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SYSTEMATIC REVIEW

Efficacy and Safety of New Oral Anticoagulants for Extended Treatment of Venous Thromboembolism: Systematic Review and Meta-Analyses of Randomized Controlled Trials

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Abstract
Introduction Currently available anticoagulants have limitations for long term treatment of venous thromboembolism (VTE).
Objective A meta-analysis was performed to evaluate the efficacy and safety of new oral anticoagulants (NOACs) for extended treatment of VTE.
Methods PubMed, Cochrane Library, EMBASE, Web of Science and CINAHL databases were searched from January 01, 2001 through February 28, 2013. Randomized controlled trials (RCTs) comparing NOACs (apixaban, rivaroxaban and dabigatran) with placebo or warfarin for extended treatment of VTE were selected. Primary efficacy outcome was recurrent VTE or VTE related death, and primary safety outcome was major bleeding. We used random-effects models.
Results Four RCTs included 7,877 participants. NOACs significantly lowered the risk of recurrent VTE or VTE-related death compared to placebo/warfarin (odds ratio [OR] 0.25, 95 % confidence interval [CI] 0.07 to 0.86; number needed to treat [NNT] = 30). All-cause mortality was significantly lower in NOACs group compared to placebo (OR 0.38, 95 % CI 0.18 to 0.80). Risk of major bleeding was not different with NOACs compared to placebo/warfarin (OR 0.88, 95 % CI 0.27 to 2.91). However, NOACs caused significantly higher rate of major or clinically relevant bleeding compared to placebo (OR 2.69, 95 % CI 1.25 to 5.77; number needed to harm [NNH] = 39). All three NOACs (apixaban, rivaroxaban and dabigatran) individually significantly reduced recurrent VTE or VTE-related death compared to placebo. Major or clinically relevant bleeding was higher with dabigatran and rivaroxaban but not with apixaban.
Conclusion NOACs are effective for the extended treatment of venous thromboembolism and may reduce the risk of all-cause mortality. Dabigatran and rivaroxaban may cause more major or clinically relevant bleeding.

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1 Introduction

The risk of recurrence of venous thromboembolism (VTE) persists even after initial anticoagulation therapy [1, 2]. For patients with unprovoked venous thromboembolism the 5 year risk of recurrence is higher and may reach upto 40 % [3]. These patient may need long term anticoagulation to prevent recurrence of venous thromboembolism. However, balancing the risks and benefits of extended duration of anticoagulation therapy is challenging. Although warfarin is effective for the prevention of recurrent events of venous thromboembolism, the use of warfarin is related to higher risk of bleeding, need for frequent monitoring and clinic visits, drug- drug interactions and drug-food interactions [4–6]. Low-intensity warfarin therapy for extended treatment resulted in

decreased efficacy without less bleeding [7, 8]. Newer agents dabigatran, rivaroxaban and apixaban have been evaluated recently in randomized trials for extended treatment of venous thromboembolism [9–11].

We performed a meta-analysis of randomized trials to assess the clinical benefit of new oral anticoagulants for the extended treatment of venous thromboembolism.

2 Materials and Methods

2.1 Data Sources and Searches

We searched PubMed, Cochrane Library, EMBASE, Web of Science and CINAHL databases for randomized trials using the following terms: "new oral anticoagulants," "oral thrombin inhibitors," "oral factor Xa inhibitors," "apixaban," "dabigatran," "rivaroxaban," "venous thromboembolism", from January 2001 through February 2013. We limited our search using the terms human, English language, and randomized controlled trial. We checked the reference lists of all retrieved articles by our electronic searches to find other eligible trials.

2.2 Study Selection

For this study we followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses of RCTs [12]. To be included in this present analysis, eligible trials had to fulfill the following predefined criteria: randomized clinical trials of participants comparing new oral anticoagulants (apixaban, rivaroxaban or dabigatran) with any comparators (placebo or warfarin); reporting atleast on recurrent venous thromboembolism/death, and any of recurrent venous thromboembolism, death, major bleeding, major or clinically relevant bleeding, incidence of acute coronary syndrome(s), and reported duration of follow-up of atleast 6 months. We also excluded trials of primary prevention in medically-ill patients.

2.3 Data Extraction and Quality Assessment

Two authors (PS and SC) independently reviewed the trials for eligibility and risk of trial bias and extracted data. Disagreements were resolved by consensus. The risk of bias was assessed by using the components recommended by the Cochrane Collaboration in the Cochrane Handbook of Systematic Reviews [13]. When more than one dose of the study drug was used in a single trial; we added the data related to particular outcome for all doses. Longest follow up data from individual trials was incorporated in our analysis.

2.4 Data Synthesis and Analysis

2.4.1 Outcome Measures

The primary efficacy outcome of interest was recurrent venous thromboembolism or venous thromboembolism related death. Other efficacy outcomes were all-cause mortality and mortality related to venous thromboembolism. The primary safety outcome of interest was major bleeding. Other safety outcomes were major or clinically relevant bleeding and incidence of acute coronary syndrome.

