Meta-Analysis of Randomized Controlled Trials on Risk of Myocardial Infarction from the Use of Oral Direct Thrombin Inhibitors

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Dabigatran has been associated with greater risk of myocardial infarction (MI) than warfarin. It is unknown whether the increased risk is unique to dabigatran, an adverse effect shared by other oral direct thrombin inhibitors (DTIs), or the result of a protective effect of warfarin against MI. To address these questions, we systematically searched MEDLINE and performed a meta-analysis on randomized trials that compared oral DTIs with warfarin for any indication with end point of MIs after randomization. We furthermore performed a secondary meta-analysis on atrial fibrillation stroke prevention trials with alternative anticoagulants compared with warfarin with end point of MIs after randomization. A total of 11 trials (39,357 patients) that compared warfarin to DTIs (dabigatran, ximelagatran, and AZD0837) were identified. In these trials, patients treated with oral DTIs were more likely to experience an MI than their counterparts treated with warfarin (285 of 23,333 vs 133 of 16,024, odds ratio 1.35, 95% confidence interval 1.10 to 1.66, p = 0.005). For secondary analysis, 8 studies (69,615 patients) were identified that compared warfarin with alternative anticoagulant including factor Xa inhibitors, DTIs, aspirin, and clopidogrel. There was no significant advantage in the rate of MIs with the use of warfarin versus comparators (odds ratio 1.06, 95% confidence interval 0.85 to 1.34, p = 0.59). In conclusion, our data suggest that oral DTIs were associated with increased risk of MI. This increased risk appears to be a class effect of these agents, not a specific phenomenon unique to dabigatran or protective effect of warfarin. These findings support the need for enhanced postmarket surveillance of oral DTIs and other novel agents.

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The use of the oral direct thrombin inhibitor (DTI), dabigatran, was associated with lower rates of stroke and systemic embolism compared with warfarin demonstrated in the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial.[1] The study also revealed that a higher rate of clinical myocardial infarction (MI) was observed with dabigatran than with warfarin that was found to be statistically not significant in the post hoc analysis.[2] A recent meta-analysis revealed that the rate of coronary events was increased with the use of dabigatran compared with various types of controls.[3] Ximelagatran, another oral thrombin inhibitor no longer available for clinical use, was associated with a significantly increased risk of myocardial ischemia compared with warfarin in patients who had acute deep vein thrombosis.[4] It has been proposed that warfarin might provide a protective effect against MI compared with non-warfarin anticoagulants in patients with atrial fibrillation who are prescribed anticoagulation for stroke thromboprophylaxis.[5] The purpose of this study was twofold. The first objective was to investigate whether the excess rate of MIs with dabigatran compared with warfarin was related to the effect of dabigatran alone or was an effect consistent for the entire class of oral DTIs. The second objective was to evaluate whether the use of warfarin indeed is associated with less incidence of MI in the more recent large-scale atrial fibrillation stroke prevention trials compared with non-warfarin anticoagulants.

Methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[6] To reduce the signal-to-noise ratio, a deliberate decision was made to include only the data on "myocardial infarction" as compared with "acute coronary syndrome" or other coronary ischemia related terms that are more likely to be influenced by subjective interpretation because detailed description of clinical history at the time of initial presentation or information on electrocardiographic changes, cardiac enzyme levels, and the result of possible coronary ischemia evaluation was not disclosed in the individual published trials. Based on the objectives of

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See page 1978 for disclosure information.

