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ORIGINAL RESEARCH

Dabigatran Etexilate and Risk of Myocardial Infarction, Other Cardiovascular Events, Major Bleeding, and All-Cause Mortality: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Jonathan Douxfils, PharmD; Fanny Buckinx, MS; François Mullier, PharmD, PhD; Valentine Minet, PharmD; Véronique Rabenda, MSc; Jean-Yves Reginster, MD, PhD; Philippe Hainaut, MD, PhD; Olivier Bruyère, PhD; Jean-Michel Dogné, PharmD, PhD

***Background*—**Signals of an increased risk of myocardial infarction (MI) have been identified with dabigatran etexilate in randomized controlled trials (RCTs).

***Methods and Resules*—**We conducted searches of the published literature and a clinical trials registry maintained by the drug manufacturer. Criteria for inclusion in our meta-analysis included all RCTs and the availability of outcome data for MI, other cardiovascular events, major bleeding, and all-cause mortality. Among the 501 unique references identified, 14 RCTs fulfilled the inclusion criteria. Stratification analyses by comparators and doses of dabigatran etexilate were conducted. Peto odds ratio (OR_{PETO}) values using the fixed-effect model (FEM) for MI, other cardiovascular events, major bleeding, and all-cause mortality were 1.34 (95% CI 1.08 to 1.65, *P*=0.007), 0.93 (95%CI 0.83 to 1.06, *P*=0.270), 0.88 (95% CI 0.79 to 0.99, *P*=0.029), and 0.89 (95% CI 0.80 to 1.00, *P*=0.041). When compared with warfarin, OR_{PETO} values using FEM were 1.41 (95% CI 1.11 to 1.80, *P*=0.005), 0.94 (95%CI 0.83 to 1.06, *P*=0.293), 0.85 (95% CI 0.76 to 0.96, *P*=0.007), and 0.90 (95% CI 0.81 to 1.01, *P*=0.061), respectively. In RCTs using the 150-mg BID dosage, the OR_{PETO} values using FEM were 1.45 (95% CI 1.11 to 1.91, *P*=0.007), 0.95 (95% CI 0.82 to 1.09, *P*=0.423), 0.92 (95% CI 0.81 to 1.05, *P*=0.228), and 0.88 (95% CI 0.78 to 1.00, *P*=0.045), respectively. The results of the 110-mg BID dosage were mainly driven by the RE-LY trial.

***Conclusions*—**This meta-analysis provides evidence that dabigatran etexilate is associated with a significantly increased risk of MI. This increased risk should be considered taking into account the overall benefit in terms of major bleeding and all-cause mortality.
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Key Words: all-cause mortality • dabigatran etexilate • major bleeding • myocardial infarction

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Accompanying Figures S1 through S3 are available at http://jaha.ahajournals.org/content/3/3/e000515/suppl/DC1

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Dabigatran etexilate, the prodrug of dabigatran, an oral direct thrombin inhibitor, is used in Europe and Canada for the prevention of venous thromboembolic events in major orthopaedic surgery. Based on the results of the RE-LY study (Randomized Evaluation of Long-term anticoagulant therapY with dabigatran etexilate), dabigatran etexilate has also been approved for prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) by both the European Commission and the Food and Drug Administration (FDA) as well as in many countries worldwide. Interestingly, myocardial infarction (MI) rates were increased with dabigatran etexilate 110 mg BID and 150 mg BID compared with warfarin. This concern over the increase in MI with dabigatran etexilate has prompted an additional detailed analysis where there was no excess of new angina hospitalizations or revascularization in dabigatran etexilate–treated patients. The net clinical benefit, defined as a composite of stroke, MI, cardiovascular death,

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pulmonary embolism, systemic embolic event, and major bleeding, was in favor of dabigatran etexilate with a rate by 1000 person-years of 73.4, 71.1, and 79.1 for dabigatran etexilate 150 mg BID, dabigatran etexilate 110 mg BID, and warfarin, respectively.[1] A recent systematic review and meta-analysis of the literature evaluating the safety and efficacy of the non–vitamin K antagonist (VKA) oral anticoagulants (NOACs) in atrial fibrillation (AF) showed a significant reduction in total and cardiovascular mortality as well as in the composite outcome of stroke and systemic embolism. No difference in MI was observed. Nevertheless, the fact that all NOACs were pooled together and that only AF population was included, prevents the assessment of the risk related to a specific product.[2]

The risk of MI associated with the use of dabigatran etexilate was assessed in a previous meta-analysis of 7 noninferiority randomized controlled trials (RCTs) showing a significant 33% increase in MI corresponding to an absolute risk increase of 0.27% during follow-up.[3] Unfortunately, this analysis incorporated the initial RE-LY publication and did not take into account the additional events subsequently reported.[4] Moreover, the study only included 7 RCTs and did not take into account studies having not demonstrated noninferiority (ie, the RE-MOBILIZE trial).[5] Another recently published meta-analysis, including these additional events as well as data from more recent studies, demonstrated once again an overall significant 30% increase of MI. This meta-analysis also evaluated other NOACs, especially apixaban and rivaroxaban. Nevertheless, even if stratification by indication of use was performed, no information about the risk stratified by dose of dabigatran etexilate or comparator was provided.[6] Moreover, the most recent studies were not included (ie, RE-COVER II and RE-ALIGN).[7,8]

Thus, the question of whether dabigatran etexilate causes MI or is less efficacious than warfarin or other active comparators for the prevention of such events remains unanswered. Today, there is a need for regulators and clinicians to have robust evidence on the potential increased risk of MI when dabigatran etexilate at either a high or a low dose is compared with other anticoagulants or placebo. The need for a more-detailed analysis of the effects of dabigatran on coronary events against the different comparators was pointed out by Holnloser et al[1] Therefore, we performed a meta-analysis of RCTs comparing dabigatran etexilate with active comparators versus placebo to assess the effect of this agent on MI risk as a primary objective. The outcome of other cardiovascular events, major bleeding, and all-cause mortality was also assessed to provide global safety and efficacy measure. Stratifications by comparators (enoxaparin, warfarin, or placebo) were performed. Additional analyses with studies using the 2 licensed doses in the European Union for AF (150 mg BID and 110 mg BID) were also provided.

Methods

Analyzed Studies

The primary aim of this meta-analysis was to assess the risk of MI, other cardiovascular events, major bleeding, and all-cause mortality associated with the use of dabigatran etexilate. We extracted the data from published RCTs mainly due to the fact that a meta-analysis based on individual data would have been too complicated to establish since we did not have access to the data from each RCTs. Therefore, we performed an exhaustive meta-analysis based on data provided in the literature or available in specific registries (ClinicalTrial.gov and the registry maintained by Boerhinger Ingelheim).

Eligibility Criteria

To be included in the meta-analysis, clinical trials should present the following criteria: (1) it should be an RCT and (2) the follow-up should have been the same between the different groups. In addition, (3) the control groups should receive a placebo or the reference treatment when applicable. This meant (3a) warfarin was the reference treatment in patients with NVAF and in the treatment of venous thromboembolism (VTE) or pulmonary embolism; (3b) enoxaparin was the reference treatment for the prevention of VTE events in patients undergoing total hip or knee surgery; and (3c) placebo was used for the prevention of recurrence of coronary events in patients receiving antiplatelet therapy or for the prevention of recurrence of VTE events in patients who had completed a first period of anticoagulant therapy.

Literature Search

We conducted a literature search of journal articles in 3 different databases (PubMed, Scopus, and The Cochrane Database–Trials Results) published on or before December 8, 2013, assessing dabigatran etexilate versus control group in RCTs. The following key words were used: “dabigatran,” “dabigatran etexilate,” “BIBR 1048,” “randomized controlled trial,” “randomized clinical trial,” “randomized trial,” “randomised controlled trial,” “randomised clinical trial,” or “randomised trial” (see Supporting information for the complete literature search). We considered only English-language publications. We also searched for abstracts published during the past 3 years at international congresses (American Heart Association, International Society on Thrombosis and Haemostasis, and American Society of Haematology). Moreover, we performed a hand search of all the references of previous meta-analyses of RCTs with dabigatran etexilate.[3,9] The initial search of the 3 databases was performed by JD; the references obtained were screened independently by 2

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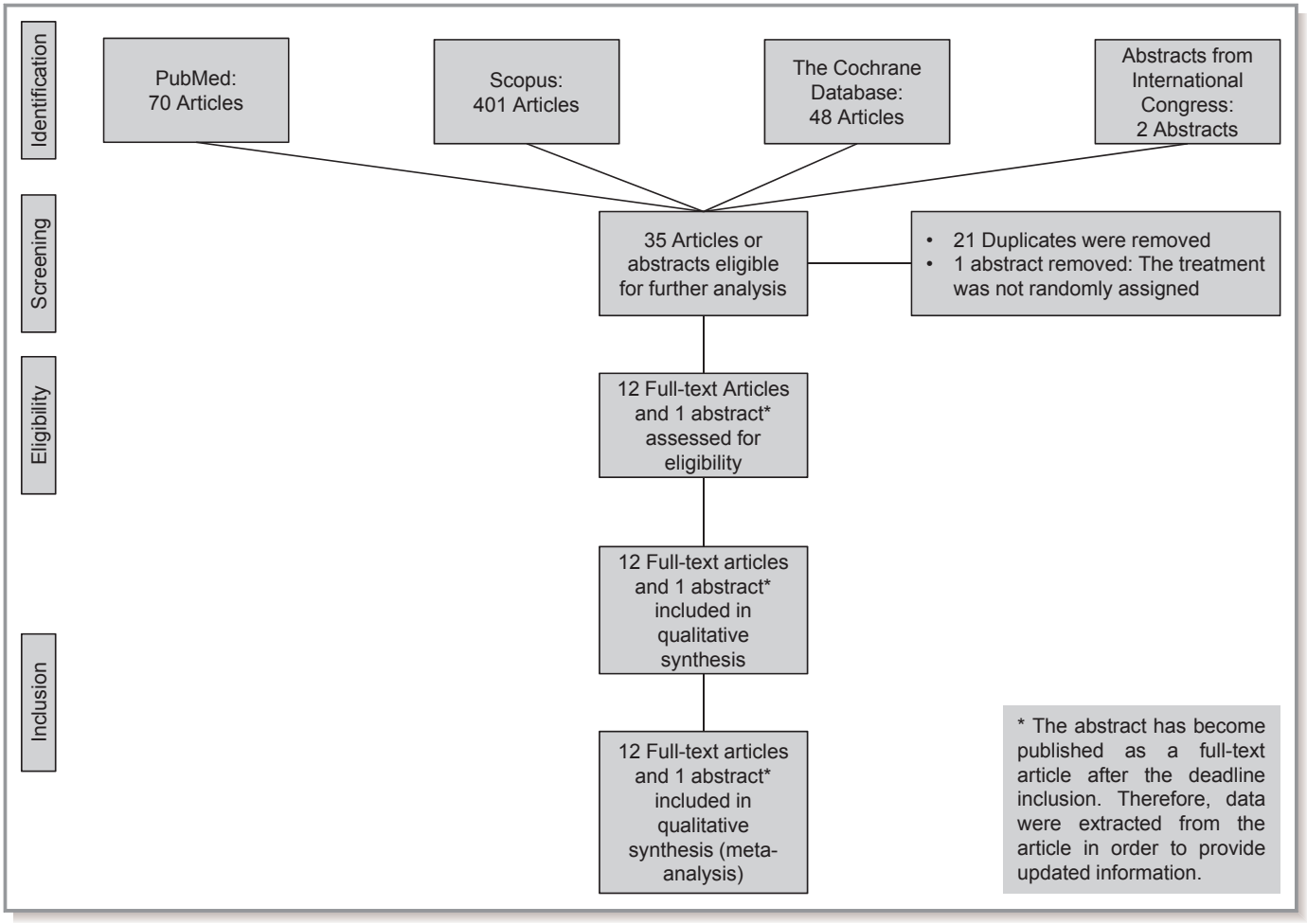