2.4.2 Statistical Analysis

The statistical analysis was done in line with recommendations from the Cochrane Collaboration and the PRISMA statement [12]. We did data analyses using RevMan 5.2.4 software (Nordic Cochrane Centre, Cochrane Collaboration, 2013). We assessed heterogeneity with the I^2 test. I^2 is the proportion of total variation observed between the studies attributable to differences between studies rather than sampling error (chance). $I^2 < 25$ % was considered as low heterogeneity and $I^2 > 75$ % as high. Intention to treat principle was followed and we represent data as odds ratio and corresponding 95 % confidence interval. The odds ratio was calculated with the random effects models described by DerSimonian and Laird. Publication bias was assessed through visual inspection of the asymmetry in funnel plots.

For the purpose of adjustment, considering different lengths of follow-up for individual trials, and to account for censored data, we used the rate of recurrent VTE or VTE related death as person years to obtain the log rate ratio of NOACs versus the comparators in individual trials (assuming a constant rate of incidence of primary efficacy outcomes of interest for individual trials in a random-effects Poisson regression model). Patient years of follow-up were calculated for each trial by multiplying the trial sample size with the mean duration of follow-up of the trial. Rate ratio was estimated from the median and the accompanying 95 % confidence intervals, assuming a constant rate of hazard of VTE or VTE related death for the individual trials over the period of follow up. We considered the longest reported follow up data for our follow-up adjusted analysis.

3 Results

3.1 Study Selection

We initially identified 2258 potentially eligible records using the database and other searches (Fig. 1). From the

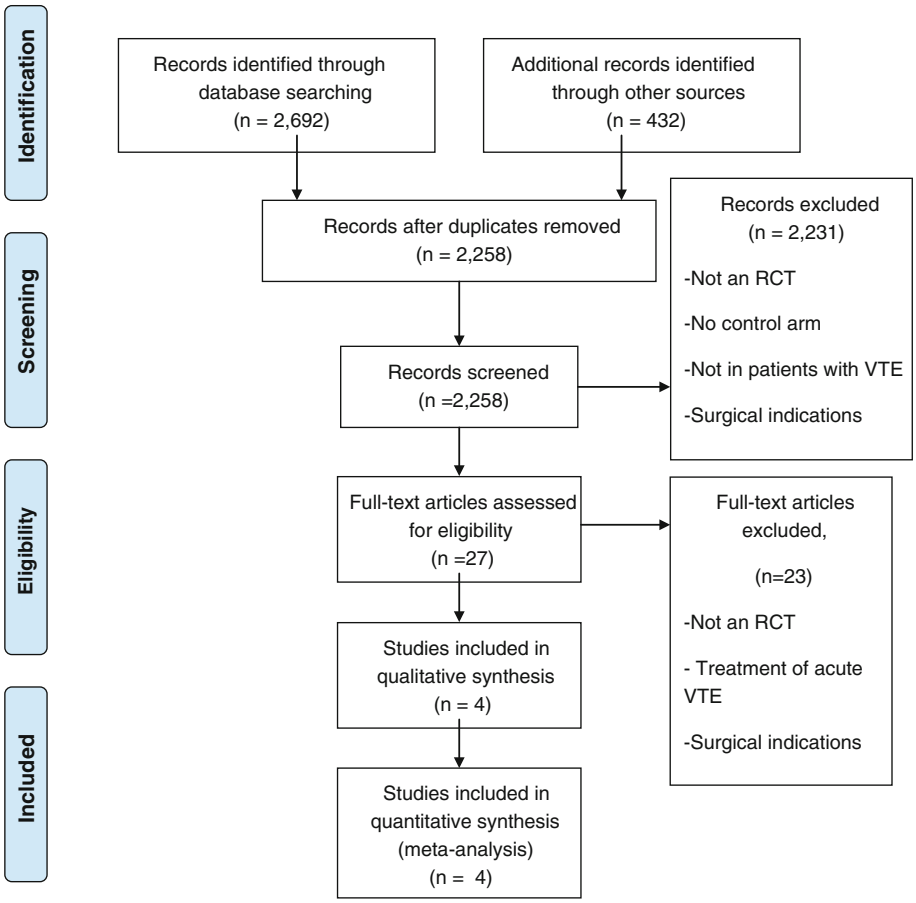

Fig. 1 Search strategy and study selection as per PRISMA checklist

identified records, 2231 articles were excluded for various reasons as mentioned in Fig. 1. Finally we assessed 27 full text articles for eligibility, of which four trials met the inclusion criteria and were selected for final analysis. The four trials enrolled 7,877 patients, 4366 in the NOAC group and 3511 in the comparator group.

3.2 Study Characteristics

Of the identified trials, two trials evaluated dabigatran [11] and one trial each evaluated rivaroxaban [10] and apixaban [9]. Rivaroxaban trial was sponsored by Bayer Schering Pharma and Ortho-McNeil, dabigatran trials by Boehringer Ingelheim and apixaban trial by Bristol-Myers Squibb and Pfizer.

The basic baseline characteristics of the included trials are summarized in Table 1. Comparator group in all included trails were placebo, except RE-MEDY [11] trial (evaluated dabigatran versus warfarin). The length of follow-up ranged from six months to 36 months. The mean age of the patients ranged from 53.9–58.4 years and 56–61 % were men. Percentage of patients with unprovoked venous thromboembolism ranged from 73–93 %. Patients with cancer ranged from 1.1 % to 4.7 % and outcomes related cancer patients were not consistently reported in individual trials.

All the included trials were double blind randomized controlled trials and the risk of bias assessment showed overall quality of the included trials was considered to be good (Table 2).

