Rivaroxaban and risk of myocardial infarction: insights from a meta-analysis and trial sequential analysis of randomized clinical trials

Saurav Chatterjee[a], Abhishek Sharma[b], Ken Uchino[c], Giuseppe Biondi-Zoccai[e], Edgar Lichstein[b] and Debabrata Mukherjee[d]

Objective **To evaluate the risk of myocardial infarction (MI) associated with the use of rivaroxaban.**

Methods **We searched PubMed, CINAHL, Cochrane CENTRAL, Scopus, and the Web of Science for randomized controlled trials of rivaroxaban that reported on MI as clinical outcomes. We express the associations as odds ratios and their 95% confidence intervals. A trial sequential analysis was carried out to ensure validity of our findings.**

Results **Nine trials were selected ($N=53\,827$), including one study on stroke prophylaxis in atrial fibrillation, two in acute coronary syndrome, four of short-term prophylaxis of deep venous thrombosis, and two for treatment of deep venous thrombosis/pulmonary embolism. Control arms included warfarin, enoxaparin, or placebo administration. Rivaroxaban was associated with a significantly lower risk of MI compared with the agents used in the control group (odds ratio, 0.82; 95% confidence interval, 0.72–0.94; $P=0.004$). No heterogeneity was noted in the risk ($I^2=0\%$; $P=0.55$); trial sequential analysis reinforced the validity of our findings.**

Conclusion **Rivaroxaban is associated with a significantly lower risk of MI in a broad spectrum of patients when tested against different controls.** ***Coron Artery Dis*** **00:000–000** © **2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Coronary Artery Disease 2013, **00**:000–000

Keywords: meta-analysis, myocardial infarction, rivaroxaban

[a]St Luke's-Roosevelt Hospital, Columbia University, New York, [b]Maimonides Medical Center, Brooklyn, New York, [c]Cleveland Clinic Foundation, Cleveland, Ohio, [d]Texas Tech University Health Sciences Center, El Paso, Texas, USA and [e]Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Rome, Italy

Correspondence to Saurav Chatterjee, MD, Division of Cardiology, St. Luke's-Roosevelt Hospital Center, 1111 Amsterdam Avenue, Clark Building, 3rd floor, New York, NY 10025, USA
Tel: +1 484 988 0084; fax: +1 347 244 7148;
e-mail: sauravchatterjeemd@gmail.com

Received 11 June 2013 **Revised** 1 August 2013 **Accepted** 6 August 2013

Introduction

Patients with unstable angina and myocardial infarction (MI) show marked thrombin generation and have increased coagulation system activity even months after clinical stabilization, hence resulting in post-acute coronary syndrome (ACS) ischemic complications [1]. Platelet aggregation and thrombus formation are the key steps in the pathogenesis of most of these complications, and addition of antiplatelet and antithrombotic drugs has been shown to improve clinical outcomes [2–8]. These drugs have synergistic action as they act on different targets and have different mechanisms of action [2–8]. Although significant reduction in the ischemic event rate has been reported with standard dual antiplatelet therapy with aspirin and thienopyridine, the annual rate of post-ACS ischemic complications (including stroke, MI, and even death) still remains as high as 10% [2].

Because of high ischemic complication rates despite standard therapy, addition of oral anticoagulation with warfarin to standard therapy has been proposed. Although initial data were encouraging, subsequent follow-up studies reported higher rates of bleeding complication without conferring any cardiovascular benefit with the addition of warfarin [9–12]. Thus, the search for a better anticoagulation option in ACS continues. Recently, newer classes of anticoagulation have been introduced; most notable among them are direct thrombin inhibitor and factor Xa inhibitor. Dabigatran is the first direct thrombin inhibitor initially approved by the European Medicine Agency for prophylaxis of venothromboembolism in surgical patients and the latter by the FDA (USA) for prevention of stroke and systemic embolism in nonvalvular atrial fibrillation (AF) on the basis of the results of the RE-LY trial (Randomized Evaluation of Long-term Anticoagulant Therapy). Recently, Uchino and Hernandez [13] reported a higher risk of ACS with the use of dabigatran in their meta-analysis, hence raising concerns on the use of dabigatran.

