by established referenced criteria)	Dabigatran etexilate, 50 mg (n = 369), 75 mg (n = 368), 110 mg (n = 406), or 150 mg (n = 347), PO twice daily	Placebo (n = 371)	Design: 6 mo Result: mean, 158-164 d by group	4
RE-NOVATE II,[15] 2011	DB, DVT prophylaxis in hip replacement	Primary: DVT and death Analysis: MI (undefined)	Dabigatran etexilate, 220 mg, PO once daily (n = 1010)	Enoxaparin sodium, 40 mg, SC once daily (n = 1003)	Design: 28-35 d Result: median, 32 d	5

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; DB, double-blind; MI, myocardial infarction; DVT, deep venous thrombosis; OL, open-label; PETRO, Prevention of Embolic and Thrombotic Events in Patients With Persistent AF Study; PO, orally; RE-LY, Randomized Evaluation of Long-term Anticoagulant Therapy; SC, subcutaneously.

[a] Result duration not mentioned.

META-ANALYSIS

When using the original RE-LY results,[2] dabigatran was significantly associated with a higher risk of MI or ACS than the control group (dabigatran, 237 of 20 000 [1.19%] vs control, 83 of 10 514 [0.79%]; odds ratio [OR_{M-H}], 1.33; 95% CI, 1.03-1.71; $P = .03$) (**Table 2** and **Figure 2**). This association was consistent across different measures of association and methods. Absolute risk differences for MI or ACS were small (between 0.14% and 0.17% by different methods). Heterogeneity of effects was low among studies. There was no evidence of publication bias in the funnel plot (**Figure 3**) and with the Egger regression test ($P = .60$).

Six studies reported on overall mortality. Dabigatran was significantly associated with lower mortality than the control group (dabigatran, 945 of 19 555 [4.83%] vs control, 524 of 10 444 [5.02%]; OR_{M-H}, 0.89; 95% CI, 0.80-0.99; $P = .04$) (eTable 2, eFigure 1).

Although relative measures such as odd ratios and relative risks did not demonstrate significant heterogeneity, heterogeneity in the measures of risk differences likely reflected the

Table 2. Risk of MI/ACS Across 7 Studies, Including Original RE-LY Results

Measure of Association	Method	Association (95% CI)	*P* Value for Effect	Degree of Heterogeneity (I^2)	*P* Value for Heterogeneity
Odds ratio	M-H	1.33 (1.03 to 1.71)	.03	0% for all	.80
	Peto	1.29 (1.03 to 1.62)	.03		.80
	IV	1.30 (1.02 to 1.65)	.04		.80
	RE	1.32 (1.03 to 1.70)	.03		.80
Relative risk	M-H	1.33 (1.03 to 1.70)	.03	0% for all	.80
	IV	1.31 (1.02 to 1.69)	.03		.80
	RE	1.32 (1.02 to 1.69)	.03		.80
Risk difference	M-H	0.27% (0.04% to 0.50%)	.02	0% for all	.30
	IV	0.14% (–0.03% to 0.31%)	.10		.40
	RE	0.14% (–0.03% to 0.32%)	.10		.40

Abbreviations: ACS, acute coronary syndrome; IV, inverse variance; M-H, Mantel-Haenszel; MI, myocardial infarction; RE, random effects; RE-LY, Randomized Evaluation of Long-term Anticoagulant Therapy.