Figure 1. PRISMA (preferred reporting items for systematic reviews and meta-analysis) flow diagram of study selection.

investigators (JD and FB). The reason for exclusion was noted for rejected articles (Figure 1). Consensus for inclusion was reached after assessment by an other reviewer (JMD). Data were encoded by an independent analyst (VR).

Outcome Definitions

Table 1 summarizes outcomes definitions provided in included RCTs. For all outcomes of interest (ie, MI, other cardiovascular events, major bleeding, and all-cause mortality), we referred to the definition provided the studies to identify and extract the data.

Table 2 identifies all outcomes of interest provided in the included RCTs. When specified, only MI was considered for inclusion. With the exception of the RE-DEEM, RE-COVER, and RE-MEDY trials and the updated results of the RE-LY study,[1,4,10–12] included trials did not describe adjudication of MI or other cardiovascular events. Thus, when unspecified, acute coronary syndromes (ACS) or cardiac serious adverse events were classified as MI for conservative purposes. When adjudicated, fatal MI events were not added in the MI group since they were already counted as MI in trials identified in the meta-analysis (eg, in the RE-LY trial, fatal MI was considered as MI leading to death within 30 days).[1] For the RE-DEEM trial, we only included nonfatal MI since cardiovascular death included cardiac fatal outcome other than MI.[10] When specified, other cardiovascular events were defined as unstable angina; cardiac arrest; cardiac death including sudden death, arrhythmic death, pump failure of post-MI; coronary artery bypass graft surgery; and percutaneous coronary intervention. Importantly, the definition of major bleeding varied among studies. Therefore, we use the definition of major bleeding proposed within each study.

Data Extraction

Information was extracted from each included trial on (1) study design and other information (year of publication, design), (2) characteristics of trial participants (including number of patients, age, sex), (3) type of intervention (including type,

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Table 1. Characteristics of Included Randomized Controlled Trials

Source	Design and Population	Cardiac Outcome	Efficacy Outcome	Safety Outcome	Dabigatran Etexilate Regimen	Control Regimen	Treatment Duration	Mean Age (±SD)	% Male	Jadad Score
BISTRO II[21], 2004 (NCT01225822)	DB, DD, phase II, DVT prophylaxis in hip or knee replacement	None provided	Incidence of VTE	Major bleedings	DE50 (N=389) DE150 (N=390) DE225 (N=393) per os, BID DE300 (N=385) per os, once daily	Enoxaparin 40 mg (N=392)	Design : 6 to 10 days Result: median 7 days Follow-up: 4 to 6 weeks	D50: 66 (31 to 88) D150: 66 (34 to 89) D225: 66 (33 to 93) D300: 67 (33 to 93)	D50: 166 (43%) D150:1386 (35%) D225: 164 (42%) per os, BID D300: 139 (36%) per os, once daily	5
RE-NOVATE[23], 2007 (NCT00168818)	DB, DD, NI DVT prophylaxis in hip replacement	Composite of confirmed unstable angina, myocardial infarction and cardiac death	Composite of total VTE and all-cause mortality during treatment period	Occurrence of bleeding events during study treatment	DE150 (N=1163) DE220 (N=1146) per os, once daily	Enoxaparin 40 mg (n=1154) subcutaneous, once daily	Design: 28 to 35 days Result: median 33 days Follow-up: 94 days	DE150: 63±11 DE220: 65±10 Enoxaparin: 64±11	DE150: 496 (43%) DE220: 510 (44%) Enoxaparin: 503 (44%)	5
RE-MODEL[24], 2007 (NCT00168805)	DB, NI, DVT prophylaxis in knee replacement	Composite of confirmed unstable angina, myocardial infarction, and cardiac death	Composite of total VTE and all-cause mortality during treatment period	Occurrence of bleeding events during study treatment	DE150 (N=703) DE220 (N=679) per os, once daily	Enoxaparin 40 mg (n=694) subcutaneous, once daily	Design: 6 to 10 days Result: median 8 days Follow-up: 3 months	DE150: 68±9 DE220: 67±9 Enoxaparin: 68±9	DE150: 252 (36%) DE220: 238 (35%) Enoxaparin: 216 (31%)	5
PETRO[22], 2007 (NCT01227629)	OL for DE or warfarin, DB for DE dose Atrial fibrillation	Angina, acute coronary syndrome	*Primary outcome:* frequency of bleeding events		DE50 (N=105) DE150 (N=166) DE300 (N=161) per os, BID	Adjusted-dose warfarin (target INR 2.0 to 3.0) (N=70)	Design: 12 weeks	DE50: 70±9 DE150: 70±8 DE300: 70±8 Warfarin: 69±8	DE50: 84 (80%) DE150: 135 (81%) DE300: 133 (83%) Warfarin: 59 (84%)	2
RE-MOBILIZE[5], 2009 (NCT00152971)	DB, NI, DVT prophylaxis in knee replacement	Cardiac serious adverse events (undefined)	Composite of total VTE events and all-cause mortality during treatment	Incidence of bleeding events during study treatment	DE150 (N=871) DE220 (N=857) per os, once daily	Enoxaparin 30 mg (N=868) subcutaneous, BID	Result: median 14 days in both groups Follow-up: 6 months	DE150: 66±10 DE220: 66±10 Enoxaparin: 66±10	DE150: 364 (42%) DE220: 371 (43%) Enoxaparin: 364 (42%)	5

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Table 1. Continued

Source	Design and Population	Cardiac Outcome	Efficacy Outcome	Safety Outcome	Dabigatran Etexilate Regimen	Control Regimen	Treatment Duration	Mean Age (±SD)	% Male	Jadad Score
RE-LY[25], 2009 (NCT00262600)	OL for warfarin, DB for DE dose Atrial Fibrillation	Myocardial infarction, unstable angina, cardiac death, cardiac arrest, PCI, or CABG	Stroke or systemic embolism	Major hemorrhage	DE110 (N=6015) DE150 (N=6076) per os, BID	Adjusted-dose warfarin (target INR 2.0 to 3.0) (N=6022)	Design: duration of recruitment, with more than 1 year for all participant Result: median 2 years	DE110: 71±9; DE150:72±9; warfarin: 72±9 All: 72	DE110: 3865 (64%) DE150: 3840 (63%) warfarin: 3809 (60%) All: 64%	3
RE-COVER[11], 2009 (NCT00291330)	DB, DD treatment of acute venous thromboembolism	Acute coronary syndrome (stratified as any or myocardial infarction)	Composite of symptomatic VTE or deaths associated with VTE in the 6 months after random assignment	Major bleeding events	DE150 (N=1273) per os, BID	Adjusted-dose warfarin (target INR 2.0 to 3.0) (N=1266)	Design: 6 months Result: median DE 150: 163±50 warfarin: 164±50	DE150: 55±16 warfarin : 54±16	DE150: 738 (58%) warfarin: 746 (59%)	5
Fuji[20], 2010 (NCT00246025)	DB, parallel-group placebo controlled, DVT prophylaxis in knee arthroplasty	None provided	Composite of total VTE events and all-cause mortality during treatment	Occurrence of bleeding events	DE110 (N=133) DE150 (N=126) DE220 (N=129) per os, once daily	Placebo (N=124)	Design: 11 to 14 days Results: median 12 days Follow-up: 7 to 10 days	DE110: 71±8 DE150: 71±8 DE220: 73±7 Placebo: 71±9	DE110: 27 (20%) DE150: 21 (17%) DE220: 20 (16%) Placebo: 19 (15%)	5
RE-NOVATE II[26], 2011 (NCT00657150)	DB, DD, DVT prophylaxis in hip replacement	Myocardial infarction (undefined)	Composite of total VTE and all-cause mortality during treatment period	Incidence of major bleedings during treatment	DE220 (N=1010) per os, once daily	Enoxaparin 40 mg (N=1003) Subcutaneous, once daily	Design: 28 to 35 days Result: median 32 days Follow-up: DE: 92 days Enoxaparin: 93 days	DE220: 62±12 Enoxaparin : 62±11	DE220: 469 (46%) Enoxaparin: 502 (50%)	5
RE-DEEM[10], 2011 (NCT00621855)	DB, dose escalation Acute coronary syndrome	Nonfatal MI, severe recurrent ischemia	*Secondary outcome:* Indicators of efficacy such as reduction in D-dimer levels and incidences of cardiovascular ischemic events	*Primary outcome:* Incidence of major or clinically relevant minor bleeding	DE50 (N=369) DE75 (N=368) DE110 (N=406) DE150	Placebo (N=371)	Design: 6 month Results: mean 158 to 164 day by group	DE 50: 62±12 DE 75: 61±12 DE 110:62±11 DE 150: 62±11	DE 50: 77.2% DE 75: 79.9% DE 110: 71.2% DE 150: 73.2%	4