Rivaroxaban is an oral factor Xa inhibitor with high bioavailability. Its anticoagulation action is more consistent and predictable than warfarin, and because of once a day dosing, it has good compliance [14,15]. In a multicenter, randomized, double-blind ROCKET AF trial (the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), rivaroxaban was found to be noninferior to warfarin for the prevention of stroke or systemic embolism in patients

0954-6928 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/MCA.0000000000000031

with nonvalvular AF and was associated with a lower rate of fatal bleeding [16]. It has also been reported that the rate of MI trended lower in the rivaroxaban arm [16]. A subsequent ATLAS ACS TIMI 51 trial (Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 51) also showed a reduction in cardiovascular mortality and rate of MI with rivaroxaban [17], although the reduction in mortality was best appreciable in the lower dose arm of rivaroxaban. Rivaroxaban has also been successfully studied in various randomized clinical trials and recommended for prophylaxis of venous thromboembolic events in surgical patients [18–21]. In the present meta-analysis, we systematically evaluated the risk of MI with the use of rivaroxaban for several clinical indications and against various control arms.

Methods

PubMed, EMBASE, CINAHL, Scopus, the Web of Science, and Cochrane register of Controlled Clinical Trials (CENTRAL) were searched for randomized trials evaluating the safety and efficacy of rivaroxaban that reported on MIs as a secondary outcome. The search terms rivaroxaban or BAY 59-7939 (name for rivaroxaban in development) and randomized clinical trial or randomized trial or controlled clinical trial were used (last updated on 11 December 2012). Pertinent trials were also searched in clinicaltrials.gov and major international cardiology meetings (American College of Cardiology, American Heart Association, European Society of Cardiology, Transcatheter Cardiovascular Therapeutics). References of original and review articles were cross-checked. Study selection was carried out by two independent reviewers (S.C., A.S.), with divergences resolved by consensus. Citations were first scanned at the title/abstract level. Shortlisted studies were then retrieved in full text. They were considered suitable for inclusion if reporting on randomized trials, comparing rivaroxaban with a comparator, and reported rates of MI. Nonrandomized studies were excluded.

Abstraction and appraisal

Data abstraction and study appraisal were carried out by two independent reviewers (S.C., A.S.), with divergences resolved by consensus. Key study and patient characteristics were extracted, including the following outcomes, reported at the longest available follow-up according to intention-to-treat principles: (a) MI (as defined by the individual primary publications) and (b) cardiovascular mortality.

Review Manager 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and trial sequential analysis (TSA) (Copenhagen Trial Unit) were used for analysis. The outcomes were assessed using random-effects models initially, to exclude the presence of significant heterogeneity (evaluated and quantified with the I^2 statistic), and then pooled random-effects (Der-Simonian and Laird) odds ratios (ORs) were calculated with 95% confidence intervals (CIs). Publication bias was ascertained by visual inspection of funnel plots and the regression test of Egger.

Trial sequential analysis

In a single trial, interim analyses increase the risk of type I error. To avoid an increase in the overall type I error, monitoring boundaries can be applied to decide whether a single randomized trial could be terminated early because of the P value being sufficiently small. Because no reason exists why the standards for a meta-analysis should be less rigorous than those for a single trial, analogous trial sequential monitoring boundaries can be applied to meta-analysis as TSA [22,23]. Cumulative meta-analyses of trials are at risk of producing random errors because of few data and repetitive testing of accumulating data, and because the requirement for the amount of information analogous to the sample size of a single optimally powered clinical trial might not be met [22,24].

The underlying assumption for TSA is that significance testing and calculation of the CIs are performed each time a new trial is published. TSA depends on the quantification of the required amount of information. In this context, the smaller the required amount, the more lenient the TSA, thus the more lenient the criteria for significance [22,23]. A required diversity (D^2)-adjusted information size was calculated, D^2 being the relative variance reduction when the meta-analysis model is changed from a random-effects to a fixed-effect model [23]. D^2 is the percentage of the variability between trials and constitutes the sum of the variability between trials. It is an estimate of sampling error after consideration of the required information size. D^2 is different from the intuitively obvious adjusting factor on the basis of the common quantification of heterogeneity, the inconsistency (I^2), which might underestimate the required information size [23].

The TSA was carried out with a desire to maintain an overall 5% risk of type I error, being the standard in most meta-analyses and systematic reviews, and we calculated the required information size (i.e. the meta-analysis information size needed to detect or reject an intervention effect of a 20% relative risk reduction for benefit with a risk of type II error of 10%, at a power of 90%) [22–25].

Results

Our MEDLINE search returned 73 studies. After elimination of duplicate results, the EMBASE and Cochrane and the other registries did not return any additional studies, leaving 73 studies for evaluation. Through a review of titles and abstracts, 44 studies were rejected for relevance. The remaining 11 articles

were reviewed and assessed for satisfaction of the inclusion or exclusion criteria. The nine studies that fulfilled all criteria were included in this analysis (Fig. 1). We used the total event rates associated with all dosages of rivaroxaban in individual studies, when more than one dose of rivaroxaban was used in a trial.