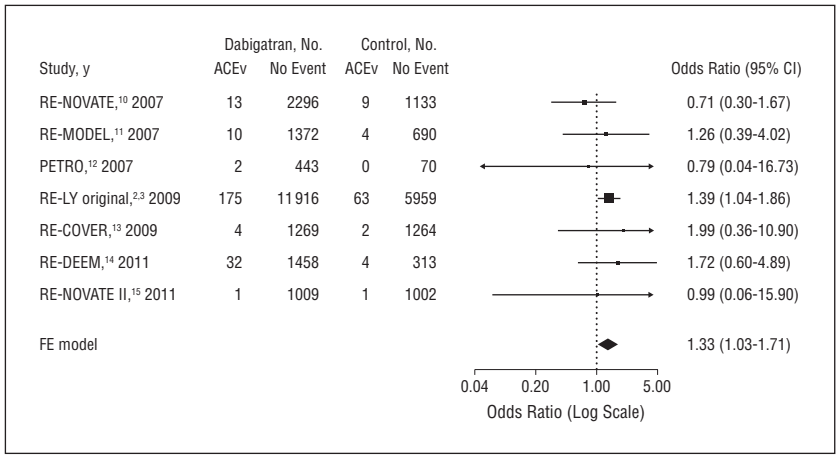

Figure 2. Risk of myocardial infarction and acute coronary syndrome across 7 studies, including original Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) results. ACEv indicates acute coronary events; FE, fixed effects; PETRO, Prevention of Embolic and Thrombotic Events in Patients With Persistent AF Study; rectangles, odds ratios; limit lines, 95% CIs; diamond, overall odds ratio and 95% CI; and arrows, 95% CIs that exceed the limits of the graph (0.04-5.00).

differences in absolute mortality risk in different disease cohorts.

SENSITIVITY ANALYSIS

The RE-LY investigators[3] found previously unreported events of stroke, bleeding, and MI after further search for events, including 4 clinical MIs and 28 silent MIs (new Q waves on electrocardiogram). Additional MIs included 20 in the dabigatran group and 12 in the control group, but distribution of the 4 clinical MIs was not reported. All 28 silent MIs were discovered in the later review. The higher risk of MI or ACS associated with dabigatran remained significant when using revised RE-LY trial results (OR_{M-H}, 1.27; 95% CI, 1.00-1.61; $P=.05$) (eTable 3 and eFigure 2).

Dabigatran may increase risk of MI and ACS with longer duration of exposure, and 3 short-term studies (≤1 month) were therefore excluded. These were studies of DVT prophylaxis after joint replacement. The risk of MI or ACS associated with dabigatran remained high and significant (OR_{M-H}, 1.33; 95% CI, 1.03-1.72; $P=.03$) (eTable 4 and eFigure 3). For all sensitivity analyses, risks were not heterogeneous ($I^2=0\%$; $P\geq.40$) and were consistent when using different methods and measures of association.

One open-label trial[12] that compared dabigatran with warfarin in a population with AF received a low Jadad study quality score of 2. When this study was excluded from analysis, the results remained significant (OR_{M-H}, 1.34; 95% CI, 1.04-1.67; $P=.03$) (eTable 5 and eFigure 4).

We did not find any relationship between the baseline risk of acute coronary events and the odds ratio for acute coronary events associated with dabigatran use ($P=.61$, **Figure 4**).

COMMENT

Our meta-analysis indicates that the risk of MI or ACS is increased with dabigatran compared with various control treatments, which included adjusted-dose warfarin, enoxaparin, or placebo. We used several meta-analytic methods and several association measures, and the results were consistent. Although the relative risk increase was 33%, the absolute risk increase was very small, at 0.27%.

We do not know the pharmacologic mechanism that may result in dabigatran increasing the risk of MI or ACS. Pharmaceutical agents have multiple effects, and unexpected risks are sometimes found in the process of drug development or clinical use. The development of another direct thrombin inhibitor, ximelagatran, was halted when a higher risk of increase in hepatic transaminase levels was observed.[17,18] Although the anticoagulant property of ximelagatran may reduce cardiovascular events, it was found to increase some proinflammatory markers.[19] Thus, as a member of the same drug class, dabigatran might have effects that are unfavorable to atherosclerosis or atherosclerotic thrombotic events. No such signal has been found in recent large RCTs of the oral factor Xa inhibitors apixaban and rivaroxaban among persons with AF.[20-22]

If comparator drugs in selected studies had effects on MI prevention that dabigatran did not have, then dabigatran might be associated with a higher risk of MI. Warfarin was the comparator therapy in 3 of the studies. Adjusted-dose war-

farin reduces the occurrence of MI as monotherapy or with concomitant use of aspirin.[23,24] Lip and Lane[25] conducted a recent meta-analysis of the occurrence of MI in clinical trials of AF and compared warfarin with other anticoagulants. Warfarin also reduced stroke better than various nonaspirin comparator therapies, but the study results were greatly affected by RE-LY study results. Dabigatran might not directly increase the risk of MI, but it may lack the beneficial effects that warfarin and aspirin have in MI prevention.