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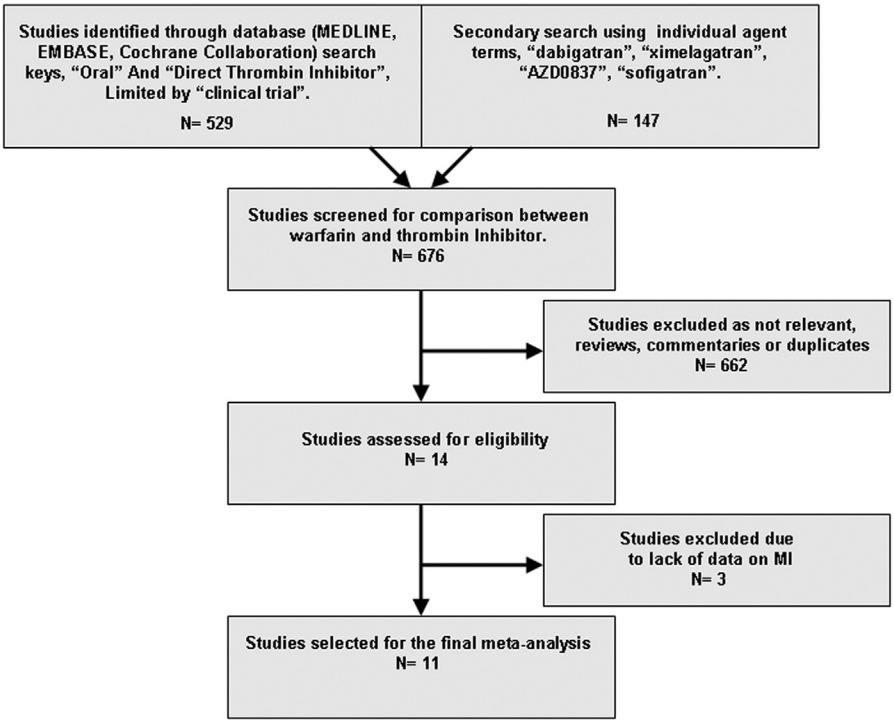

Figure 1. Flow diagram of the study selection for comparison of oral DTIs versus warfarin.

the study, we performed 2 separate systematic literature searches.

To address the observation of incidence of MI in trials with oral DTIs, we searched MEDLINE, Embase, and the Cochrane Collaboration, up to March 2013 using key words: "oral," "direct thrombin inhibitor" with the limiting term "clinical trial" without language or publication date restrictions. We then performed a secondary search using the individual agent name: "dabigatran" with the limiting term "clinical trial," "ximelagatran" with the limiting term "clinical trial," and lastly "AZD0837" and "sofigatran" with no limitations. Studies were included in meta-analysis if (1) the comparison between an oral DTI and warfarin was made for any indication and (2) the occurrence of MI after randomization was reported by investigators by any definition.

Regarding the possible protective effect of warfarin in preventing MI in more recent atrial fibrillation stroke prevention trials, we performed a MEDLINE search using the PubMed medical subject heading database using terms: "atrial fibrillation," "stroke prevention and control," "anticoagulants/therapeutic use," and "warfarin/therapeutic use" with the limiting term of "randomized trials" and time limit of "10 years." Studies were included in the meta-analysis if (1) comparison between warfarin and any alternative antithrombotic agent was performed and (2) the occurrence of MI after randomization was reported by investigators by any definition.

The data were analyzed using Comprehensive Meta-Analysis, version 2 (Biostat, Englewood, New Jersey). The pooled odds ratio (OR) with 95% confidence interval (CI) for MI was calculated using the fixed-effects Mantel-Haenszel model, whereas in the case of significant heterogeneity across studies, the random-effects model was used instead. The likelihood of statistical heterogeneity was assessed using the Cochrane Q test and quantified with the I^2 statistic. An I^2 >50% was considered statistically significant heterogeneity. In addition, an influence analysis, in which meta-analysis estimates are computed omitting 1 study at a time, was performed for the primary end point. Publication bias was evaluated with the funnel plot and the Egger regression test.