3.3 Efficacy Outcomes

Recurrent VTE or VTE related death occurred in 1.5 % patients receiving NOACs, as compared with 4.8 % receiving placebo/warfarin (Odds ratio [OR] 0.25, 95 % confidence interval [CI] 0.07 to 0.86, I^2 = 92 %), absolute risk reduction (ARR) of 3.3 % or a number needed to treat (NNT) of 30 (Fig. 2). Similar beneficial results of NOACs was observed with separate analysis compared to placebo only (OR 0.16, 95 % CI 0.11 to 0.24, I^2 = 0 %; 1.3 % versus 7.3 %, ARR = 6 % and NNT = 17). All-cause mortality was significantly lower in the NOACs group compared to placebo (OR 0.38, 95 % CI 0.18 to 0.80, I^2 = 0 %) (Fig. 2). All-cause mortality compared with placebo/warfarin showed borderline significance (OR 0.61, 95 % CI 0.37 to 1.00, I^2 = 0 %). Mortality related to VTE was not different with NOACs compared to the comparators (Fig. 2).

Table 1 Characteristics of Randomized Clinical Trials

Trial (Reference)	Trial Design	Intervention	Control	Mean age (years) NOAC/ Comparator	Men (%) NOAC/ Comparator	Unprovoked VTE (%) NOAC/ Comparator	Patient with cancer (%); NOAC/ Comparator	Follow up
AMPLIFY-EXT 2013 (9)	Double-blind randomized trials	Apixaban 2.5 mg twice daily (n = 840)	Placebo (n = 829)	56.6 ± 15.3/ 57.1 ± 15.2	58.0/56.5	93.2/91.1	1.8/2.2	12 months
	Double-blind randomized trials	Apixaban 5 mg twice daily (n = 813)		56.4 ± 15.6	57.7	90.7	1.1	
EINSTEIN-Ext. 2010 (10)	Double-blind randomized event-driven superiority trials	Rivaroxaban 20 mg daily (n = 602)	Placebo (n = 594)	58.2 ± 15.6/ 58.4 ± 16	58.8/57.1	73.1/74.2	4.7/4.4	6 or 12 months
RE-MEDY (2013) (11)	Double-blind randomized trials	Dabigatran 150 mg twice daily (n = 1430)	Warfarin (n = 1426)	55.4 ± 15.0/ 53.9 ± 15.3	60.9/61.1	77.5/77.5 #	4.2/4.1	6 to 36 months
RE-SONATE (2013) (11)	Double-blind randomized trials	Dabigatran 150 mg twice daily (n = 681)	Placebo (n = 662)	56.1 ± 15.5/ 55.5 ± 15.1	55.9/55.0	87.2/89.7 #	##	Up to 12 months

Causes of thrombophilia unknown

Active cancer was an exclusion criterion

AMPLIFY-EXT = Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy–Extended Treatment; NOAC = New oral anticoagulants; VTE = venous thromboembolism

Table 2 Risk of bias assessments for included randomized clinical trials #

Study Name	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
AMPLIFY-EXT 2013	Low	Low	Low	Low	Low	Low	Low
EINSTEIN-Ext. 2010	Low	Low	Low	Low	Low	Low	Low
RE-MEDY (2013)	Low	Low	Low	Low	Low	Low	Low
RE-SONATE (2013)	Low	Low	Low	Low	Low	Low	Low

In the double-blind RE-MEDY trial, investigators initially decided the need for anticoagulation by considering the risk for recurrence of venous thromboembolism (After that, patients were randomly assigned to dabigatran or warfarin). In the RE-SONATE trial and AMPLIFY-EXT trials, treating physicians were uncertain about the need for continued anticoagulation. In the EINSTEIN–Extension trial, 25 % of patients in each group had shorter-than-intended follow-up due to event-driven early termination

3.3.1 Stratification by Individual Drug

Data were also stratified according to different new oral anticoagulants. All three NOACs (apixaban, rivaroxaban and dabigatran) individually significantly reduced the combined end-point of recurrent VTE or VTE related death compared to placebo (Table 3). Individual effects of NOACs in reduction of risk of all-cause mortality or VTE related mortality compared to placebo did not reach statistical significance.

3.4 Safety Outcomes

Major bleeding occurred 0.5 % patients with NOACs compared to 0.8 % with placebo/warfarin (OR 0.88, 95 % CI 0.27 to 2.91, I^2 = 49 %) (Fig. 3). Similar results were