Study characteristics

Trials were varied with respect to inclusion and exclusion criteria, with a few key differences (Table 1). Among the comparators in the different trials, rivaroxaban was compared against enoxaparin only or followed by warfarin in six trials [18–21,27,28], against placebo in two trials [17,26], and against warfarin in one trial [16].

Trial quality

We used the published standard criteria for reporting of randomized clinical trials studies (PRISMA) [29] checklist to select the studies for this review (Fig. 1). Among the nine trials included, all were low bias risk trials as assessed by the Cochrane risk of bias evaluation tool (section 8.5 in the Cochrane handbook) [30].

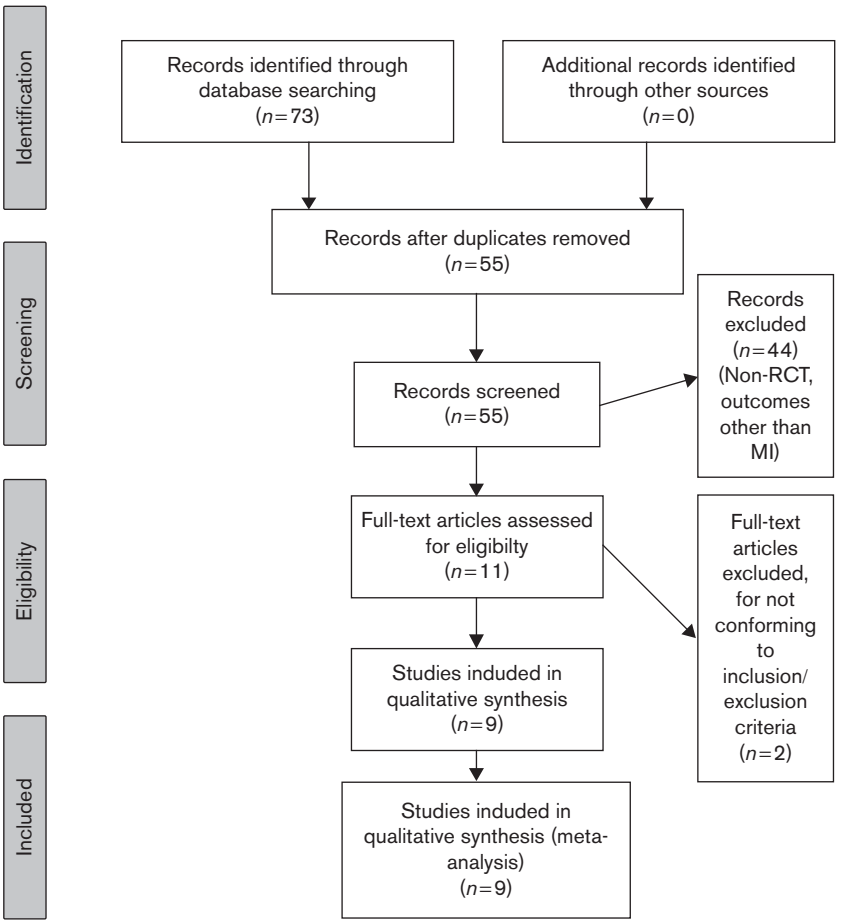
Primary outcome

We identified nine articles [16–21,26–28], accounting for 53 827 participants who fulfilled our inclusion and exclusion criteria. Rivaroxaban was significantly associated with a lower risk of MI compared with the agents used in the comparator groups (OR, 0.82; 95% CI, 0.72–0.94; $P = 0.004$). Risks were not heterogeneous ($I^2 = 0\%$; $P = 0.55$) (Fig. 2). There was no appreciable publication bias on inspection of the funnel plot or with the regression test of Egger (two-tailed $P = 0.54$). A cumulative meta-analysis was carried out to identify the influence of outliers, which showed a consistent association of rivaroxaban with reduced MI.

Secondary outcome

Rivaroxaban was significantly associated with a lower risk of cardiovascular mortality compared with the agents used in the comparator groups (OR, 0.84; 95% CI,

Fig. 1



Search strategy according to the PRISMA checklist. MI, myocardial infarction; RCT, randomized clinical trial.