Results

The results of the literature search on oral DTIs versus warfarin are shown in Figure 1. A total of 676 publications were identified and screened. Of those, 14 full-text manuscripts were found eligible for detail review. Eleven randomized controlled trials fulfilled the inclusion criteria and were selected for meta-analysis, with the total number of 39,357 participants. The individual study details are listed in Table 1. The MI definition was prespecified in the trial design in less than half of the studies. None of the studies had prespecified definition of other ischemic coronary terms such as "acute coronary syndrome," "ischemic coronary event," or "unstable angina." Overall, the entire cohort of oral DTIs was associated with a significantly higher rate of MI compared with warfarin. MI was reported in 285 of 23,333 subjects treated with oral DTIs versus 133 of 16,024 subjects treated with warfarin, with an OR of 1.35 (95% CI 1.10 to 1.66), $p = 0.005$ using the fixed-effects model. There was no significant heterogeneity among the studies ($Q = 15.3$, degree of freedom [DF] $= 9$, $I^2 = 41.1\%$ and $P = 0.084$ for heterogeneity; Figure 2). Among the 4 trials that compared dabigatran to warfarin, there were significantly higher rates of MI among those randomized to dabigatran.

Table 1
Characteristics of the included randomized controlled trials of oral direct thrombin inhibitor compared with warfarin

Study Name	Population	Design	Primary End Point	Number of Subjects	Prespecified MI Definition*	Thrombin Inhibitor†	Duration (Mo)
RE-LY[2]	Atrial fibrillation	Noninferiority open label	Stroke and SE	18,113	Yes	Dabigatran 150 and 110 mg BID	24
RE-COVER[7]	Acute VTE	Noninferiority double blind	VTE or related death	2,539	No	Dabigatran 150 mg BID	6
RE-MEDY[8]	VTE	Noninferiority double blind	VTE or related death	2,866	‡	Dabigatran 150 mg BID or placebo	18
RE-ALIGN[§]	Mechanical valves	Phase II, open label	Mortality and morbidity	249‖	No¶	Dabigatran 150, 220, and 300 mg BID	3
SPORTIF III[9]	Atrial fibrillation	Noninferiority open label	Stroke and SE	3,410	Yes	Ximelagatran 36 mg BID	17.4
SPORTIF V[10]	Atrial fibrillation	Noninferiority double blind	Stroke and SE	3,922	Yes	Ximelagatran 36 mg BID	20
THRIVE[4]	Acute VTE	Noninferiority double blind	Recurrent VTE	2,489	No	Ximelagatran 36 mg BID	6
EXULT A and B[11–13]	Thromboprophylaxis	Superiority double blind	VTE and all-cause death	3,800	No	Ximelagatran 24 and 36 mg BID	1–1.5
Lip et al[14]	Atrial fibrillation	Tolerability and dose guiding	Bleeding and adverse events	955	No	AZD0837, 150 to 450 mg QD and 200 mg BID	5
Olsson et al[15]	Atrial fibrillation	Safety and tolerability	Bleeding and adverse events	249	No	AZD0837, 150 and 300 mg BID	3

BID = twice daily; EXULT = Exanta Used to Lessen Thrombosis; QD = once daily; RE-ALIGN = The Randomized, phase II study to Evaluate the sAfety and pharmacokinetics of oraL dabIGatran etexilate in patients after heart valve replacement; RE-COVER = Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism; RE-MEDY = Extended Use of Dabigatran Warfarin or Placebo in Venous Thromboembolism; SE = systemic embolism; THRIVE = Thrombin Inhibitor in Venous Thromboembolism; VTE = venous thromboembolism.

* The original study publication and additional publications including supplementary appendices and trial design publications were screened for prespecified definition of MI or any related terms as any type of end point or an adverse event after randomization.

† Comparison in this table was against adjusted dose warfarin to an international normalized ratio of 2.0-3.0.

‡ As per study protocol, all suspected acute coronary syndromes (ACS) were evaluated centrally and blindly by ACS Adjudication Committee. The operating procedures containing all details regarding ACS will be available as a separate document. This document is currently not available in the public domain.[8]

§ *http://www.fda.gov/Drugs/DrugSafety/ucm332912.htm*. The study had blinded end point that also included dabigatran plasma drug levels.