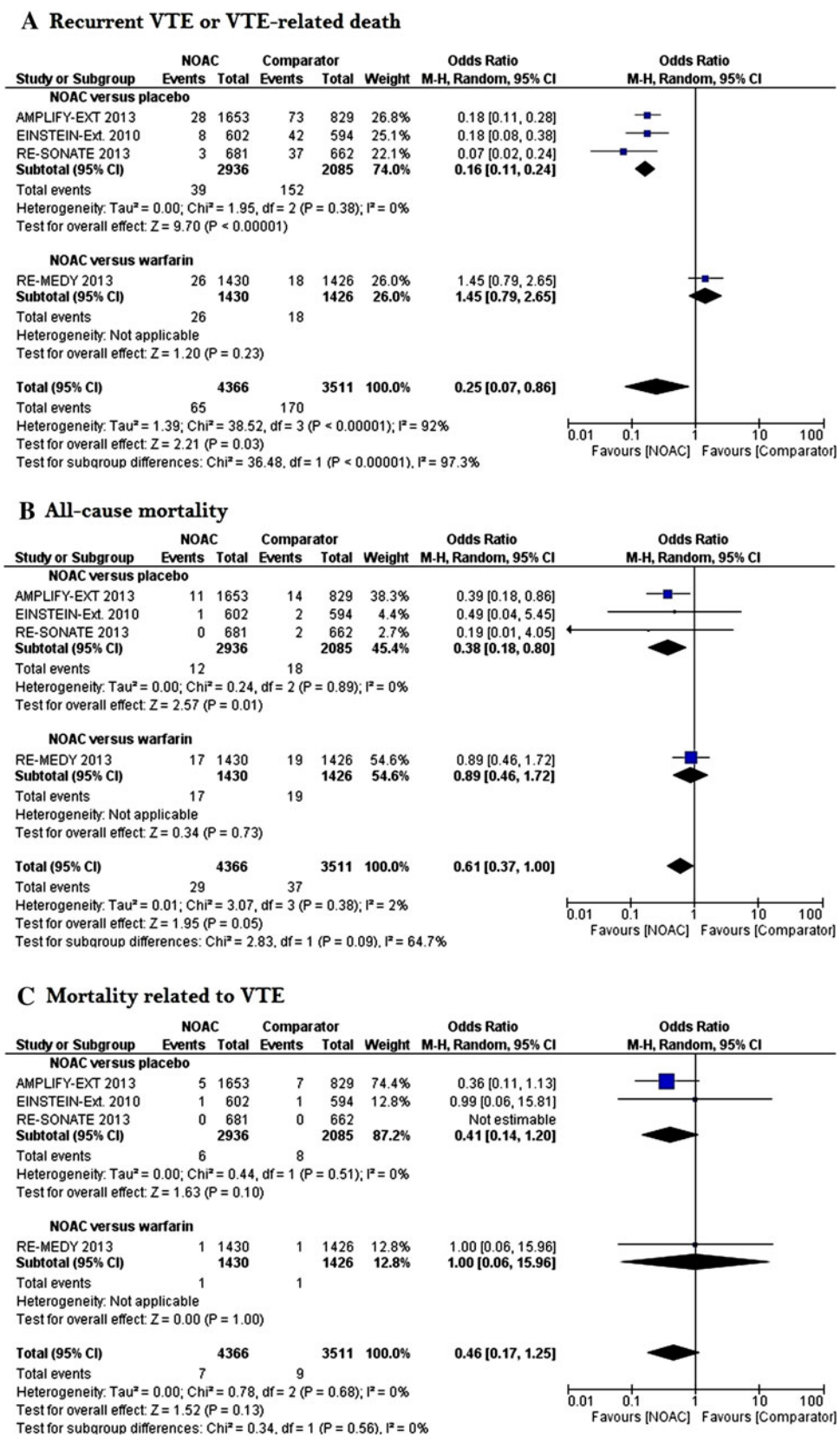

Fig. 2 Forest plot(s) comparing NOAC and comparator (placebo/warfarin) for extended treatment of venous thromboembolism (VTE): for recurrent VTE or VTE-related death (**a**), and all-cause mortality (**b**), Mortality related to VTE (**c**). *M-H* Mantel-Haenszel, *NOAC* new oral anticoagulant

Table 3 Efficacy and safety of individual NOAC versus comparator (placebo/warfarin)

	Odds ratio (Confidence interval)		Odds ratio [Confidence interval]
Recurrent VTE or VTE-related death		**Major bleeding**	
Apixaban versus placebo	**0.18 [0.11, 0.28]**	Apixaban versus placebo	0.38 [0.08, 1.68]
Rivaroxaban versus placebo	**0.18 [0.08, 0.38]**	Rivaroxaban versus placebo	8.94 [0.48, 166.41]
Dabigatran versus placebo	**0.13 [0.06, 0.30]**	Dabigatran versus placebo	4.83 [0.23, 100.83]
Dabigatran versus comparator	0.34 [0.02, 7.39]	Dabigatran versus comparator	0.95 [0.13, 6.84]
All-cause mortality		**Major or clinically relevant bleeding**	
Apixaban versus placebo	0.39 [0.18, 0.86]	Apixaban versus placebo	1.43 [0.87, 2.34]
Rivaroxaban versus placebo	0.49 [0.04, 5.45]	Rivaroxaban versus placebo	**5.34 [2.35, 12.09]**
Dabigatran versus placebo	0.19 [0.01, 4.05]	Dabigatran versus placebo	**3.00 [1.54, 5.81]**
Dabigatran versus comparator	0.83 [0.44, 1.58]	Dabigatran versus comparator	1.22 [0.22, 6.76]
Mortality related to VTE		**Adverse events**	
Apixaban versus placebo	0.36 [0.11, 1.13]	Apixaban versus placebo	**0.81 [0.67, 0.97]**
Rivaroxaban versus placebo	0.99 [0.06, 15.81]	Rivaroxaban versus placebo	Not reported
Dabigatran versus placebo	Not estimable	Dabigatran versus placebo	1.06 [0.85, 1.31]
Dabigatran versus comparator	1.00 [0.06, 15.96]	Dabigatran versus comparator	1.06 [0.93, 1.20]
Acute coronary syndrome		**Adverse event leading to discontinuation of study drug**	
Apixaban versus placebo	Not estimable	Apixaban versus placebo	**0.43 [0.34, 0.56]**
Rivaroxaban versus placebo	3.97 [0.44, 35.59]	Rivaroxaban versus placebo	Not reported
Dabigatran versus placebo	0.96 [0.06, 15.43]	Dabigatran versus placebo	**0.56 [0.39, 0.81]**
Dabigatran versus comparator	**3.37 [1.07, 10.58]**	Dabigatran versus comparator	0.82 [0.40, 1.67]
ALT > 3x ULN + bilirubin > 2x ULN			
Apixaban versus placebo	0.17 [0.02, 1.60]		
Rivaroxaban versus placebo	Not estimable		
Dabigatran versus placebo	Not estimable		
Dabigatran versus comparator	2.00 [0.18, 22.03]		