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Table 1. Continued

Source	Design and Population	Cardiac Outcome	Efficacy Outcome	Safety Outcome	Dabigatran Etexilate Regimen	Control Regimen	Treatment Duration	Mean Age (±SD)	% Male	Jadad Score
					(N=347) per os, BID			Placebo: 62±11	Placebo : 78.4% *no absolute number reported*	
RE-MEDY[12], 2013 (NCT00291330)	DB patient with VTE who had completed 3 to 12 months of anticoagulant therapy	Acute coronary syndromes (stratified as MI or unstable angina)	Recurrent symptomatic and objectively verified VTE or death associated with VTE	Major bleeding and clinically relevant nonmajor bleeding	DE150 (N=1430) per os, BID	Adjusted-dose warfarin (target INR: 2.0 to 3.0) (N=1426)	Design: 6 to 36 months Results: DE150: 473±211 days warfarin: 474±206 days	DE150: 55±15 warfarin: 54±15	DE150: 871 (61%) warfarin: 871 (61%)	5
RE-SONATE[12], 2013 (NCT00558259)	DB patient with VTE who had completed 6 to 18 months of anticoagulant therapy	Acute coronary syndromes (stratified as MI or unstable angina)	Recurrent symptomatic and objectively verified VTE or death associated with VTE	Major bleeding and clinically relevant nonmajor bleeding	DE150 (N=681) per os, BID	Placebo (N=662)	Design: 6 months Results: DE150: 165±45 days Placebo: 162±47 days	DE150: 56±16 Placebo: 56±15	DE150: 381 (56%) Placebo: 364 (55%)	5
RE-ALIGN[8], 2013 (NCT01452347)	DB, patients undergoing implantation of a mechanical bileaflet valve in the aortic or mitral position or both (population A) or patients having undergone implantation of a mechanical bileaflet mitral valve (with or without mechanical bileaflet aortic valve replacement) more than 3 months before randomization (population B)	Myocardial infarction	Stroke, systemic embolism, transient ischemic attack, valve thrombosis, bleeding, venous thromboembolism, and death.	Bleeding	DE150 (N=11) DE220 (N=71) DE300 (N=45) per os, BID	warfarin (N=84)	Design: 12 weeks Results: Population A: DE group: 143 days warfarin group: 152 days Population B: DE group: 136 days warfarin group: 143 days	DE: 56±9 warfarin: 56±10	DE: 107 (64%) warfarin: 56 (67%)	5

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Table 1. Continued

Source	Design and Population	Cardiac Outcome	Efficacy Outcome	Safety Outcome	Dabigatran Etexilate Regimen	Control Regimen	Treatment Duration	Mean Age (±SD)	% Male	Jadad Score
RE-COVER II[18], 2013 (NCT00680186)	DB, DD, Treatment of acute venous thromboembolism	Acute coronary syndrome (stratified as any or myocardial infarction)	Frequency of recurrent symptomatic, objectively confirmed VTE and deaths related to VTE during 6 months	Bleedings events	DE150 (N=1279) per os, BID	Adjusted-dose warfarin (target INR 2.0 to 3.0) (N=1289)	Design: 6 months	DE150: 55±16 warfarin: 55±16	DE150: 499 (39%) warfarin: 512 (40%)	5

CABG indicates coronary artery bypass graft surgery; DB, double-blind; DD, double dummy; DE, dabigatran etexilate; DVT, deep vein thrombosis; MI, myocardial infarction; NI, noninferiority; OL, open-label; PCI, percutaneous coronary intervention; VTE, venous thromboembolism.

duration, control and dabigatran etexilate regimens), and data on (4) MI, (5) other cardiovascular events, (6) major bleeding and (7) all-cause mortality, when available. When no information concerning MI, other cardiovascular events, major bleeding, or all-cause mortality was available, corresponding authors were contacted to collect missing data, with a reminder after 15 days.

Secondary Analysis

Stratification by comparators and a specific analysis of 2 European Union–licensed doses of dabigatran etexilate for NVAF (ie, the 150 mg BID and 110 mg BID dosage regimens) were performed as secondary analysis. In the primary analysis, multiple groups of patients who received dabigatran etexilate within a single trial were pooled together while for secondary analysis, only patients treated by dabigatran etexilate 150 mg BID or 110 mg BID regimen were included versus the control group. The control group was defined as patients receiving any drug regimen other than dabigatran etexilate.

Assessment of the Quality of the Included Studies

To ascertain the validity of the eligible randomized trials, pairs of reviewers (JD and FB), working independently, assessed study quality using a validated scale (Jadad score)[13] based on the following criteria: method used to generate the randomization sequence, method of double blinding, and description of patient withdrawals and dropouts. A score of 1 point was given for each criterion satisfied and 1 additional point for high-quality randomization and double blinding, for a maximum of 5 points. Studies with a score >2 were considered high quality and studies with a score ≤2 points were considered low quality.

Statistical Analysis

We performed the analysis using a fixed-effect model and a random-effect model to give all relevant results even when the heterogeneity might be high. For the fixed-effect model, the odds ratio (OR) and 95% CI were calculated with the use of the Peto method since there were few events in the included trials.[14,15] This method, also known as the 1-step method, works on the log OR scale and is a variant of the basic inverse-variance approach. Thus, the use of this method allows calculation of an OR even with zero events in 1 treatment arm. However, trials in which patients had no outcome of interest in either group were excluded from analyses because OR cannot be calculated with the Peto method in this case.[14] It has been shown that the Peto method provides the least biased and most powerful results

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Table 2. Summary of the Odds Ratios for the Different Analysis Using the Fixed-Effect Model (Using the Peto Method) or the Random-Effect Model (Using the Inverse-Variance Method)

	Odds Ratios (95% CI)				Heterogeneity for the Fixed-Effect Model	
	Fixed-Effect Model (Peto Method)	*P* Value	Random-effect model (Inverse-Variance Method)	*P* Value	I^2 Statistics	Q Test *P* Value
Myocardial infarction						
Any dose vs any control treatments	1.34 (1.08 to 1.65)	0.007	1.30 (1.04 to 1.63)	0.021	0	0.577
Any dose vs enoxaparin	0.96 (0.57 to 1.60)	0.869	0.95 (0.57 to 1.59)	0.849	0	0.869
Any dose vs warfarin	1.41 (1.11 to 1.80)	0.005	1.38 (1.06 to 1.78)	0.015	22.990	0.261
Any dose vs placebo	1.67 (0.76 to 3.69)	0.202	1.84 (0.69 to 4.89)	0.222	0	0.689
150 mg BID vs any control treatments	1.45 (1.11 to 1.91)	0.007	1.41 (1.06 to 1.86)	0.018	13.558	0.328
150 mg BID vs enoxaparin	NA		NA		NA	NA
150 mg BID vs warfarin	1.43 (1.08 to 1.89)	0.014	1.77 (0.89 to 3.52)	0.105	43.173	0.152
150 mg BID vs placebo	1.89 (0.66 to 5.41)	0.239	1.91 (0.63 to 5.77)	0.254	0	0.613
110 mg BID vs any control treatments	1.33 (0.99 to 1.77)	0.057	1.33 (0.99 to 1.78)	0.058	0	0.760
110 mg BID vs enoxaparin	NA		NA		NA	NA
110 mg BID vs warfarin	NA		NA		NA	NA
110 mg BID vs placebo	NA		NA		NA	NA
Other cardiovascular events						
Any dose vs any control treatments	0.93 (0.83 to 1.06)	0.270	0.94 (0.83 to 1.05)	0.270	0	0.963
Any dose vs enoxaparin	NA		NA		NA	NA
Any dose vs warfarin	0.94 (0.83 to 1.06)	0.293	0.94 (0.83 to 1.06)	0.293	0	0.873
Any dose vs placebo	NA		NA		NA	NA
150 mg BID vs any control treatments	0.95 (0.82 to 1.09)	0.423	0.94 (0.82 to 1.09)	0.423	0	0.962
150 mg BID vs enoxaparin	NA		NA		NA	NA
150 mg BID vs warfarin	0.95 (0.82 to 1.09)	0.454	0.95 (0.82 to 1.09)	0.454	0	0.879
150 mg BID vs placebo	NA		NA		NA	NA
110 mg BID vs any control treatments	0.91 (0.79 to 1.05)	0.206	0.91 (0.79 to 1.05)	0.208	0	0.455
110 mg BID vs enoxaparin	NA		NA		NA	NA
110 mg BID vs warfarin	NA		NA		NA	NA
110 mg BID vs placebo	NA		NA		NA	NA
Major bleeding						
Any dose vs any control treatments	0.88 (0.79 to 0.99)	0.029	0.90 (0.75 to 1.08)	0.241	24.232	0.192
Any dose vs enoxaparin	1.07 (0.78 to 1.47)	0.685	1.04 (0.68 to 1.61)	0.847	41.876	0.142
Any dose vs warfarin	0.85 (0.75 to 0.96)	0.007	0.85 (0.76 to 0.96)	0.007	0	0.495
Any dose vs placebo	2.03 (0.82 to 5.06)	0.128	2.24 (0.73 to 6.90)	0.160	0	0.639
150 mg BID vs any control treatments	0.92 (0.81 to 1.05)	0.228	0.91 (0.67 to 1.23)	0.520	42.907	0.105
150 mg BID vs Enoxaparin	NA		NA		NA	NA
150 mg BID vs warfarin	0.90 (0.79 to 1.02)	0.101	0.84 (0.68 to 1.05)	0.129	19.506	0.292
150 mg BID vs placebo	2.86 (0.71 to 11.47)	0.139	2.62 (0.59 to 11.56)	0.205	0	0.450
110 mg BID vs any control treatments	0.82 (0.71 to 0.95)	0.007	1.41 (0.33 to 5.97)*	0.644*	77.276*	0.036*
110 mg BID vs enoxaparin	NA		NA		NA	NA
110 mg BID vs warfarin	NA		NA		NA	NA
110 mg BID vs placebo	NA		NA		NA	NA