‖ Study was prematurely terminated. The planned study population was 405.

¶ An independent adjudication committee was established for the blinded adjudication of MI among other efficacy outcome end points.

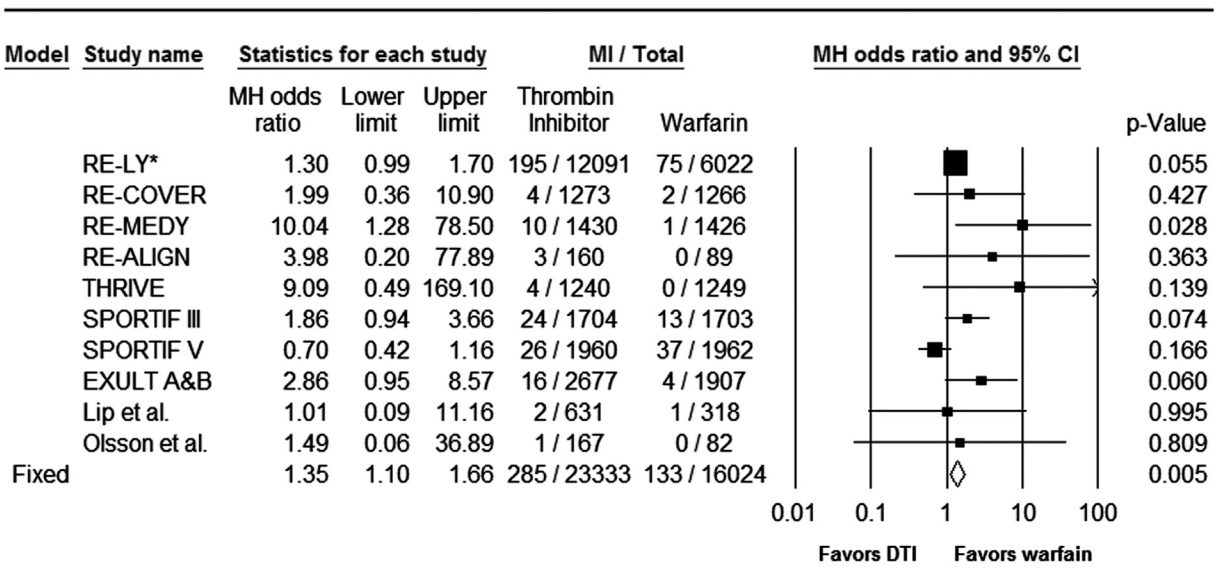

Figure 2. Forest plot of risk of MI in trials with oral DTIs compared with warfarin. *Combined dabigatran 150 and 110 mg results from the revised version of the study.[2] EXULT = Exanta Used to Lessen Thrombosis; MH = Mantel-Haenszel method; RE-ALIGN = The Randomized, phase II study to Evaluate the sAfety and pharmacokinetics of oraL dabIGatran etexilate in patients after heart valve replacement; RE-COVER = Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism; RE-MEDY = Extended Use of Dabigatran Warfarin or Placebo in Venous Thromboembolism; THRIVE = Thrombin Inhibitor in Venous Thromboembolism

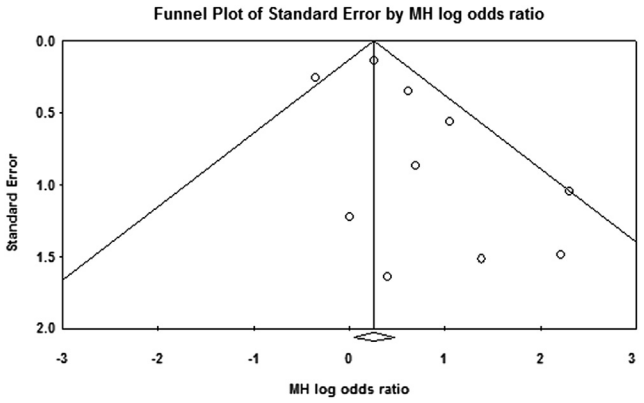

Figure 3. Funnel plot for evaluation of publication bias for comparison between oral DTIs and warfarin.