ALT Alanine aminotransferase; *NOAC* new oral anticoagulant; *ULN* upper limit of normal; *VTE* venous thromboembolism

observed with NOACs compared to placebo (0.3 % versus 0.2 %, OR 1.87, 95 % CI 0.19 to 17.96, $I^2 = 61$ %). However NOACs caused significantly higher rate of major or clinically relevant bleeding compared to placebo [4.6 % versus 2.0 %, OR 2.69, 95 % CI 1.25 to 5.77, $I^2 = 76$ %; absolute risk increase (ARI) of 2.6 % or a number needed to harm (NNH) of 39] (Fig. 3). No significant difference was observed for any adverse events between NOACs and comparators (placebo/warfarin) or only placebo (Fig. 4). Adverse event leading to discontinuation of study drug was significantly lower with NOACs compared to placebo. Risk of acute coronary syndrome was higher with newer agents (Fig. 3); however this risk was contributed majorly by dabigatran (dabigatran versus comparator; OR 3.37, 95 % CI 1.07, 10.58); and a trend towards higher (statistically non-significant) acute coronary syndrome was also observed with rivaroxaban 3.97 [0.44, 35.59], but not with apixaban (no incidence of ACS reported) (Table 3).

3.4.1 Stratification by Individual Drug

Compared to placebo major or clinically relevant bleeding was higher with dabigatran (OR 3.00, 95 % CI 1.54 to 5.81) and rivaroxaban (OR 5.34, 95 % CI 2.35 to 12.09) but not with apixaban (OR 1.43, 95 % CI 0.87 to 2.34) (Table 3).

3.5 Follow up Adjusted Analysis

Our follow up adjusted analysis showed that there is 73 % lower relative rate of occurrence of the primary endpoint for recurrent venous thromboembolism or venous thromboembolism related death with use of NOACs in comparison to placebo/warfarin for extended treatment of venous thromboembolism (Rate Ratio [RR] 0.27, 95 % CI 0.08 to 0.86, $I^2 = 92$ %) (Fig. 5).

We did not found any significant publication bias with examination of funnel plots for any of the above