Continued

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Table 2. Continued

	Odds Ratios (95% CI)				Heterogeneity for the Fixed-Effect Model	
	Fixed-Effect Model (Peto Method)	*P* Value	Random-effect model (Inverse-Variance Method)	*P* Value	I^2 Statistics	Q Test *P* Value
All-cause mortality						
Any dose vs any control treatments	0.89 (0.80 to 1.00)	0.041	0.89 (0.80 to 0.99)	0.033	11.026	0.339
Any dose vs enoxaparin	2.24 (0.68 to 7.39)	0.186	1.55 (0.38 to 6.39)	0.542	8.532	0.350
Any dose vs warfarin	0.90 (0.81 to 1.01)	0.061	0.90 (0.81 to 1.01)	0.061	0	0.813
Any dose vs placebo	0.47 (0.23 to 0.947)	0.035	0.54 (0.29 to 1.00)	0.050	0	0.354
150 mg BID vs any control treatments	0.88 (0.78 to 1.00)	0.045	0.88 (0.78 to 1.00)	0.049	0	0.636
150 mg BID vs enoxaparin	NA		NA		NA	NA
150 mg BID vs warfarin	0.89 (0.79 to 1.01)	0.078	0.89 (0.79 to 1.01)	0.079	0	0.955
150 mg BID vs placebo	0.48 (0.21 to 1.09)	0.078	0.48 (0.20 to 1.16)	0.105	0	0.341
110 mg BID vs any control treatments	0.90 (0.79 to 1.02)	0.103	0.74 (0.40 to 1.39)*	0.354*	57.176*	0.126*
110 mg BID vs enoxaparin	NA		NA		NA	NA
110 mg BID vs warfarin	NA		NA		NA	NA
110 mg BID vs placebo	NA		NA		NA	NA

Results are given for all stratifications proposed in this meta-analysis. Results of the heterogeneity are also provided to facilitate the choice of the best model effect.
*A heterogeneity for the fixed-effect model above 50% using the I^2 statistics, or below 0.10 using the Q test, should suggest the use of a random-effect model.
NA indicates not applicable.

when applied to simulated sparse event data with less extreme group imbalances that are typically observed in RCT designs.[14] For the random-effect model, we used a basic inverse-variance analysis. In case that 1 of the arms of 1 study has zero events, 0.5 is added to all cells of the study results table.[14] However, it has been previously asked whether the assumption of the within-study normal distribution is appropriate in case of sparse events. Effectively, in case where the majority or all studies have few events, the choice of the continuity correction really matters.[16] Nevertheless, this method is conceptually simpler and has been proved to work well in cases where there are enough events. In the present study, only a minority of the studies has zero cells so the kind of continuity correction will not matter much and the application of a basic inverse-variance analysis can be justified.

The different comparators had different durations in follow-up, but within a specific comparator, the durations in follow-up were broadly similar (ie, short-term duration: <2 months or long-term duration: ≥6 months). Therefore, the use of ORs represents a valid approach to assess the risk associated with the use of dabigatran etexilate. All reported *P* values were 2-sided.

When applicable, one-way sensitivity analyses were performed by removing a single study, one at the time, to assess the stability of the results. This technique was used in a previous meta-analysis.[17]

Statistical heterogeneity across the various trials was tested using Cochran's Q statistic and quantified using the I^2 value, which indicated the proportion of variability across studies that was due to heterogeneity rather than sampling error. Because there are few studies, Cochran's Q test is not effective at detecting heterogeneity if present. For this reason, a *P* value of <0.10 is often used to indicate heterogeneity rather than the conventional cut-point of $P=0.05$. The I^2 is less dependent on the number of studies. I^2 values of ≈25%, ≈50%, and ≈75% would mean low, medium, and high heterogeneity, respectively. Based on this measure of heterogeneity, we proposed a fixed-effect model or a random-effect model when applicable. Thus, when the heterogeneity is >50% when using the I^2 statistics or when the Q test statistic is <0.10, it is preferable to refer to the random-effect analysis. Otherwise, the use of the fixed-effect model should be recommended.

To investigate whether publication bias might affect the validity of the estimates, funnel plots were constructed. Funnel plot asymmetry was assessed by the method of Egger's linear regression test, a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of OR. The significance of the intercept was determined by the t-test suggested by Egger ($P<0.05$ was considered representative of statistically significant publication bias). The Begg and Mazumdar rank correlation test has also been performed to assess an eventual publication bias. Data were analyzed

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with the use of Comprehensive Meta-Analysis software, version 2.2.046 (Biostat).

Results

Selected Studies

We screened 501 abstracts from the 3 different databases: PubMed (70 sources), Scopus (401 sources), and The Cochrane Database–Trials Results (48 sources). Two abstracts were found from abstracts published in the past 2 years at international congresses (1 from the American Heart Association and 1 from the American Society of Haematology). One abstract (the RE-COVER II study) has become published as a full-text article after the deadline inclusion. Data were therefore extracted from the article to provide the most relevant and up-to-date information.[18] After the abstracts were read, 35 articles were included for further analysis. After duplicates and ineligible articles were removed, 13 articles (for a total of 14 RCTs; 1 article reports the results of 2 RCTs) met the predefined inclusion criteria of having a randomized comparator group, a similar duration of treatment in all groups, and the presence of a treatment arm featuring the use of dabigatran etexilate and a control arm with comparator use (Figure 1). Two of the 14 trials did not report numerically interpretable MI events.[7,19,20] Only 4 studies reported other cardiovascular events.[1,10–12] Three of the 14 trials did not report mortality information.[20–22] No supplementary information was obtained from the investigators, and therefore these trials were not included in the analysis of MI and all-cause mortality. Outcome of major bleeding was available for all trials. Table 1 lists the 14 trials included in this meta-analysis. All of these studies were published in peer-reviewed journals as full articles.[5,8,10–12,18,20–26] Data from these trials were also reported in a summary fashion on a clinical trial registry website maintained by the drug manufacturer Boerhinger Ingelheim.[27]

Baseline Characteristics

Table 1 reports the doses of dabigatran etexilate and comparator; the design of the study and the population; the treatment duration; the efficacy, safety, and cardiac outcomes; and the Jadad score of included studies. All studies gave a Jadad score of 5, except the PETRO, RE-LY, and RE-DEEM trials.[10,22,25] For the PETRO trial, the method used to generate the sequence of randomization was not described and the study was described as double-blind but the method of blinding was inappropriate (open-label for warfarin). For the RE-LY trial, the study was described as double-blind but the method of blinding was inappropriate (open-label for warfarin). For the RE-DEEM trial, the method of blinding was not described.

MI, Other Cardiovascular Events, Major Bleedings, and All-Cause Mortality

Table 2 reports all ORs for the fixed-effect model analysis using the Peto method and for the random-effect model analysis using the inverse-variance method. It also includes testing results for heterogeneity for the risk of MI, other cardiovascular events, major bleeding, and all-cause mortality.

Myocardial Infarction

Data for MI were available for 12 studies.[1,5,8,10–12,18,22–24,26] Figure 2A provides the forest plot for MI stratified by comparator. Table 3 reports all MI events in the included trials. MI occurred in 294 (1.16%) of 25 286 patients treated with dabigatran etexilate and in 108 (0.72%) of 14 909 patients treated with controls. The use of dabigatran etexilate was associated with a significant increase of MI (Peto odds ratio (OR_{PETO}) 1.34, 95% CI 1.08 to 1.65, I^2=0%, Q test P=0.577). When compared with warfarin regimen, MI occurred in 218 (1.31%) of 16 686 patients treated with dabigatran etexilate and in 80 (0.79%) of 10 157 patients treated with control (OR_{PETO} 1.41, 95% CI 1.11 to 1.80, I^2=23%, Q test P=0.261). The 150-mg BID dosage was associated with a higher risk of MI (OR_{PETO} 1.45, 95% CI 1.11 to 1.91, I^2=14%, Q test P=0.328). When compared with warfarin, the OR_{PETO} for MI with the 150-mg BID dosage was 1.43 (95% CI 1.08 to 1.89, I^2=43%, Q test P=0.152) (Figure 3A). Regarding the 110-mg BID dosage, the OR_{PETO} is 1.33 (95% CI 0.99 to 1.77, I^2=0%, Q test P=0.760).

Overall one-way sensitivity analysis shows that similar results are obtained regardless of which study is excluded from the primary analysis, even when RE-LY is removed (see Figure S1A). All one-way sensitivity analyses preserve a significant increase of MI associated with dabigatran etexilate when compared with warfarin (see Figure S2A).

Other Cardiovascular Events

Other cardiovascular events were provided in only 4 RCTs (in the RE-DEEM, RE-LY, RE-COVER, and RE-MEDY studies). Table 4 mentions all other cardiovascular events reported in the included trials. There were 844 (5.18%) of 16 284 and 432 (4.76%) of 9085 in the dabigatran etexilate and comparator groups, respectively. No results were statistically significant (Table 2). A forest plot comparing dabigatran etexilate or dabigatran etexilate at the dosage of 150 mg BID with any control treatment is provided in Figures 2B and 3B, respectively. One-way sensitivity analysis reveals similar results regardless of what study is removed from the result (see Figures S1B and S2B).