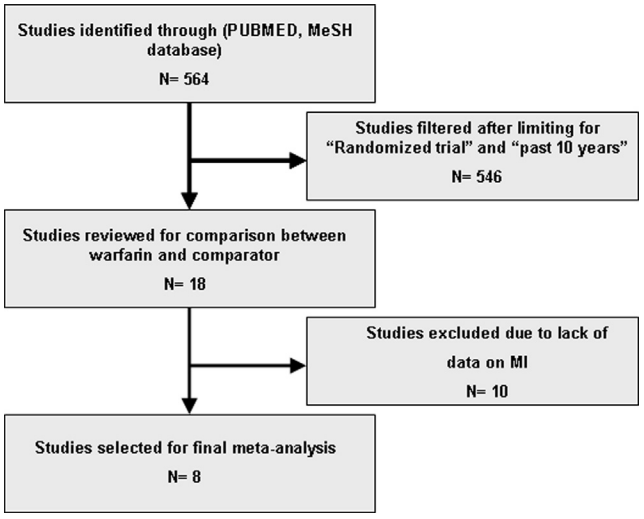

Figure 4. Flow diagram of the study selection of primary stroke prevention atrial fibrillation trials for comparison between warfarin and non-warfarin anticoagulant.

These included 212 out of 14,954 subjects treated with dabigatran versus 78 out of 8,803 subjects treated with warfarin (OR 1.41, 95% CI 1.09 to 1.83, p = 0.009, Q = 4.5, DF = 3, I^2 = 33.2% and P = 0.21 for heterogeneity).

In the 5 trials comparing ximelagatran versus warfarin, there was a trend toward increased rates of MI among those treated with ximelagatran but subgroup meta-analysis did not reach statistical significance. There were 70 out of 7,581 in the ximelagatran group compared with 54 out of 6,821 in the warfarin group (OR 1.23, 95% CI 0.86 to 1.76, p = 0.25, Q = 10.3, DF = 3, I^2 = 70.8% and P = 0.016 for heterogeneity). Among the trials with ximelagatran, the meta-analysis by treatment indication revealed more than 3 times increased risk of MI for those treated with ximelagatran compared with warfarin in the subgroup of venous thromboembolism and thromboprophylaxis. There were 20 MIs out of 3,917 subjects treated with ximelagatran versus 4 out of 3,156 subjects treated with warfarin (OR 3.46, 95% CI 1.25 to 9.57, p = 0.017, Q = 0.53, DF = 1, I^2 = 0.0% and P = 0.46 for heterogeneity).

Among the trials with AZD0837, there was no significant difference between rates of MI among the groups. There were 3 MIs out of 798 subjects treated with AZD0837 versus 1 out of 400 subjects treated with warfarin (OR 1.17, 95% CI 0.17 to 7.94, p = 0.87, Q = 0.036, DF = 1, I^2 = 0.0% and P = 0.85 for heterogeneity).

Influence analysis of the entire cohort demonstrated that none of the individual studies appeared to have significant impacts on the overall combined effect sizes ranging from 1.29 to 1.54 (p value ranging from 0.0 to 0.034) for fixed effect. There was no evidence of significant publication bias demonstrated by funnel panel and Egger regression test intercept at 0.90, p = 0.13 (2 tailed) (Figure 3).