Table 1 Baseline characteristics of studies

Trial names (duration of follow-up)	Rivaroxaban arm	Comparator arm	Inclusion criteria	Exclusion criteria
ATLAS ACS TIMI 46 [26] (6 months) (*N*=3491)	Three dose tiers were tested in stratum 1 (5, 10, and 20 mg) and four dose tiers were tested in stratum 2 (5, 10, 15, and 20 mg); given once or twice daily	Placebo [1148 (99·0%)]; on aspirin [940 (81·0%)]	ACS or a TIMI risk score of 3 or more	Hemoglobin concentration <100 g/l, a platelet count <90 000/μl of blood, or a history of any intracranial hemorrhage, warfarin use, planned PCI, concomitant severe disease
ATLAS ACS 2 TIMI 51 [17] (31 months) (*N*=15 342)	2.5 mg or 5.0 mg of rivaroxaban; given twice daily	Placebo [5108 (98.7%)]; on aspirin [4811 (92.9%)]; on thienopyridine	Adults with ACS and those <55 years of age had either diabetes mellitus or a previous myocardial infarction in addition to the index event	A platelet count <90 000/mm^3, a hemoglobin level <10 g/dl, or a creatinine clearance <30 ml/min at screening; clinically significant gastrointestinal bleeding within 12 months before randomization; previous intracranial hemorrhage; and previous ischemic stroke or transient ischemic attack in patients who were taking both aspirin and thienopyridine
RECORD 1 [18] (36 days) (*N*=4433)	Once-daily oral rivaroxaban 10 mg tablets	40 mg of enoxaparin sodium administered subcutaneously	18 years of age who were scheduled to undergo elective total hip arthroplasty	Staged, bilateral hip arthroplasty, pregnant or breastfeeding, had active bleeding or a high risk of bleeding, or had a contraindication for prophylaxis with enoxaparin or a condition that might require an adjusted dose of enoxaparin
RECORD 2 [19] (31–39 days) (*N*=2457)	Once-daily oral rivaroxaban 10 mg tablets	Subcutaneous injections of enoxaparin sodium 40 mg once daily	Patients, aged ≥ 18 years, who were scheduled to undergo elective total hip arthroplasty	Staged, bilateral hip arthroplasty, pregnant or breastfeeding, had active bleeding or a high risk of bleeding, or had a contraindication for prophylaxis with enoxaparin or a condition that might require an adjusted dose of enoxaparin
RECORD 3 [20] (31–39 days) (*N*=2459)	Once-daily oral rivaroxaban 10 mg tablet	Once-daily injection of enoxaparin sodium 40 mg	≥ 18 years of age and were scheduled for total knee arthroplasty	Active bleeding or a high risk of bleeding that contraindicated the use of low-molecular-weight heparin and patients with any contraindication to the use of enoxaparin
RECORD 4 [21] (30–35 days) (*N*=3148)	10 mg once daily oral rivaroxaban	Subcutaneous injections of 30 mg enoxaparin sodium every 12 h	Adults scheduled for total knee arthroplasty	Active bleeding or a high risk of bleeding that contraindicated the use of low-molecular-weight heparin and patients with any contraindication to the use of enoxaparin
ROCKET AF [16] (30–35 days) (*N*=14 236)	Rivaroxaban 20 mg daily or 15 mg daily in patients with a creatinine clearance of 30–49 ml/min	Warfarin (target INR 2.0–3.0)	Nonvalvular atrial fibrillation, as documented on electrocardiography, who were at moderate-to-high risk for stroke	Increased cardiac or hemorrhage risk, or serious medical illness, or allergies to the study drugs
EINSTEIN-DVT [27] (*N*=3449)	Rivaroxaban 15 mg twice daily for 3 weeks, then 20 mg daily	Enoxaparin 1 mg/kg twice daily for ≥ 5 days, then warfarin with target INR 2.0–3.0	Acute, symptomatic, objectively confirmed proximal DVT, without symptomatic pulmonary embolism	Therapy with low-molecular-weight heparin, fondaparinux, or unfractionated heparin for >48 h, if they had been treated with thrombectomy, a vena cava filter or a fibrinolytic agent for the current episode of thrombosis
EINSTEIN-PE [28] (*N*=4832)	Rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) for 3, 6, or 12 months	Standard therapy with enoxaparin followed by an adjusted dose of vitamin K antagonist	Acute, symptomatic pulmonary embolism with objective confirmation, with or without symptomatic deep-vein thrombosis	Low-molecular-weight heparin, fondaparinux, or unfractionated heparin for >48 h or if they had received more than a single dose of a vitamin K antagonist before randomization; if thrombectomy had been performed, a vena cava filter placed, or a fibrinolytic agent administered for current episode