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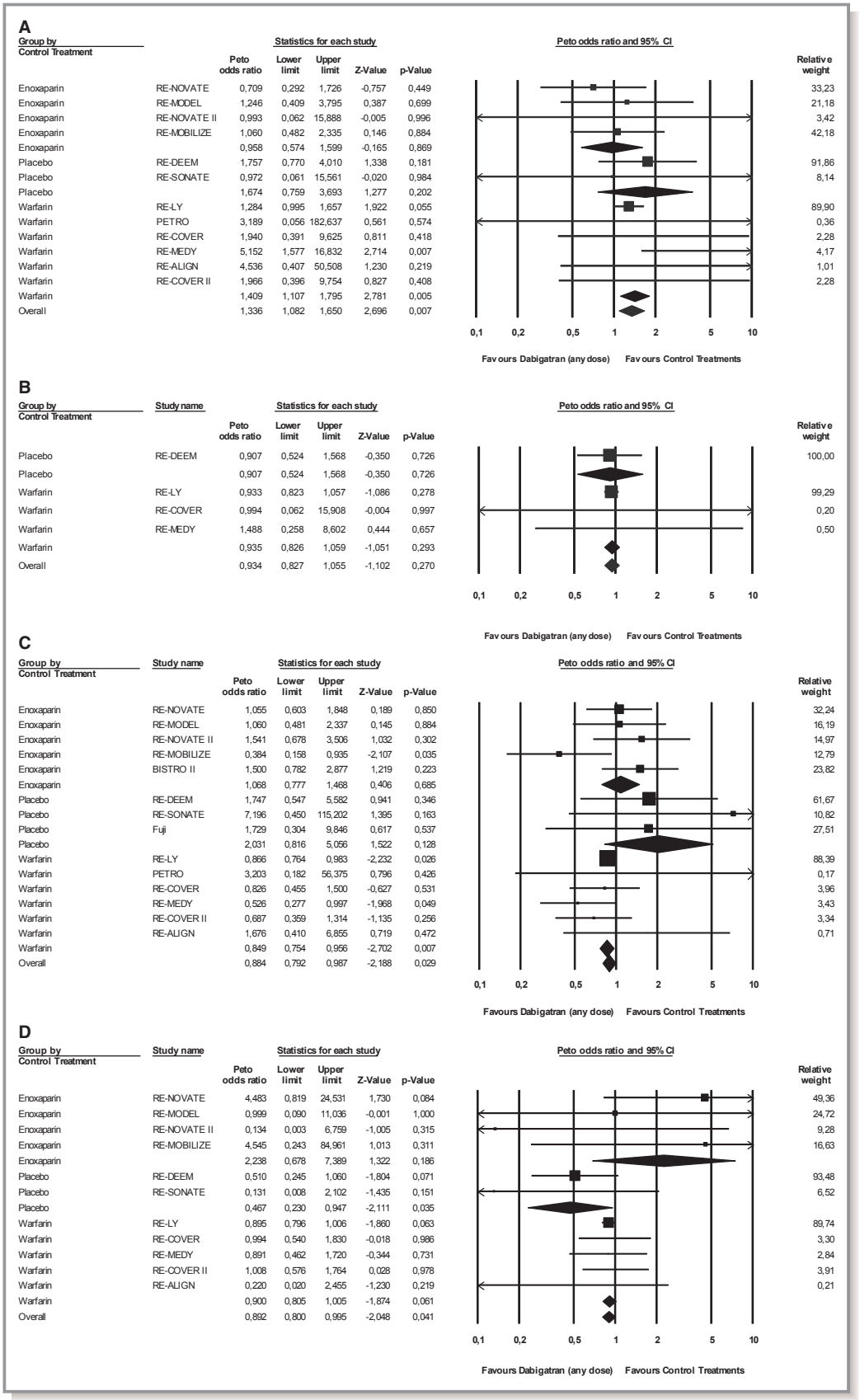

Figure 2. Forest plot of the included studies for the risk of (A) myocardial infarction, (B) other cardiovascular events, (C) major bleeding, and (D) all-cause mortality (fixed-effect model analyses using the Peto method).

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Table 3. Rates of Myocardial Infarction Across the Included Studies, Stratified by Comparator

Study	Dabigatran Etexilate	Control	Odds Ratio (95% CI)		Relative Weight (%)	
	No. of Events/Total No. (%)		Fixed-Effect Model	Random-Effect Model	Fixed-Effect Model	Random-Effect Model
BISTRO II[21] (NCT01225822) 2004	No myocardial infarction reported					
RE-NOVATE[23] (NCT00168818) 2007	13/2309 (0.56)	9/1154 (0.78)	0.71 (0.29 to 1.73)	0.72 (0.31 to 1.69)	5.62	6.90
RE-MODEL[24] (NCT00168805) 2007	10/1382 (0.72)	4/694 (0.58)	1.25 (0.41 to 3.80)	1.26 (0.39 to 4.02)	3.58	3.71
RE-MOBILIZE[5] (NCT00152971) 2009	19/1728 (1.10)	9/868 (1.04)	1.06 (0.48 to 2.34)	1.06 (0.48 to 2.36)	7.14	7.90
RE-NOVATE II[26] (NCT00657150) 2011	1/1010 (0.10)	1/1003 (0.10)	0.99 (0.06 to 15.89)	0.99 (0.06 to 15.90)	0.58	0.65
Overall enoxaparin	43/6429 (0.67)	23/3719 (0.62)	0.96 (0.57 to 1.60) *P*=0.869	0.95 (0.57 to 1.59) *P*=0.849	16.92	19.16
PETRO[22] (NCT01227629) 2007	2/445 (0.45)	0/70 (0.00)	3.19 (0.06 to 182.64)	0.80 (0.04 to 16.73)	0.27	0.54
RE-LY[25] (NCT00262600) 2009	195/12 091 (1.61)	75/6022 (1.25)	1.28 (1.00 to 1.66)	1.30 (0.99 to 1.70)	68.31	69.83
RE-COVER[11] (NCT00291330) 2009	4/1273 (0.31)	2/1266 (0.16)	1.94 (0.39 to 9.63)	1.99 (0.36 to 10.90)	1.73	1.74
RE-MEDY[12] (NCT00291330) 2013	10/1430 (0.70)	1/1426 (0.07)	5.15 (1.58 to 16.83)	10.04 (1.28 to 78.50)	3.17	1.19
RE-ALIGN[8] (NCT01452347) 2013	3/168 (0.02)	0/84 (0.00)	4.54 (0.41 to 50.51)	3.57 (0.18 to 70.00)	0.77	0.57
RE-COVER II[18] (NCT00680186) 2011	4/1279 (0.31)	2/1289 (0.16)	1.97 (0.40 to 9.75)	2.02 (0.37 to 11.04)	1.73	1.74
Overall warfarin	218/16 686 (1.31)	80/10 157 (0.79)	1.41 (1.11 to 1.80) *P*=0.005	1.38 (1.06 to 1.78) *P*=0.015	75.98	75.61
Fuji[20] (NCT00246025) 2010	No myocardial infarction reported					
RE-DEEM[10] (NCT00621855) 2011	32/1490 (2.15)	4/371 (1.08)	1.76 (0.77 to 4.01)	2.01 (0.71 to 5.73)	6.52	4.59
RE-SONATE[12] (NCT00558259) 2013	1/681 (0.15)	1/662 (0.15)	0.97 (0.06 to 15.56)	0.97 (0.06 to 15.57)	0.58	0.65
Overall placebo	33/2171 (1.52)	5/1033 (0.48)	1.67 (0.76 to 3.69) *P*=0.202	1.84 (0.69 to 4.89) *P*=0.222	7.10	5.24
Overall	287/23 839 (1.20)	106/13 536 (0.78)	1.34 (1.08 to 1.65) *P*=0.007	1.30 (1.04 to 1.63) *P*=0.021	100.00	100.00

For the pooled results of 1 comparator, the odds ratio is provided for a fixed-effect model using the Peto method and for a random-effect model using the inverse-variance method. Relative weight of each study is also mentioned for these 2 different models. NA indicates not applicable.

Major Bleeding

Figure 2C provides a forest plot for major bleeding stratified by comparator. Table 5 reports all major bleeding events mentioned in the included trials. Major bleeding occurred in 955 (3.51%) of 27 231 patients treated with dabigatran etexilate and in 553 (3.59%) of 15 425 patients treated with controls. Use of dabigatran etexilate was associated with a significant reduction of major bleeding (OR_{PETO} 0.88, 95% CI 0.79 to 0.99, I^2=24%, Q test *P*=0.192). Compared with warfarin regimen, major bleeding occurred in 800 (4.79%) of 16 686 of patients treated with dabigatran etexilate and in 494 (4.86%) of 10 157 patients treated with warfarin. The OR_{PETO} for major bleeding versus warfarin regimen was 0.85 (95% CI 0.75 to 0.96, I^2=0%, Q test *P*=0.495). Figure 3B reports the overall OR_{PETO} for the 150-mg BID dosage according to the comparator. No results are statistically significant. Regarding the 110-mg BID dosage, the OR_{PETO} was 0.82 (95% CI 0.71 to 0.95, I^2=77%, Q test *P*=0.036). However, when using the random-effect model, the $OR_{inverse\text{-}variance}$ was 1.41 and not statistically significant (95% CI, 0.33 to 5.97).

For the main analysis, overall one-way sensitivity analysis showed that similar results were obtained regardless of which study was excluded except when RE-LY, RE-MEDY, or RE-MOBILIZE was removed, when a trend of a reduction in the

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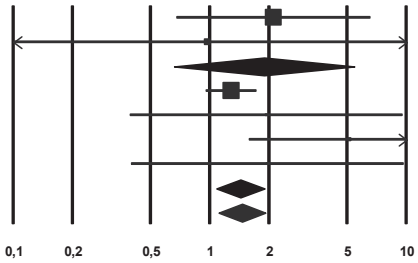
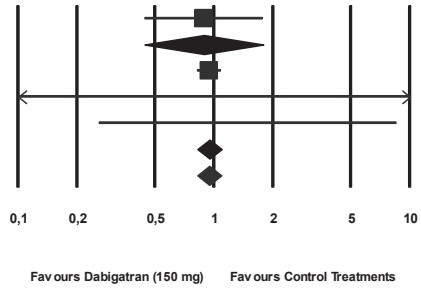
A

Group by Control Treatment		Statistics for each study: Peto odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Placebo	RE-DEEM	2,108	0,674	6,598	1,281	0,200	85,52
Placebo	RE-SONATE	0,972	0,061	15,561	-0,020	0,984	14,48
Placebo		1,885	0,656	5,413	1,177	0,239	
Warfarin	RE-LY	1,285	0,951	1,736	1,631	0,103	88,08
Warfarin	RE-COVER	1,940	0,391	9,625	0,811	0,418	3,11
Warfarin	RE-MEDY	5,152	1,577	16,832	2,714	0,007	5,69
Warfarin	RE-COVER II	1,966	0,396	9,754	0,827	0,408	3,11
Warfarin		1,427	1,076	1,893	2,467	0,014	
Overall		1,454	1,107	1,910	2,687	0,007	