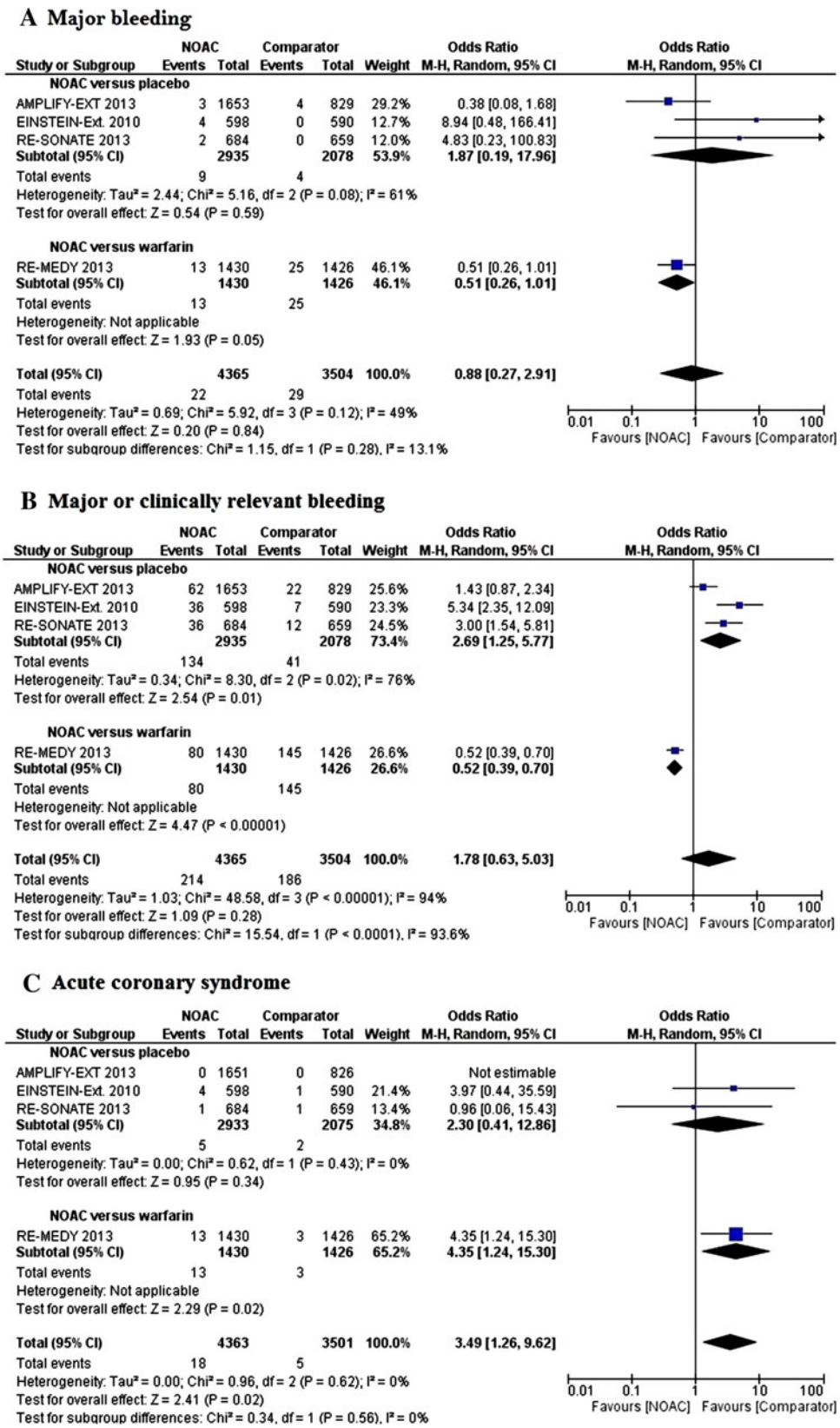

Fig. 3 Forest plot(s) comparing NOAC and comparator (placebo/warfarin) for extended treatment of venous thromboembolism: for major bleeding (**a**), major or clinically relevant bleeding (**b**), acute coronary syndrome (**c**). *M-H* Mantel-Haenszel, *NOAC* new oral anticoagulant

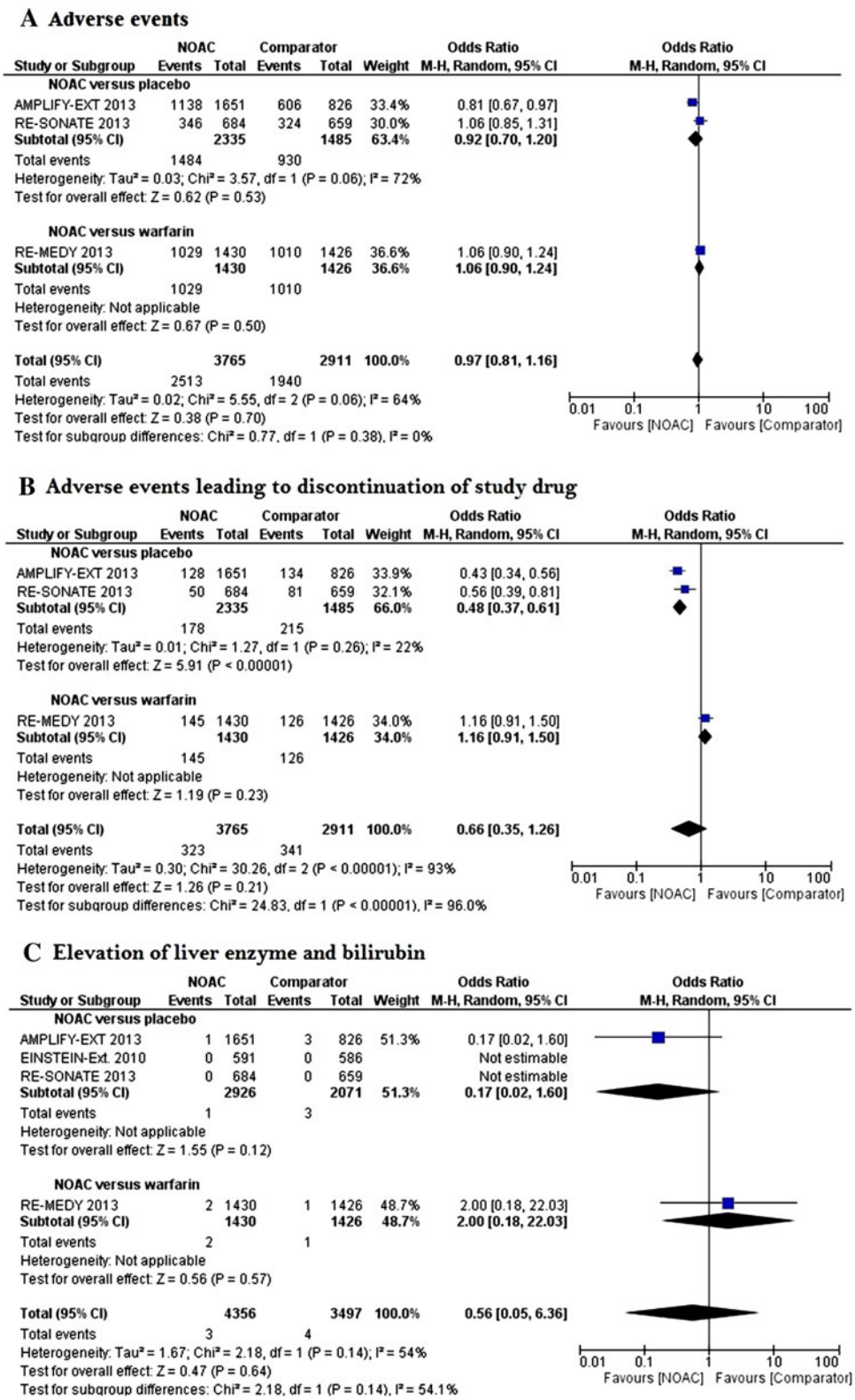

Fig. 4 Forest plot(s) comparing NOAC and placebo for extended treatment of venous thromboembolism: for adverse events (**a**), adverse events leading to discontinuation of study drug (**b**), elevation of liver enzyme and bilirubin (**c**). *M-H* Mantel-Haenszel, *NOAC* new oral anticoagulant

analyses (Fig. 6). We also performed an Egger's test of regression for publication bias, which results not revealing any significant bias from the 4 trials included ($p = 0.127$).