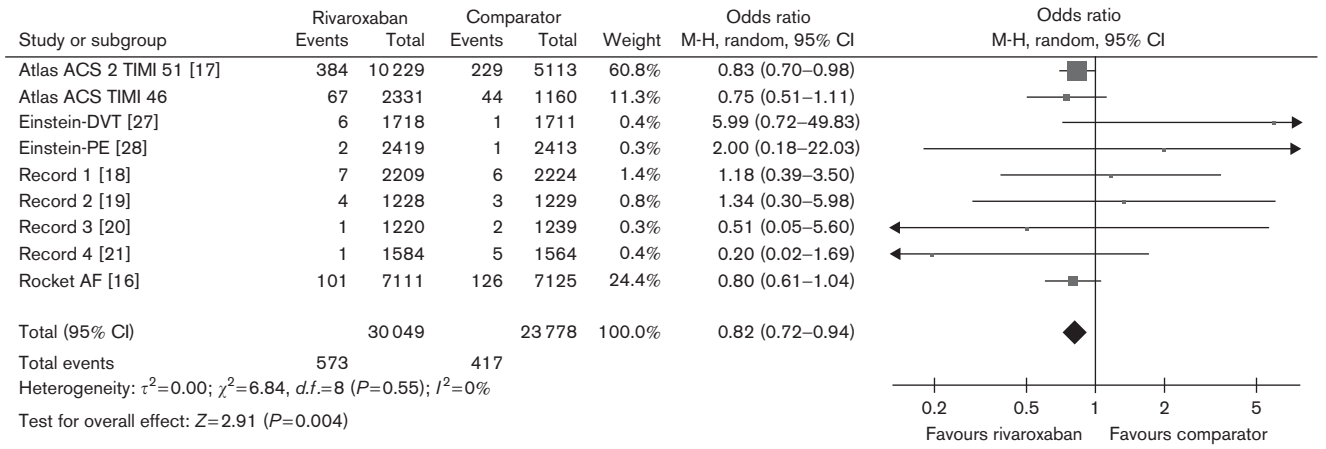
ACS, acute coronary syndrome; AF, atrial fibrillation; DVT, deep venous thrombosis; INR, international normalized ratio; PCI, percutaneous coronary intervention; PE, pulmonary embolism; TIMI, thrombolysis in myocardial infarction.

0.72–0.97; $P = 0.02$). Risks were not heterogeneous ($I^2 = 0\%$; $P = 0.73$) (Fig. 3).

Trial sequential analysis

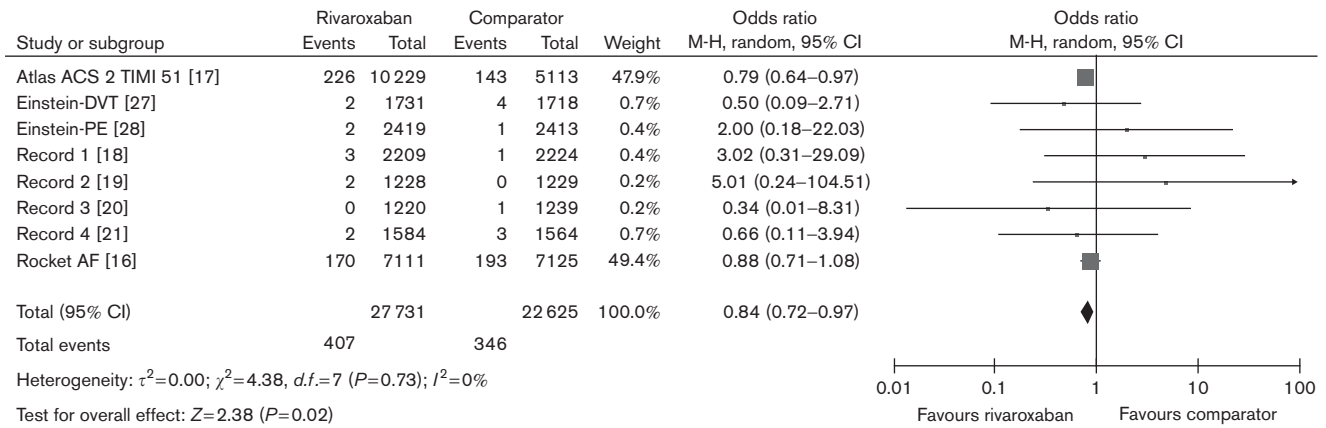
The required diversity ($D^2 = 0\%$)-adjusted information size for the outcome of MI was calculated on the basis of a proportion of 1.91% events in the control group and evaluating for a 20% relative risk reduction with rivaroxaban at $\alpha = 5\%$ and $\beta = 10\%$ (90% power). The cumulative z curves (calculated using both the conventional test boundary and the law of the iterated logarithm method [25]) crossed the trial sequential monitoring boundary of superiority, suggesting robust evidence of a decreased risk of MI with rivaroxaban compared with controls (Fig. 4). This is similar to interim analyses in a single trial, where monitoring boundaries are used to decide whether a trial could be terminated early when a P value is sufficiently small to show the

Fig. 2



Risk of myocardial infarction with rivaroxaban. 95% CI, 95% confidence interval.

Fig. 3



Risk of cardiovascular mortality with rivaroxaban. 95% CI, 95% confidence interval.