Aspirin and other antiplatelets reduce MI and their use varied across the 7 studies. All the trials allowed concomitant aspirin. In RE-DEEM, dabigatran was added to standard antiplatelet therapy in persons with ACS.[14] In double-blind trials, the use of aspirin should be equal between dabigatran and the comparator. In RE-LY, the use of aspirin by approximately 20% of the participants was similar across the treatment groups. It is unlikely that differential antiplatelet use led to the finding.

The revision of the RE-LY results with additional events found during site closing and rereview of documents present methodologic issues.[3] New appearance of Q waves on electrocardiogram meets the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation consensus definition of prior MI and reportedly was a part of the MI definition of the RE-LY study.[26] However, no silent MI was reported during the study until the efforts to uncover additional events were made. It may be more meaningful to analyze clinical acute MIs rather than to include silent ones, since an acute MI is a patient-oriented outcome and other studies in the analysis reported acute MIs or ACS. We were unable to obtain the data on how many of the additional MIs were silent vs were diagnosed on clinical grounds.

Our results on the reduction of overall mortality should be interpreted with caution. Mortality was not the primary outcome of the meta-analysis and we selected trials by reporting of MI or ACS. There was high heterogeneity in risk difference among the trials, likely reflecting the differences in underlying disease processes. Long-term studies of AF are expected to report different causes and rates for death compared with shorter studies of VTE prophylaxis or treatment. The impact of dabigatran use is also expected to vary in these different populations.

An important limitation of our study is the dominant effect of the

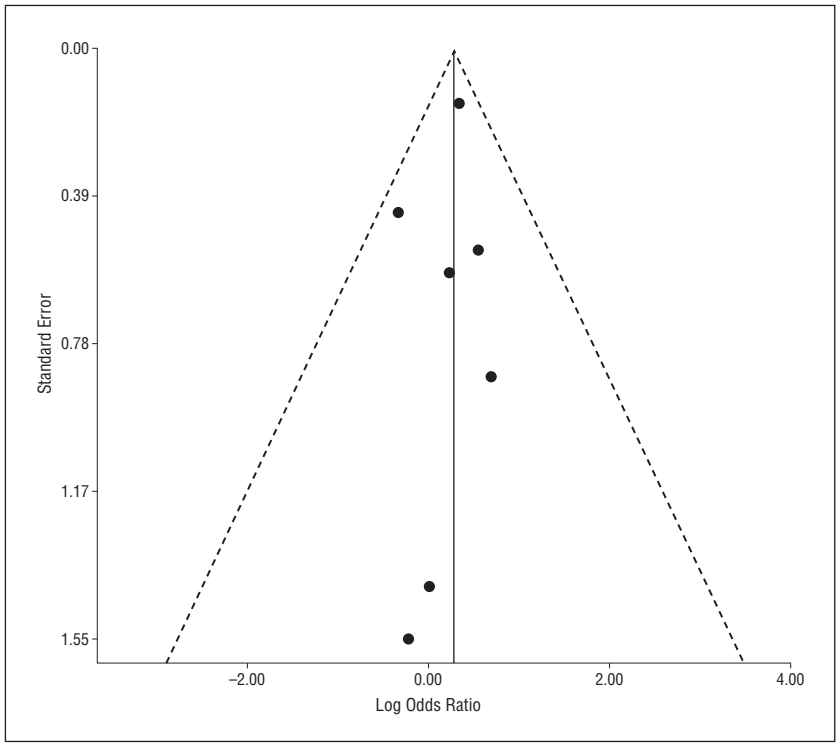

Figure 3. Funnel plot for fixed-effects evaluation of publication bias.