4 Discussion

This meta-analysis attempts to provide a comprehensive summary of the effects of new oral anticoagulants for

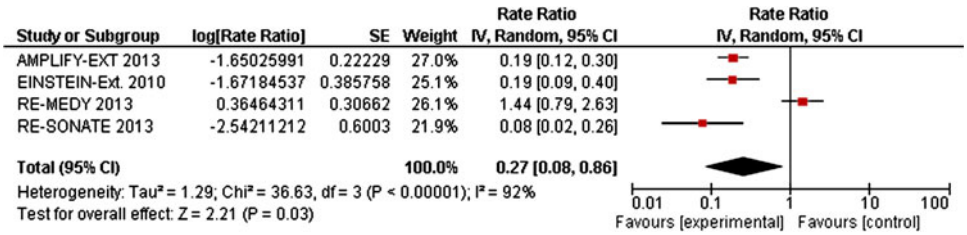

Fig. 5 Follow up adjusted analysis for recurrent VTE or VTE-related death (NOAC versus comparator). *IV* inverse variance, *NOAC* new oral anticoagulant, *SE* standard error, *VTE* venous thromboembolism

extended treatment of venous thromboembolism. The present meta-analysis shows that new oral anticoagulants significantly reduced the risk of recurrent venous thromboembolism or thromboembolism related death compared to placebo. All three new agents (apixaban, rivaroxaban, and dabigatran) were effective compared to placebo. Newer agents may reduce the risk of all-cause mortality compared to placebo. NOACs did not cause higher risk of major bleeding; however dabigatran and rivaroxaban caused a higher degree of major or clinically relevant bleeding compared to placebo.

4.1 Comparisons with Prior Studies

Meta-analysis evaluating NOACs in acute venous thromboembolism showed that efficacy of the new oral anticoagulants were not significantly different compared with conventional anticoagulation (vitamin K antagonists) [14]. Rivaroxaban showed lower risk of major bleeding for treatment in acute VTE [14]. However our analyses for extended treatment of venous thromboembolism showed newer agents are more efficacious than placebo, and apixaban caused less major or clinically relevant bleeding. A previous trial has shown that aspirin therapy (100 mg daily) reduced the risk of recurrence by 42 % compared to placebo and did not cause any extra major bleeding when given to patients with unprovoked venous

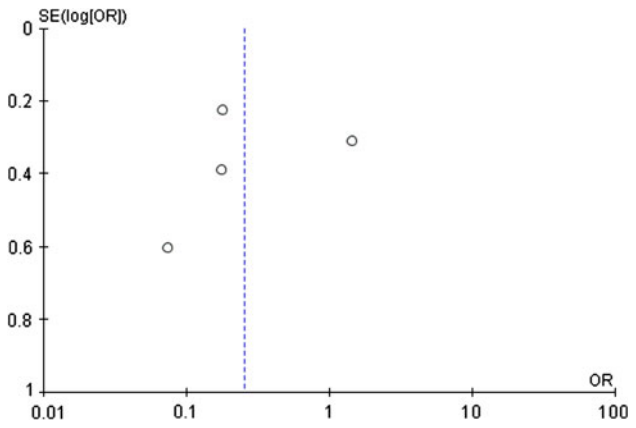

Fig. 6 Funnel plot to assess publication bias for studies assessing recurrent VTE or VTE-related death with NOAC and comparator; *NOAC* new oral anticoagulant, *OR* odds ratio, *SE* standard error, *VTE* venous thromboembolism

thromboembolism [15]. Use of warfarin may result in as high as 95 percent reduction in the risk of recurrent venous thromboembolism but is related to an increased risk of major bleeding of 1 to 2 % per year [16, 17]. Our analysis revealed that newer agents may reduce the risk of recurrence of venous thromboembolism or related death by 84 % compared to placebo, with a number needed to treat of only 17; and use of NOACs caused low absolute rates of major bleeding (0.3 % to 0.5 %). Our result showed there might be a chance of higher risk of acute coronary syndrome(s) with dabigatran compared to warfarin, however a recent large propensity score matched nationwide cohort study from Denmark in patient with atrial fibrillation showed lower risk of myocardial infarction with dabigatran, compared to warfarin [18].

4.2 Interpretation of Our Results and Applicability

The NOACs showed superiority in efficacy over placebo but not against an active comparator like warfarin. Only, the, RE-MEDY trial directly compared a new oral anticoagulant (dabigatran) with warfarin for this indication and the efficacy result (recurrent venous thromboembolism) just marginally met the prespecified noninferiority boundary [11]. No trials have yet evaluated newer agents in comparison to aspirin. In practice, choice of preferred agents for extended treatment of venous thromboembolism should be individualized depending on risks of recurrence and bleeding. NOACs should be considered in patients with high risk of recurrence after unprovoked venous thromboembolism. Risk of bleeding with newer agents should also be kept in mind while prescribing these drugs, as there is no reliable reversal agent available. Apixaban might be a better choice among newer agents for patients with high risk of bleeding for extended treatment of venous thromboembolism. In view of recent disappointing results seen with extended thromboprophylaxis in 'medically-ill' patients [19], our results indicate that in many patients, the NOACs may provide effective secondary prevention/therapy of thromboprophylaxis.