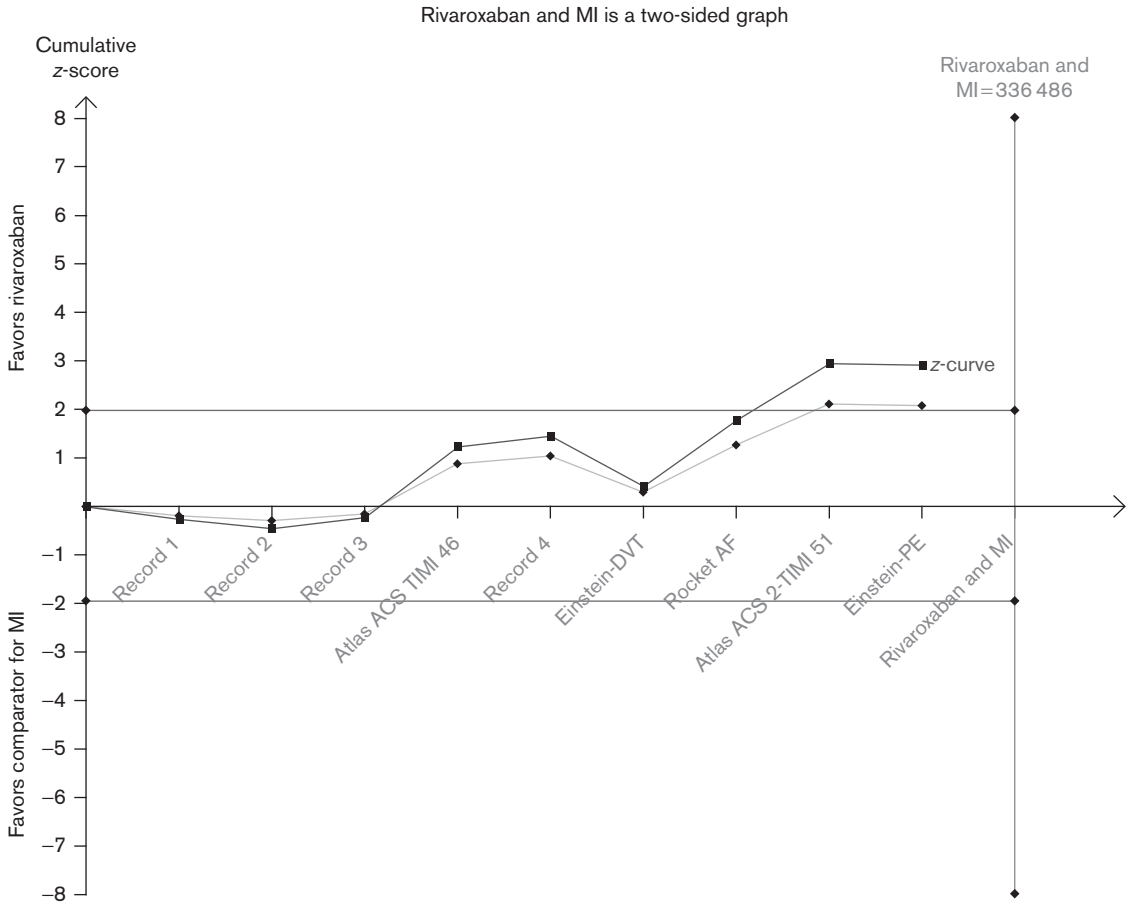
anticipated effect. Our analysis indicates statistically significant superiority for the association of rivaroxaban with a reduced rate of MI, even without the inclusion of the largest ACS trial [17], when conventional monitoring boundaries are considered. After adjustment with the law of the iterated logarithm method [25] and inclusion of the data from ATLAS ACS 2 TIMI 51 [17], the association of rivaroxaban with reduced rates of MI persisted.

Discussion

Our meta-analysis indicates a consistent and significantly lower risk of MIs and cardiovascular mortality with the use of rivaroxaban across a wide range of indications and against different comparators such as warfarin, enoxaparin, and placebo. On the basis of this, rivaroxaban appears especially attractive for stroke prevention in patients at a high risk of cardiovascular adverse events [31]. With a relative risk reduction for MI of 18%, rivaroxaban might be the preferred therapy for stroke prevention in AF among those at a high cardiovascular risk [32], although the superiority of this agent needs to be validated in high-quality randomized head-to-head trials of rivaroxaban against drugs of the same class with a similar mechanism of action and other new oral anticoagulants.