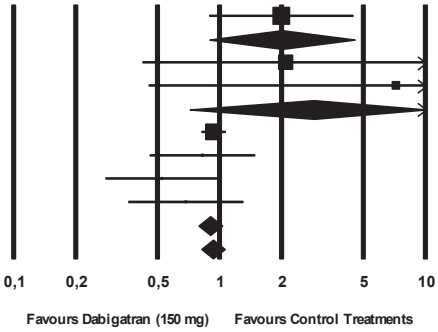
B

Group by Control Treatment	Study name	Statistics for each study: Peto odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Placebo	RE-DEEM	0,887	0,441	1,783	-0,338	0,735	100,00
Placebo		0,887	0,441	1,783	-0,338	0,735	
Warfarin	RE-LY	0,944	0,818	1,089	-0,788	0,431	99,08
Warfarin	RE-COVER	0,994	0,062	15,908	-0,004	0,997	0,26
Warfarin	RE-MEDY	1,488	0,258	8,602	0,444	0,657	0,66
Warfarin		0,947	0,821	1,092	-0,748	0,454	
Overall		0,945	0,822	1,086	-0,801	0,423	



C

Group by Control Treatment	Study name	Statistics for each study: Peto odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Enoxaparin	BISTRO II	1,998	0,887	4,501	1,670	0,095	100,00
Enoxaparin		1,998	0,887	4,501	1,670	0,095	
Placebo	RE-DEEM	2,095	0,420	10,447	0,902	0,367	74,87
Placebo	RE-SONATE	7,196	0,450	115,202	1,395	0,163	25,13
Placebo		2,857	0,711	11,473	1,480	0,139	
Warfarin	RE-LY	0,935	0,811	1,077	-0,928	0,353	86,70
Warfarin	RE-COVER	0,826	0,455	1,500	-0,627	0,531	4,91
Warfarin	RE-MEDY	0,526	0,277	0,997	-1,968	0,049	4,25
Warfarin	RE-COVER II	0,687	0,359	1,314	-1,135	0,256	4,14
Warfarin		0,895	0,785	1,022	-1,640	0,101	
Overall		0,923	0,811	1,051	-1,207	0,228	



D

Group by Control Treatment	Study name	Statistics for each study: Peto odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Placebo	RE-DEEM	0,539	0,226	1,284	-1,395	0,163	91,08
Placebo	RE-SONATE	0,131	0,008	2,102	-1,435	0,151	8,92
Placebo		0,475	0,208	1,088	-1,760	0,078	
Warfarin	RE-LY	0,883	0,772	1,010	-1,818	0,069	87,15
Warfarin	RE-COVER	0,994	0,540	1,830	-0,018	0,986	4,22
Warfarin	RE-MEDY	0,891	0,462	1,720	-0,344	0,731	3,63
Warfarin	RE-COVER II	1,008	0,576	1,764	0,028	0,978	5,00
Warfarin		0,894	0,789	1,013	-1,760	0,078	
Overall		0,881	0,779	0,997	-2,003	0,045	

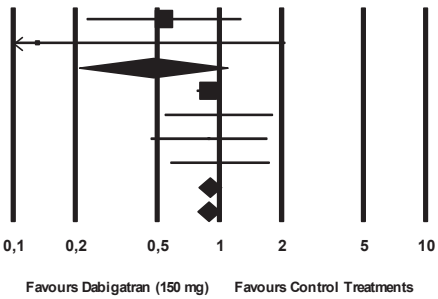


Figure 3. Forest plot of the included studies for the risk of (A) myocardial infarction, (B) other cardiovascular events, (C) major bleeding, and (D) all-cause mortality with the 150-mg BID dosage regimen (fixed-effect model analyses using the Peto method).

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Table 4. Rates of Other Cardiovascular Events Across the Included Studies, Stratified by Comparator

Study	Dabigatran etexilate	Control	Odds Ratio (95% CI)		Relative Weight (%)	
	No. of Events/Total No. (%)		Fixed-Effect Model	Random-Effect Model	Fixed-Effect Model	Random-Effect Model
BISTRO II[21] (NCT01225822) 2004	No other cardiovascular events reported					
RE-NOVATE[23] (NCT00168818) 2007	No other cardiovascular events reported					
RE-MODEL[24] (NCT00168805) 2007	No other cardiovascular events reported					
RE-MOBILIZE[5] (NCT00152971) 2009	No other cardiovascular events reported					
RE-NOVATE II[26] (NCT00657150) 2011	No other cardiovascular events reported					
Overall enoxaparin	Not applicable					
PETRO[22] (NCT01227629) 2007	No other cardiovascular events reported					
RE-LY[25] (NCT00262600) 2009	774/12 091 (6.40)	411/6022 (6.83)	0.93 (0.82 to 1.06)	0.93 (0.83 to 1.06)	94.41	94.29
RE-COVER[11] (NCT00291330) 2009	1/1273 (0.08)	1/1266 (0.08)	0.99 (0.06 to 15.91)	0.99 (0.06 to 15.92)	0.19	0.19
RE-MEDY[12] (NCT00291330) 2013	3/1430 (0.21)	2/1426 (0.14)	1.49 (0.26 to 8.60)	1.50 (0.25 to 8.97)	4.92	5.07
RE-ALIGN[8] (NCT01452347) 2013	No other cardiovascular events reported					
RE-COVER[18] ((NCT00680186) 2013	No other cardiovascular events reported					
Overall warfarin	778/15 239 (5.10)	414/8784 (4.71)	0.94 (0.83 to 1.06) *P*=0.293	0.94 (0.83 to 1.05) *P*=0.293	99.52	99.52
Fuji[20] (NCT00246025) 2010	No myocardial infarction reported					
RE-DEEM[10] (NCT00621855) 2011	66/1490 (4.43)	18/371 (4.85)	0.91 (0.52 to 1.57)		0.48	0.45
RE-SONATE[12] (NCT00558259) 2013	No other cardiovascular events reported					
Overall placebo	Not applicable					
Overall	844/16 284 (5.18)	432/9085 (4.76)	0.93 (0.83 to 1.06) *P*=0.270	0.94 (0.83 to 1.05) *P*=0.270	100.00	100.00

For the pooled results of 1 comparator, the odds ratio is provided for a fixed-effect model using the Peto method and for a random-effect model using the inverse-variance method. Relative weight of each study is also mentioned for these 2 different models. NA indicates not applicable.

risk of major bleeding was maintained but no longer statistically significant (see Figure S1C). All one-way sensitivity analyses preserved a significant reduction in the risk of major bleeding with dabigatran etexilate when compared with warfarin except when RE-LY was removed (see Figure S2C).

All-Cause Mortality

Data for all-cause mortality were available in 11 studies.[1,5,7,10–12,23,24,26] Figure 2D provides a forest plot for all-cause mortality stratified by comparator. Table 6 reports all-cause mortality events in the included studies. Death occurred in 990 (4.07%) of 24 330 patients treated with dabigatran etexilate and in 572 (3.92%) of 14 582 patients treated with controls. Use of dabigatran etexilate was associated with a significant reduction of all-cause mortality (OR_{PETO} 0.89, 95% CI 0.80 to 1.00, I^2=11%, Q test *P*=0.339). When compared with warfarin regimen, all-cause mortality occurred in 948 (5.84%) of 16 241 patients treated with dabigatran etexilate and in 554 (5.49%) of 10 087 patients treated with warfarin. The OR_{PETO} for all-cause mortality versus warfarin regimen was 0.90 (95% CI 0.81 to 1.01, I^2=0%, Q test *P*=0.813). There was a significant reduction of all-cause mortality with the 150-mg BID dosage (OR 0.88, 95% CI 0.78 to 1.00, I^2=0%, Q test *P*=0.636) (Figure 3C). The 110-mg BID dosage showed an OR_{PETO} of 0.90 (95% CI 0.79 to 1.02, I^2=57%, Q test *P*=0.126). The use of a random-effect model using the inverse-variance method did not change the result, which was also nonsignificant.

Overall one-way sensitivity analysis showed that similar results were obtained regardless of which study was excluded except when RE-LY and RE-DEEM were removed, when a trend

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Table 5. Rates of Major Bleeding Across the Included Studies, Stratified by Comparator

Study	Dabigatran Etexilate	Control	Odds Ratio (95% CI)		Relative Weight (%)	
	No. of Events/Total No. (%)		Fixed-Effect Model	Random-Effect Model	Fixed-Effect Model	Random-Effect Model
BISTRO II[21] (NCT01225822) 2004	50/1557 (3.21)	8/392 (2.04)	1.50 (0.78 to 2.88)	1.59 (0.75 to 3.39)	2.87	5.23
RE-NOVATE[23] (NCT00168818) 2007	38/2309 (1.65)	18/1154 (1.56)	1.06 (0.60 to 1.85)	1.06 (0.60 to 1.86)	3.88	8.74
RE-MODEL[24] (NCT00168805) 2007	19/1382 (1.37)	9/694 (1.30)	1.06 (0.48 to 2.34)	1.06 (0.48 to 2.36)	1.95	4.72
RE-MOBILIZE[5] (NCT00152971) 2009	10/1728 (0.58)	12/868 (1.38)	0.38 (0.16 to 0.94)	0.42 (0.18 to 0.97)	1.54	4.26
RE-NOVATE II[26] (NCT00657150) 2011	14/1010 (1.39)	9/1003 (0.90)	1.54 (0.68 to 3.51)	1.55 (0.67 to 3.60)	1.80	4.28
Overall enoxaparin	131/7986 (1.64)	56/4111 (1.36)	1.07 (0.78 to 1.47) *P*=0.685	1.04 (0.68 to 1.61) *P*=0.847	12.04	27.23
PETRO[22] (NCT01227629) 2007	4/445 (0.90)	0/70 (0.00)	3.20 (0.18 to 56.38)	1.44 (0.08 to 26.98)	0.15	0.38
RE-LY[25] (NCT00262600) 2009	741/12 091 (6.13)	421/6022 (6.99)	0.87 (0.76 to 0.98)	0.87 (0.77 to 0.98)	76.46	47.62
RE-COVER[11] (NCT00291330) 2009	20/1273 (1.57)	24/1266 (1.90)	0.83 (0.46 to 1.50)	0.83 (0.45 to 1.50)	3.43	7.92
RE-MEDY[12] (NCT00291330) 2013	13/1430 (0.91)	25/1426 (1.75)	0.53 (0.28 to 1.00)	0.51 (0.26 to 1.01)	2.97	6.42
RE-ALIGN[8] (NCT01452347) 2013	7/168 (4.17)	2/84 (2.38)	1.68 (0.41 to 6.86)	1.78 (0.36 to 8.78)	0.61	1.26
RE-COVER II[18] (NCT00680186) 2011	15/1280 (1.17)	22/1288 (1.71)	0.69 (0.36 to 1.31)	0.68 (0.35 to 1.32)	2.89	6.65
Overall warfarin	800/16 687 (4.79)	494/10 156 (4.86)	0.85 (0.75 to 0.96) *P*=0.007	0.85 (0.76 to 0.96) *P*=0.007	86.51	70.25
Fuji[20] (NCT00246025) 2010	6/388 (1.55)	1/124 (0.81)	1.73 (0.30 to 9.85)	1.93 (0.23 to 16.20)	0.40	0.71
RE-DEEM[10] (NCT00621855) 2011	16/1490 (1.07)	2/371 (0.54)	1.75 (0.55 to 5.58)	2.00 (0.46 to 8.75)	0.90	1.46
RE-SONATE[12] (NCT00558259) 2013	2/681 (0.29)	0/662 (0.00)	7.20 (0.45 to 115.20)	4.88 (0.23 to 101.73)	0.16	0.35
Overall placebo	24/2559 (0.94)	3/1157 (0.26)	2.03 (0.82 to 5.06) *P*=0.128	2.03 (0.82 to 5.06) *P*=0.128	1.46	2.52
Overall	955/27 232 (3.51)	553/15 426 (3.59)	0.88 (0.79 to 0.99) *P*=0.029	0.93 (0.75 to 1.15) *P*=0.483	100.00	100.00