The results of the literature search on warfarin versus comparator anticoagulant are shown in Figure 4. We identified 564 published reports and reviewed 18 full-text manuscripts. Eight randomized controlled trials fulfilled the inclusion criteria and were selected for meta-analysis with the total number of 69,615 participants. The comparator in different studies included aspirin with and without clopidogrel, oral and parenteral factor Xa inhibitors, and oral DTIs. The individual study details are outlined in Table 2. There was significant heterogeneity among the studies with Q = 15.9, DF = 7, I^2 = 56.1%, P = 0.026. Overall, subjects treated with warfarin had similar rate of MI than those treated with comparator agents. There were 403 out of 31,867 subjects treated with warfarin compared with 503 out of 37,748 subjects treated with comparator agents (OR 1.06, 95% CI 0.85 to 1.34, p = 0.59), using random-effects model (Figure 5). Influence analysis demonstrated that none of the individual studies appeared to have significant impacts on the overall combined effect sizes ranging from 1.01 to 1.14 (p value ranging from 0.31 to 0.92) for random effect. There was no evidence of significant publication bias demonstrated by funnel panel and Egger regression test, intercept at 1.29, p = 0.38 (2 tailed) (Figure 6).

Discussion

In the present meta-analysis, we have demonstrated that oral DTIs as a group were associated with an increased risk of MI compared with warfarin among 39,357 patients analyzed. To our knowledge, this is the first analysis to extend the findings of an increased risk of MI with dabigatran to other oral thrombin inhibitors. The second meta-analysis on 69,615 subjects showed no significant difference in the rates of MI among those treated with warfarin versus those in the combined cohort of aspirin alone, aspirin plus clopidogrel, factor Xa inhibitors, and oral DTIs. Hence, the increased risk of MI among patients treated with oral DTIs versus their counterparts treated with warfarin is likely due to a class effect of oral DTIs and not due to protective effect of warfarin.

The present meta-analysis differs from previous reports evaluating the risk of MI among those treated with dabigatran because we were able to include the results from the recently published randomized trials on Extended Use of Dabigatran Warfarin or Placebo in Venous Thromboembolism and The Randomized phase II study to Evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (Table 1). The list of trials included in the present analysis provides the most

Table 2
Characteristics of the included randomized controlled primary stroke prevention trials of warfarin compared with non-warfarin anticoagulant*

Study Name	Design	Primary End Point	Number of Participants	Prespecified MI Definition	Comparator Regimen*	Duration (Mo)
AMADEUS[16]	Noninferiority open label	Stroke and SE	4,576	No	Idraparinux 2.5 mg SC once weekly	10.7
ACTIVE W[17]	Noninferiority open label	Stroke and SE, MI and vascular death	6,706	Yes	Clopidogrel 75 and aspirin 75−100 mg daily	15.4
BAFTA[18]	Randomized open label	Fatal or disabling stroke, SE	937	No	Aspirin 75 mg daily	32.4
ROCKET AF[19]	Noninferiority double blind	Stroke and SE	14,264	Yes	Rivaroxaban 20 mg daily	23.2
ARTISTOTLE[20]	Noninferiority double blind	Stroke and SE	18,201	No	Apixaban 5 mg twice daily	21.6

ACTIVE = Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events; AMADEUS = Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation; ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; BAFTA = Birmingham Atrial Fibrillation Treatment of the Aged Study; ROCKET AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SC = subcutaneously; SE = systemic embolism.

* Comparison in this table was against adjusted dose warfarin to an international normalized ratio of 2.0-3.0. For characteristics data on RE-LY, SPORTIF III and V trials, please see Table 1.