Rivaroxaban has been shown to reduce the risk of subsequent ACS after an event in a dose-dependent manner [26]. It has been postulated to reduce the risk of ACS by virtue of its inhibitory action on factor X, and prevention of its conversion into factor Xa, which initiates the final common pathway of the coagulation cascade and

Fig. 4



Effect of rivaroxaban versus controls on myocardial infarction (MI) using a 0% diversity model: (estimated) to detect or reject a 20% relative risk reduction with a power of 90%. The two horizontal lines parallel to the *x*-axis represent the sequential monitoring boundaries of superiority and futility. The upper and lower curved lines represent the unadjusted cumulative *z*-score of the pooled data for assessment of the adequacy of sample size and the weighted, penalized cumulative *z*-score for assessment of the adequacy of sample size, respectively.

leads to the formation of thrombin, which catalyzes additional coagulation-related reactions and promotes platelet activation. When compared against pharmacologically active molecules with proven (aspirin, thienopyridines, and enoxaparin) [33,34] and postulated (warfarin) [35] benefits in ACS, rivaroxaban showed consistent noninferiority to comparators in the rates of MI and cardiovascular mortality. However, caution needs to be exercised in the interpretation of the results and assigning a class effect to the outcomes seen with rivaroxaban. Recent use of another factor Xa inhibitor [36] has not been found to be of significance in net clinical benefit in the treatment of ACS, although the results of MI and other ischemic endpoints were numerically reduced without reaching statistical significance. It thus remains open to debate as to whether dosing may have played a role in the results of each trial of rivaroxaban and whether or not the reduction in risk would be anticipated across all study populations.

The limitations of our study include that the results were primarily driven by three trials (ROCKET AF, ATLAS ACS TIMI 46, and ATLAS ACS TIMI 51), which contributed 73% of patients and 97% of events. Whereas the event rates differed across studies, ORs of rivaroxaban to comparators were consistent and had low heterogeneity; it is unlikely that the benefit detected with our analysis was because of chance alone. There have been criticisms of the constituent individual trials, namely that the degree of anticoagulation in the warfarin arm in ROCKET AF was suboptimal (less than what has been reported in other recent trials), thereby arguably biasing the results toward rivaroxaban. RECORD 2 and 3 trials have been criticized for differences in treatment duration and doses that were biased toward rivaroxaban. The ATLAS ACS 2 TIMI 51 trial had substantial missing data, which challenged the interpretation of the results. However, our pooled data, with a large sample size, indicate a lower risk of MI with the use of rivaroxaban.

Also, the extent of benefit observed with the use of rivaroxaban in various trials was different, showing the greatest benefit against placebo and in the coronary artery disease trials [17,26]. The risk of bleeding, a well-known cause of mortality, has been heterogeneous in the various populations in which rivaroxaban has been tested. In the venous thromboembolism studies [18–21], when compared against enoxaparin, there was a significant reduction in the risk of bleeding, whereas in the AF study [16], when compared against warfarin, a noninferior result was achieved; however, in the ACS trials [17,26] a statistically significant increased risk of bleeding compared with placebo was observed. This evidence is consistent with the fact that both warfarin and enoxaparin are pharmacologically active moieties with associated significant risk of bleeding.

On the basis of available data of the two recently approved oral anticoagulants, one (dabigatran) appears to increase rates of MIs whereas the other (rivaroxaban) appears to lower the risk. This MI risk needs to be taken into the context of the overall risk and benefits of anticoagulation therapies from available evidence [37].

Conclusion

The oral factor Xa inhibitor, rivaroxaban, appears to lower the risk of MIs and cardiovascular mortality across a wide spectrum of patients when compared with clopidogrel and aspirin in an ACS population or warfarin in an AF population. Whether it is appropriate therapy in either of these populations must be based on this benefit versus the substantial risk of bleeding, and may be considered as the therapy of choice in patients at high risk of cardiovascular events.

Acknowledgements

Author contributions: Dr Chatterjee had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Chatterjee, Sharma, and Lichstein. Acquisition of data: Chatterjee and Sharma. Analysis and interpretation of data: Chatterjee, Uchino, Lichstein, and Mukherjee. Drafting of the manuscript: Chatterjee, Uchino, Sharma, and Mukherjee. Critical revision of the manuscript for important intellectual content: Chatterjee, Lichstein, and Mukherjee. Statistical analysis: Chatterjee and Sharma. Administrative, technical, and material support: Chatterjee and Lichstein. Study supervision: Lichstein, and Mukherjee.

Conflicts of interest

Dr Biondi-Zoccai has consulted/lectured for Astra Zeneca, Bristol Myers Squibb, and Sanofi Aventis. For the remaining authors there are no conflicts of interest.

References

1 Merlini PA, Bauer KA, Oltrona L, Ardissino D, Cattaneo M, Belli C, *et al.* Persistent activation of coagulation mechanism in unstable angina and myocardial infarction. *Circulation* 1994; **90**:61–68.