For the pooled results of 1 comparator, the odds ratio is provided for a fixed-effect model using the Peto method and for a random-effect model using the inverse-variance method. Relative weight of each study is also mentioned for these 2 different models. NA indicates not applicable.

of a reduction in the risk of all-cause mortality was maintained but no longer statistically significant (see Figure S1D). All one-way sensitivity analyses preserved a nonsignificant reduction in the risk of all-cause mortality with dabigatran etexilate compared with warfarin (see Figure S2D).

Figure S3A through S3D provides all funnel plot results as well as the Egger's test and the Begg and Mazumdar rank correlation test. These did not reveal any publication bias.

Discussion

The 2012, European Society of Cardiology guidelines for the management of AF recommend the "new (or non-VKA) oral anticoagulants," or NOACs, as broadly preferable to VKAs in the vast majority of patients with nonvalvular AF.[28] The American College of Chest Physicians Guidelines and the Canadian Cardiovascular Society Guidelines took a similar approach.[29,30] Today, deciding on the optimal oral anticoagulant is rather

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Table 6. Rates of All-Cause Mortality Across the Included Studies, Stratified by Comparator

Study	Dabigatran Etexilate	Control	Odds Ratio (95% CI)		Relative Weight (%)	
	No. of Events/Total No. (%)		Fixed-Effect Model	Random-Effect Model	Fixed-Effect Model	Random-Effect Model
BISTRO II[21] (NCT01225822) 2004	No information regarding the mortality was provided					
RE-NOVATE[23] (NCT00168818) 2007	6/2293 (0.26)	0/1142 (0.00)	4.48 (0.82 to 24.53)	6.49 (0.37 to 115.36)	0.41	0.14
RE-MODEL[24] (NCT00168805) 2007	2/1371 (0.15)	1/685 (0.15)	1.00 (0.09 -11.04)	1.00 (0.09 to 11.04)	0.21	0.20
RE-MOBILIZE[5] (NCT00152971) 2009	2/1253 (0.16)	0/643 (0.00)	4.55 (0.24 to 84.96)	2.57 (0.12 to 53.63)	0.14	0.12
RE-NOVATE II[26] (NCT00657150) 2011	0/1001 (0.00)	1/992 (0.10)	0.13 (0.00 to 6.76)	0.33 (0.01 to 8.11)	0.08	0.11
Overall enoxaparin	10/5918 (0.17)	2/3462 (0.06)	2.24 (0.68 to 7.39) *P*=0.186	1.55 (0.38 to 6.39) *P*=0.542	0.84	0.57
PETRO[22] (NCT01227629) 2007	No information regarding the mortality was provided					
RE-LY[25] (NCT00262600) 2009	884/12 091 (7.31)	487/6022 (8.09)	0.90 (0.80 to 1.01)	0.90 (0.80 to 1.01)	86.87	86.84
RE-COVER[11] (NCT00291330) 2009	21/1273 (1.65)	21/1266 (1.66)	0.99 (0.54 to 1.83)	0.99 (0.54 to 1.83)	3.19	3.10
RE-MEDY[12] (NCT00291330) 2013	17/1430 (1.19)	19/1426 (1.33)	0.89 (0.46 to 1.72)	0.89 (0.46 to 1.72)	2.75	2.66
RE-ALIGN[8] (NCT01452347) 2013	1/168 (0.60)	2/84 (2.38)	0.22 (0.02 to 2.46)	0.25 (0.02 to 2.75)	0.20	0.20
RE-COVER II[18] (NCT00680186) 2013	25/1279 (1.95)	25/1289 (1.94)	1.01 (0.58 to 1.76)	1.01 (0.58 to 1.76)	3.79	3.68
Overall warfarin	948/16 241 (5.84)	554/10 087 (5.49)	0.90 (0.81 to 1.01) *P*=0.061	0.90 (0.81 to 1.01) *P*=0.061	96.80	96.48
Fuji[20] (NCT00246025) 2010	No information regarding the mortality was provided					
RE-DEEM[10] (NCT00621855) 2011	32/1490 (2.15)	14/371 (3.77)	0.51 (0.25 to 1.06)	0.56 (0.30 to 1.06)	2.21	2.83
RE-SONATE[12] (NCT00558259) 2013	0/681 (0.00)	2/662 (0.30)	0.13 (0.01 to 2.10)	0.19 (0.01 to 4.05)	0.15	0.12
Overall placebo	32/2171 (1.47)	16/1033 (4.07)	0.47 (0.23 to 0.95) *P*=0.035	0.47 (0.23 to 0.95) *P*=0.035	2.36	2.95
Overall	990/24 330 (4.07)	572/14 582 (3.92)	0.89 (0.80 to 1.00) *P*=0.041	0.89 (0.72 to 1.09) *P*=0.252	100.00	100.00

For the pooled results of 1 comparator, the odds ratio is provided for a fixed-effect model using the Peto method and for a random-effect model using the inverse-variance method. Relative weight of each study is also mentioned for these 2 different models.

challenging. The absence of head-to-head trials precludes firm conclusions as to which NOAC is best. However, dabigatran etexilate at the dosage of 150 mg BID along with apixaban 5 mg or 2.5 mg BID and edoxaban 60 mg once daily are the only NOACs that reduce stroke or systemic embolism in prospective phase III RCT, which is the gold standard for recommendations with respect to clinical use.[4,25,31,32] Nonetheless, whatever is the indication, patients treated with NOACs may present with comorbidities such as coronary disease. In the RE-LY study, a nonsignificant but small numerical increase in MI events with dabigatran etexilate compared with warfarin was observed,[25] which led some concerned clinicians to consider the use of a VKA or an alternative NOAC (eg, rivaroxaban, apixaban, or edoxaban) in patients with an ACS. This position was vigorously debated. Thus, the 2010 Canadian Cardiovascular Society guidelines[33] included a caution against the use of dabigatran etexilate in patients with AF who are at high risk of coronary events. In the 2012 guidelines, their position concerning this

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alert has changed with the updated data of the RE-LY trials.[1] In contrast, no concern was raised in the 2011 guideline update of the American College of Cardiology Foundation and the Heart Rhythm Society atrial fibrillation, as well as in the 2012 American Heart Association guideline update and 2012 European Society of Cardiology guidelines for the management of AF.[28,30,33–35]

A recent Danish "everyday clinical practice" postapproval clinical cohort study revealed that mortality, intracranial bleeding, pulmonary embolism, and MI were lower with dabigatran etexilate, compared with warfarin.[36] The authors acknowledged that this analysis was limited by its dependence on prescribing information and that selection of treatment option was influenced by patient characteristics that might relate to outcome. In response, Sipahi et al underlined that, while examination of observational administrative dataset may sometimes be helpful to answer certain questions, the gold standard for determining drug safety and efficacy is careful analysis of all available RCTs.[37] In their analysis, they pooled 5 RCTs comparing dabigatran etexilate with warfarin and found a 48% increase in the risk of MI. However, they did not stratify their analysis by dose or other comparators and the methodology was not presented. Another previous meta-analysis, conducted by Uchino et al,[3] showed limitations because it pooled data across trials with different comparators without any stratification analysis. In addition, this previous meta-analysis used the outdated dataset from the RE-LY study for the primary analysis and obviously did not include data from recently conducted RCTs (RE-MEDY, RE-SONATE, RE-ALIGN, and RE-COVER II). The investigators also decided to not include the RE-MOBILIZE study. However, another recently published meta-analysis including the additional results of RE-LY confirmed this increase risk and provided stratification according to the indication of use.[6] Nevertheless, no direct information about the risk according to the comparator or the dabigatran etexilate dose was provided.

Holnloser et al pointed out the need for a more-detailed analysis of the effects of dabigatran on coronary events against the different comparators.[1] Therefore, the meta-analysis, by giving stratification by dose and comparator, provides robust evidence that dabigatran etexilate is associated with an overall significant 34% increase in the risk of MI (Figure 2A). The risk was principally identified when warfarin is used as comparator (41% increase for the fixed-effect model analysis; see Table 2 for comparison with the random effect model). We also showed that in RCTs using the higher licensed dabigatran etexilate dosage (ie, the 150-mg BID dosage regimen), a significant 45% overall increased risk of MI was identified (Figure 3A). No firm conclusion can be taken with the lower dabigatran etexilate dosage (110 mg BID) because of the limited number of studies. However, a trend toward an increased risk of MI (33%) was detected, which was of borderline significance (P=0.057). Two plausible explanations for these findings can be considered: either dabigatran etexilate is less efficacious than warfarin for the prevention of MI, or dabigatran etexilate causes acute coronary events.

Does Warfarin Protect Against MI?