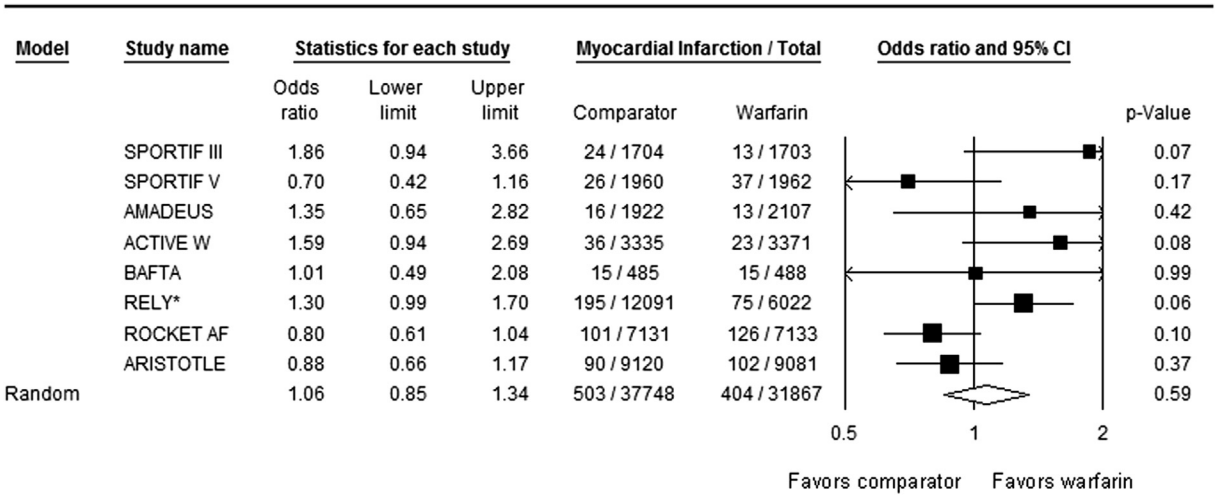

Figure 5. Forest plot of risk of MI in primary stroke prevention atrial fibrillation trials for comparison between warfarin and non-warfarin anticoagulant. *Combined dabigatran 150 and 110 mg results from the revised version of the study.[2] ACTIVE = Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events; AMADEUS = Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation; ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; BAFTA = Birmingham Atrial Fibrillation Treatment of the Aged Study; MH = Mantel-Haenszel method; ROCKET AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

updated collection of trials with dabigatran against warfarin for any indication and allows a reliable exclusive meta-analysis of dabigatran versus warfarin not previously displayed. The relative risk of MI for a patient treated with dabigatran for any indication compared with warfarin is 41%, and the absolute risk difference remains small at 0.53%. The number needed to treat to cause 1 MI compared with warfarin is 188.

The open-labeled Stroke Prevention trial using an Oral Thrombin Inhibitor Ximelagatran in Atrial Fibrillation (SPORTIF) III and double-blinded SPORTIF V trial demonstrated divergent MI outcomes.[9,10] Hylek et al[21] have argued that the disparate results in the two SPORTIF trials may have been due to much tighter control of the cardiovascular risk factors in the SPORTIF V trial, which is the only outlier in both the ximelagatran subgroup and the entire group of thrombin inhibitors (Figure 3).

In the phase II trial with AZD0837 by Olsson et al, the overall cardiac-related events including angina, MI, atrial or ventricular arrhythmias, and cardiac arrest occurred in 7 subjects treated with AZD0837 compared with 0 cardiac events in subjects treated with warfarin. It is unclear based on the data publicly available whether these events were primarily caused by ischemia alone or separate possible arrhythmogenic properties of AZD0837, but the signal with increased coronary events seems to be present with

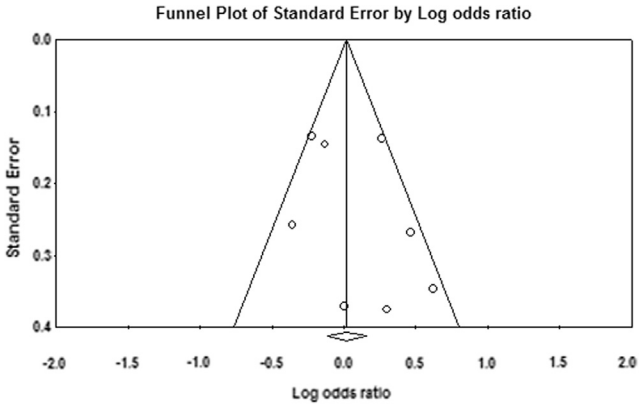

Figure 6. Funnel plot for evaluation of publication bias for comparison between warfarin and non-warfarin anticoagulants in primary stroke prevention atrial fibrillation trials.

this agent as well. To our knowledge, there are no further ongoing phase II or III trials with AZD0837.[22]

In a meta-analysis on contemporary atrial fibrillation stroke prevention trials by Lip et al[5] from 2010, the investigators hypothesized that warfarin might have a protective effect against MI compared with non-warfarin anticoagulants. The limitation of the latter study was that the results of Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) and Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trials were not included since the data were not yet available in 2010. The conclusion by Lip et al was therefore likely to be driven by the oral DTI effect from the RE-LY and SPORTIF trials.