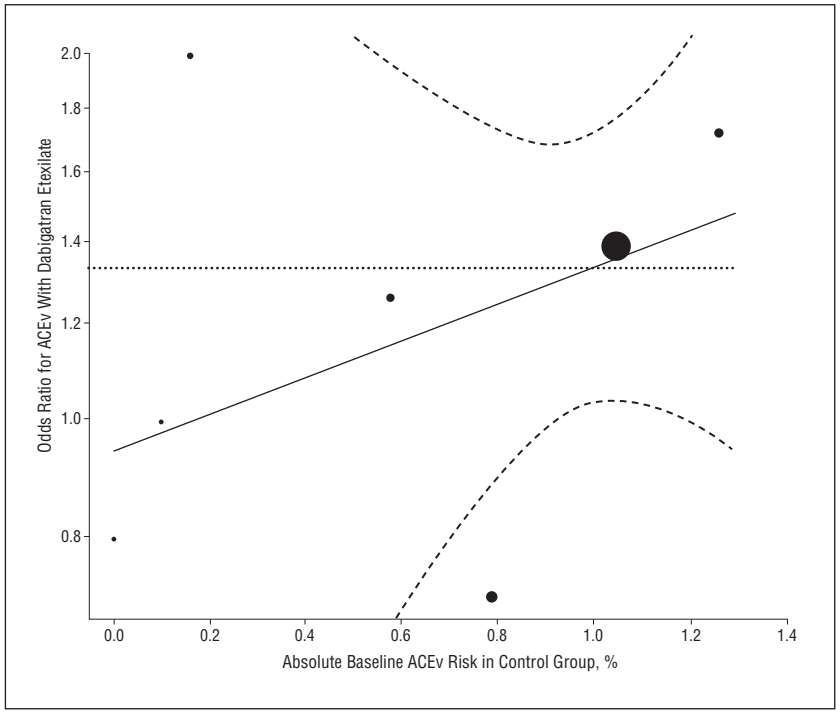

Figure 4. Meta-regression analysis comparing the baseline risk of acute coronary events (ACEv) in the control group with the odds ratio for ACEv with dabigatran. Each circle represents a study, with the size of the circle inversely proportional to the standard error (reflecting size of study). The continuous line is the regression line from the linear mixed-effects model; it is depicted with its 95% CI (dashed lines). The horizontal dotted line is the odds ratio for ACEv from the meta-analysis. The y-axis uses a logarithmic scale.

RE-LY trial on the results of the meta-analysis. The other 6 trials had cohort sizes of 515 to 3451 with durations of 6 months or less; in RE-LY, 18 113 participants were monitored for a median of 2 years. Owing to the sample size and duration of the study, RE-LY comprised 59% of the cohort and 74% of the events. The MI events were few and infrequent in the other studies, but the point estimates derived from most of the remaining trials trend toward increased risk with dabigatran. We analyzed scarce acute coronary events by using the appropriate M-H method and the fixed-effects model, as well as correcting for zero events in RCT arms; our sensitivity analysis provided similar conclusions when using different methods and models.

The overall benefit and risk balance of dabigatran use appears to be favorable in patients with AF because of reduction in ischemic stroke. However, the cardiac risk of dabigatran should be investigated further, especially if it is used in populations at high risk of MI or ACS.

Accepted for Publication: November 27, 2011.
Published Online: January 9, 2012. doi:10.1001/archinternmed.2011.1666
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Author Contributions: *Study concept and design:* Uchino and Hernandez. *Acquisition of data:* Uchino. *Analysis and interpretation of data:* Uchino and Hernandez. *Drafting of the manuscript:* Uchino and Hernandez. *Critical revision of the manuscript for important intellectual content:* Uchino and Hernandez. *Statistical analysis:* Hernandez. *Administrative, technical, and material support:* Uchino and Hernandez. *Study supervision:* Uchino and Hernandez.

Financial Disclosure: None reported.
Online-Only Material: The eAppendix, 5 eTables, and 4 eFigures are available at http://www.archinternmed.com.

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