2 Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345**:494–502.

3 Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, *et al.* Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; **358**:527–533.

4 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324**:71–86.

5 Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, *et al.* Randomized Intervention Trial of unstable Angina Investigators. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. *Lancet* 2002; **360**:743–751.

6 Kong DF, Califf RM, Miller DP, Moliterno DJ, White HD, Harrington RA, *et al.* Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. *Circulation* 1998; **98**:2829–2835.

7 Steinhubl SR, Berger PB, Mann JT III, Fry ET, DeLago A, Wilmer C, Topol EJ. CREDO Investigators, Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; **288**:2411–2420.

8 Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, *et al.* CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; **352**:1179–1189.

9 Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002; **347**:969–974.

10 Brouwer MA, van den Bergh PJ, Aengevaeren WR, Veen G, Luijten HE, Hertzberger DP, *et al.* Aspirin plus coumarin versus aspirin alone in the prevention of reocclusion after fibrinolysis for acute myocardial infarction: results of the Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT)-2 Trial. *Circulation* 2002; **106**:659–665.

11 Coumadin Aspirin Reinfarction Study (CARS) Investigators. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. Coumadin Aspirin Reinfarction Study (CARS) Investigators. *Lancet* 1997; **350**:389–396.

12 Fiore LD, Ezekowitz MD, Brophy MT, Lu D, Sacco J, Peduzzi P. Combination Hemotherapy and Mortality Prevention (CHAMP) Study Group. Department of Veterans Affairs Cooperative Studies Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study. *Circulation* 2002; **105**:557–563.

13 Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. *Arch Intern Med* 2012; **172**:397–402.

14 Kubitza D, Becka M, Wensing G, Voith B, Zuehlsdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939 – an oral, direct factor Xa inhibitor – after multiple dosing in healthy male subjects. *Eur J Clin Pharmacol* 2005; **61**:873–880.

15 Kubitza D, Becka M, Roth A, Mueck W. Dose-escalation study of the pharmacokinetics and pharmacodynamics of rivaroxaban in healthy elderly subjects. *Curr Med Res Opin* 2008; **24**:2757–2765.

16 Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, *et al.* ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**:883–891.

17 Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, *et al.* ATLAS ACS 2 TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012; **366**:9–19.

18 Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, *et al.* RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008; **358**:2765–2775.

19 Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, *et al.* RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008; **372**:31–39.

20 Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, *et al.* RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008; **358**:2776–2786.

21 Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, *et al*. RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet* 2009; **373**:1673–1680.

22 Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 2008; **61**:64–75.

23 Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Med Res Methodol* 2009; **9**:86.

24 Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *J Clin Epidemiol* 2008; **61**:763–769.

25 Lan KK, Hu M, Cappelieri J. Applying the law of the iterated logarithm to cumulative meta-analysis of a continuous endpoint. *Statistica Sinica* 2003; **13**:1135–1145.

26 Mega JL, Braunwald E, Mohanavelu S, Burton P, Poulter R, Misselwitz F, *et al*. ATLAS ACS TIMI 46 Study Group. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. *Lancet* 2009; **374**:29–38.

27 Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, *et al*. EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; **363**:2499–2510.

28 Büller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, *et al*. EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012; **366**:1287–1297.

29 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009; **6**:e1000100.

30 Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions*. 2nd ed. Hoboken, NJ: Wiley; 2008.

31 Davis EM, Packard KA, Knezevich JT, Campbell JA. New and emerging anticoagulant therapy for atrial fibrillation and acute coronary syndrome. *Pharmacotherapy* 2011; **31**:975–1016.

32 Doggrell SA. Is there evidence to support the use of direct factor Xa inhibitors in coronary artery disease? *Rev Recent Clin Trials* 2011; **6**:147–157.

33 Squizzato A, Keller T, Romualdi E, Middeldorp S. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. *Cochrane Database Syst Rev* 2011; **1**:CD005158.

34 Murphy SA, Gibson CM, Morrow DA, Van de Werf F, Menown IB, Goodman SG, *et al*. Efficacy and safety of the low-molecular weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. *Eur Heart J* 2007; **28**:2077–2086.

35 Rothberg MB, Celestin C, Fiore LD, Lawler E, Cook JR. Warfarin plus aspirin after myocardial infarction or the acute coronary syndrome: meta-analysis with estimates of risk and benefit. *Ann Intern Med* 2005; **143**:241–250.

36 Alexander JH, Becker RC, Bhatt DL, Cools F, Crea F, Dellborg M, *et al*. APPRAISE Steering Committee and Investigators. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. *Circulation* 2009; **119**:2877–2885.

37 Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**:e44S–e48S.