Many studies have shown that the VKAs are useful drugs for the management of patients with coronary artery disease.[38,39] Thus, warfarin alone or with aspirin was shown to be superior to aspirin alone in reducing the incidence of composite events (death, nonfatal reinfarction, or thromboembolic cerebral stroke) after an acute MI.[39] In a previous review, Lip et al[40] concluded that warfarin may result in a lower risk of MI compared with other (nonwarfarin) anticoagulants or an "anticoagulant equivalent (clopidogrel 75 mg and aspirin 300 mg)." In addition, specific recommendations from the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction mentioned that warfarin is an option for treatment after MI to reduce the recurrence of such events.[41]

Nonetheless, a pooled analysis of the SPORTIF program,[42] evaluating ximelagatran versus warfarin in patients with nonvalvular AF, showed similar rate of MI between the 2 groups. However, the results were heterogeneous by trial, and in SPORTIF-III, there is a suggestion that ximelagatran increases MI.[43] Based on this analysis, the possibility that warfarin may provide a protective effect against MI in patients with nonvalvular AF cannot be excluded. However, the underlying mechanisms supporting this potential beneficial effect need to be further investigated.[44]

Does Dabigatran Etexilate Cause MI?

Placebo-controlled trials provide the optimal method to examine whether dabigatran etexilate causes coronary events. Unfortunately, the results of the only large placebo-controlled study of dabigatran etexilate in patients with coronary artery disease were inconclusive. There were numerically higher cases of MI in the dabigatran etexilate arm in the RE-DEEM study, but this finding was not statistically significant. For the RE-SONATE study, similar rates of MI were observed in both arms of the study.

If we suggest that dabigatran etexilate could cause MI, therefore, the understanding of the potential underlying mechanisms for the apparent increase in MI associated with dabigatran etexilate is not straightforward. Platelet activation and aggregation contribute to the underlying mechanisms of coronary thrombosis. Therefore, a potential contributing factor may be a direct or indirect effect on platelet activation. In a phase II trial with DE (PETRO study, see Table 1), urinary

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11-dehydrothromboxane B_2 concentrations, a marker of platelet activation, were significantly increased at any dabigatran etexilate doses. However, in other studies, dabigatran showed no effect on ex vivo induced platelet aggregation and inhibited platelet aggregation induced by α-thrombin.[45,46]

A more plausible explanation could be that the rupture of a coronary plaque also triggers explosive thrombin generation. As a stoichiometric inhibitor of thrombin, the possibility exists that local concentrations of thrombin exceed those available of dabigatran at the site of injury.

Results from different studies conducted with direct or indirect thrombin inhibitors do not provide consistence evidences of a class effect. Thus, in large, phase III trials, bivalirudin and hirudin have been shown to be effective alternatives to heparin for the management of ACS. They were associated with a lower risk of MI.[47] However, smaller phase II (ie, the ESTEEM trial with ximelagatran) studies with univalent direct thrombin inhibitors yielded contradictory results.[44,48] Namely, while the reduction composite outcome of death from any cause, stroke, MI, and recurrent ischemic events was statistically significant, the reduction in MI taken alone was not.

It is suggested that if dabigatran etexilate is a cause of MI, unstable angina would also be expected to increase. Based on our findings, other cardiovascular events were not increased (Table 2). However, it should be kept in mind that "other cardiovascular events" may be contaminated by nonspecific causes of chest pain, which would dilute any signal of increased risk because such events are not expected to be affected by dabigatran.

Implications for Patient Care and Regulators

This meta-analysis reveals that dabigatran significantly reduced major bleeding and all-cause mortality compared with controls in the fixed-effect analysis. However, while the reduction of major bleeding is statistically significant versus warfarin, the reduction in all-cause mortality is not (Table 2). Compared with warfarin, pooled results from any dabigatran doses revealed a significant 15% reduction of major bleeding and a nonsignificant 10% reduction of all-cause mortality, whereas the increase in MI reached 41%. The increased risk of MI with the 150-mg BID dosage is significant using a fixed-effect model (43%). For the 150-mg BID dosage, the reduction in major bleeding and mortality is not statistically significant (Figure 3). Taken together, these findings may suggest that in frail patients presenting with comorbidities (eg, patients aged ≥75 years or with creatinine clearance ≤50 mL/min, as defined previously),[49] the choice of the 150-mg BID dosage should be carefully discussed and the 110-mg BID dosage (not available in the United States) might be considered. Based on our results, it cannot be concluded that the 110-mg BID dosage is associated with a higher risk of MI.

However, in terms of absolute risk, such an increased risk of MI should be considered taking into account the outcomes of stroke or systemic embolism, major bleeding, and all-cause mortality. Thus, the results from the RE-LY trial showed that the benefits of dabigatran etexilate over warfarin for stroke prevention, with the 150-mg BID dosage, or for the reduction of major bleeding, with the 110-mg BID dosage, outweigh the increase risk of MI (Table 7). Effectively, the risk difference was greatly in favor of dabigatran etexilate regarding the composite of stroke/systemic embolism, MI, major bleeding, and all-cause mortality.

Moreover, we suggest that healthcare professionals and regulators consider additional risk minimization to prevent the risk of MI. The switch to a factor Xa inhibitor may be an appropriate alternative. Indeed, in a recently published meta-analysis evaluating the risk of MI with NOACs, rivaroxaban significantly reduced the risk of MI (OR 0.79, 95% CI 0.69 to 0.89, $P<0.001$), while apixaban showed no difference compared with warfarin (OR 0.94, 95% CI 0.82 to 1.07, $P=0.333$).[6] This was also found with edoxaban, where there is no

Table 7. Summary Data of the RE-LY Study

Outcome	warfarin (target INR 2.0 to 3.0)	Dabigatran Etexilate 110 mg BID		Dabigatran Etexilate 150 mg BID	
	Rate per 1000 Person-Years	Rate per 1000 Person-Years	Risk Difference vs warfarin per 1000 Person-Years	Rate per 1000 Person-Years	Risk Difference vs warfarin per 1000 Person-Years
Stroke or systemic embolism	17.1	15.4	−1.7	11.1	−6.0
MI	5.9	7.8	1.9	7.7	1.8
Fatal MI	1.0	1.3	0.3	1.1	0.1
Major bleeding	35.7	28.7	−7.0	33.2	−2.5
Fatal major bleeding	3.3	1.9	−1.4	2.3	−1.0
All-cause mortality	41.3	37.5	−3.8	36.4	−4.9

MI indicates myocardial infarction.

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difference compared with warfarin (hazard ratio 0.94, 95% CI 0.74 to 1.19. P=0.60; and hazard ratio 1.19, 95% CI 0.95 to 1.49, P=0.13, for the low- and high-dose edoxaban, respectively).[32] Unlike dabigatran etexilate, twice-daily low-dose rivaroxaban (2.5 mg or 5 mg) has been used with success in ACS.[50] However, there are no data on ACS prevention relating to the dosage of rivaroxaban used in AF (20 mg daily), and we should keep in mind that these studies were performed versus placebo. There are no data comparing rivaroxaban in this context versus active comparator. It is important to underline that for long-term use, indications such as AF, and the treatment of acute venous thromboembolism, these new agents showed generally similar profiles in terms of efficacy and safety. Namely, in secondary prevention in nonvalvular AF, apixaban, rivaroxaban, edoxaban, and dabigatran had broadly similar efficacies for the main end points, although the end points of hemorrhagic stroke, vascular death, major bleeding, and intracranial bleeding were less common with dabigatran 110 mg BID than with rivaroxaban. In addition, we should keep in mind that dabigatran etexilate 150 mg BID along with apixaban 5 mg or 2.5 mg BID and edoxaban 60 mg once daily are the only NOACs showing superiority compared with warfarin in the NVAF setting for the outcome of stroke and systemic embolism.[25,31,32] For primary prevention, dabigatran etexilate, rivaroxaban, and apixaban showed some differences in relation to efficacy and bleedings.[51] In the treatment of acute venous thromboembolism, NOACs had similar efficacy and mortality profiles compared with conventional anticoagulation with VKAs, while rivaroxaban, apixaban, and edoxaban were associated with a lower risk of major bleeding.[52–54] However, in the absence of head-to-head studies, any comparison of the efficacy and safety of these NOACs should be interpreted with caution because of the differences in study designs, protocols, and population characteristics.

Strengths and Limitations of This Meta-analysis

This is the first up-to-date meta-analysis that includes the most recent studies with dabigatran etexilate that also provides subgroup analysis by comparators and doses of dabigatran etexilate. Sensitivity analysis confirmed the robustness of the results as well as the use of different model effects. No evidence of publication bias and a low heterogeneity was shown.

However, our study has important limitations. We performed a meta-analysis using OR_{PETO} from the individual results of trials that were not originally intended to explore all cardiovascular outcomes, except for RE-DEEM study, which evaluated the benefit of dabigatran etexilate in patients with ACS treated with dual-antiplatelet therapy. In addition, in most trials, the definition of MI was not available and in a conservative purpose, we adjudicated ACS as MI when not specifically described. We recognize that this might overestimate the rate of MI and lead to adjudication bias because we did not know if an ACS is a MI or, for example, unstable angina. However, the analysis of other cardiovascular events did not reveal any differences between dabigatran etexilate and control treatments, reinforcing the hypothesis that dabigatran is probably less effective than warfarin in the prevention of MI where the amount of thrombin generated in a microenvironment is higher. Another limitation of this study is that we did not have access to original source/patient-level data for any of these trials. Time-to-event data were not available in any of these trials, except for RE-LY. This did not allow the use of more statistically powerful time-to-event analysis. Globally, a meta-analysis is always considered less convincing than a large prospective trial designed to assess the outcome of interest. At this time, to the best of our knowledge, such a trial has not been completed for dabigatran etexilate (data source: clinicaltrials.gov), and it is obvious that no RCT will be undertaken to assess the comparative risk of MI.

Conclusions

This meta-analysis of RCTs provides evidence that dabigatran etexilate is associated with an overall significant 34% increase in the risk of MI. The risk was principally identified when warfarin is used as comparator (41% increase). No definitive conclusion about the absence of the risk of MI with the lower dabigatran etexilate dosage (110 mg BID) can be drawn at this time. However, this increased risk should be considered taking into account the overall benefit of dabigatran etexilate, especially in patients with NVAF. In conclusion, we suggest that healthcare professionals and regulators should consider additional risk minimization strategies to prevent the risk of MI in vulnerable populations.

Disclosures

None.

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