The question is could this observation be due to a certain mechanism/s related to the direct thrombin inhibition[23]? Evidently, there are 2 different classes of the DTIs: the bivalent including hirudin and bivalirudin and univalent including argatroban, ximelagatran, and dabigatran.[24] It has been proposed that melagatran may dissociate from thrombin, leaving some amount of free enzymatically active thrombin available for hemostatic interactions.[25] Furugohri et al[26] demonstrated that at certain lower concentrations melagatran enhanced thrombin generation in human plasma, but at higher concentrations, melagatran inhibited the thrombin generation as expected. This enhancement of thrombin generation was dependent on thrombomodulin and activated protein C concentrations. The investigators hypothesized the enhancement of thrombin generation being due to the suppression of the thrombin-thrombomodulin-induced negative feedback system by inhibiting protein C activation. In contrast, the factor Xa inhibitors fondaparinux and edoxaban demonstrated consistently increasing inhibition of thrombin generation in a nonlinear dose-dependent fashion. Dale et al[27] demonstrated a greater reduction in peak thrombin generation and endogenous thrombin potential at different in vitro concentrations of tissue factor in plasma from 18 warfarin-treated patients compared with 36 dabigatran-treated patients who entered the RE-LY trial. The difference in relative inhibition between warfarin and dabigatran was greatest at higher tissue factor concentrations favoring warfarin. What continues to be unknown is the degree of the platelet activation by any measure among the patients who did have MI while treated with dabigatran, and whether addition of aspirin would alleviate the small risk of MI for subjects treated with dabigatran.

A hypothesis unifying these latest observations could be proposed indicating that at trough levels of univalent DTIs, the remaining enzymatically active thrombin dissociated from DTI molecules when exposed to tissue factor at the site of the ruptured plaque, or a mechanical valve may generate more thrombin formation and may potentially contribute to platelet activation while thrombin-induced negative feedback system through the inhibition of protein C activation may still be inhibited by the oral DTI with insufficient amount of circulating DTI molecules to counter the thrombin generation. Further studies are required to verify such hypothesis.

This study has certain limitations. This was primarily a meta-analysis for the purpose of hypothesis generation on trials in which MI was not an a priori end point. The study was limited by the number of studies included. On the comparison between thrombin inhibitors and warfarin, there were only 11 studies analyzed. Although the RE-LY trial had a relative weight of 62%, the influence analysis revealed that the result of the meta-analysis was consistent even without the RE-LY data. The study was further limited by limited information provided about MI events in individual trials that were screened including time to event. In the Exanta Used to Lessen Thrombosis (EXULT) trials, the MI data were not disclosed in the original publications and were extracted from a later published Food and Drug Administration report.[13] The Dabigatran With or Without Concomitant Aspirin compared with Warfarin alone in patients with nonvalvular Atrial Fibrillation (PETRO) trial, not included in this analysis, reported 7 cases of angina; of which, 2 were classified as acute coronary syndrome in the arms with various doses of dabigatran compared with no ischemic events in the warfarin arm. Yet, the definition of MI, angina, or acute coronary syndrome was not prespecified in the trial design.[28] It is imperative for the future studies on any class of antithrombotics to specifically disclose clear, unequivocal, and unbundled data on all types of thromboembolic adverse events including MI at all phases of development.

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Disclosures

The authors have no conflicts of interest to disclose.

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