However, as with results of other meta-analyses, our results should be used for hypothesis generation and as a basis for randomized trials to directly compare these newer agents with one another, and with warfarin and aspirin.

Table 4 Definitions of efficacy and safety outcome in the included trails

	Recurrent VTE or VTE related death	Major bleeding	Clinically relevant non-major bleeding
AMPLIFY-EXT 2013	**Pulmonary embolism (PE)** Symptoms of PE with one of the following findings • A new intraluminal filling defect in (sub)segmental or more-proximal branches on spiral computed tomography (CT) of the chest • A new intraluminal filling defect, or an extension of an existing defect, or a new sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram • A new perfusion defect of at least 75 % of a segment, with a local normal ventilation result (high probability) on ventilation/perfusion lung scintigraphy (VQ scan) • Inconclusive spiral CT, pulmonary angiography, or VQ scan evidence of a new or recurrent PE, with demonstration of a new or recurrent deep vein thrombosis (DVT) in the lower extremities by compression ultrasound (CUS) or venography **Deep vein thrombosis (DVT)** Symptoms of DVT with one of the following findings (a) For a NEW DVT: ■ abnormal CUS, including grey-scale or color-coded Doppler, or ■ an intraluminal filling defect on venography (b) For a RECURRENT DVT: ■ abnormal CUS where compression had been normal or, if non-compressible during screening, a substantial increase (4 mm or more) in diameter of the thrombus during full compression, or ■ an extension of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of non-visualization of veins in the presence of a sudden cut-off on venography **VTE-related death** a) PE (based on objective diagnostic testing, autopsy) b) Unexplained death (and VTE cannot be ruled out) c) Sudden death (and VTE cannot be ruled out)	Major bleeding was defined as overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more, led to transfusion of 2 or more units of red cells, occurred in a critical site, or contributed to death	Clinically relevant nonmajor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but that was associated with the need for medical intervention, unscheduled contact with a physician, interruption or discontinuation of the study drug, or discomfort or impairment of activities of daily living
EINSTEIN-Ext. 2010	**Deep-vein thrombosis** A new noncompressible venous segment or a substantial increase (4 mm or more) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography . **Pulmonary embolism** Intraluminal filling defect on spiral CT or pulmonary angiography, a cutoff of a vessel of more than 2.5 mm in diameter on pulmonary angiography, a new perfusion defect of at least 75 % of a segment with corresponding normal ventilation (high probability), a new non– high-probability perfusion defect associated with deep-vein thrombosis, as documented by ultrasonography or venography **Fatal pulmonary embolism** was based on objective diagnostic testing, autopsy, or death which could not be attributed to a documented cause and for which pulmonary embolism could not be ruled out (unexplained death)	Bleeding was defined as major if it was clinically overt and associated with a fall in the hemoglobin level of 20 g per liter or more, or if it led to transfusion of two or more units of red cells, or if it was retroperitoneal, intracranial, occurred in a critical site, or contributed to death	Clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of study treatment, or associated with any other discomfort such as pain or impairment of activities of daily life

Table 4 continued

	Recurrent VTE or VTE related death	Major bleeding	Clinically relevant non-major bleeding
RE-MEDY (2013)	Recurrent symptomatic and objectively verified VTE or death associated with VTE (this included unexplained death in the placebo-control study). Clinically suspected recurrent DVT had to be objectively verified using pre-specified imaging studies	Bleeding was defined as major if it was clinically overt and associated with a fall of the hemoglobin level of 20 g/L or required transfusion of at least 2 units of red cells or, involved a critical organ or was fatal, in accordance with the recommendation of the International Society on Thrombosis and Haemostasis	At least one of the following criteria had to be fulfilled: a) Spontaneous skin hematoma of at least 25 cm b) Spontaneous nose bleed of more than 5 min duration c) Macroscopic hematuria, either spontaneous or, if associated with an intervention, lasting more than 24 h d) Spontaneous rectal bleeding (more than spotting on toilet paper) e) Gingival bleeding for more than 5 min f) Bleeding leading to hospitalization and/or requiring surgical treatment g) Bleeding leading to a transfusion of less than 2 units of whole blood or red cells h) Any other bleeding event considered clinically relevant by the investigator
RE-SONATE (2013)	Same as RE-MEDY	Same as RE-MEDY	Same as RE-MEDY

VTE venous thromboembolism

4.3 Study Limitations

Our present analysis has limitations. The results are subject to intrinsic limitations of meta-analyses: pooling of data from different trials with different study protocol, definitions for efficacy and safety outcomes, and baseline characteristics of the patients. As in other meta-analyses, given the lack of reported data in each trial, we were unable to adjust our analyses for compliance to assigned therapy. All the included trials received industry funding and the reporting of individual trial may also be influenced by expectations of the sponsors and investigators. However our assessment for quality of trials did not show any evidence of selection, assessment, attrition, or outcome reporting bias. The patient population in the included trials was comparatively younger, had a low risk of bleeding and did not have any strong indications for extended anticoagulation; which is different from the typical patient population in practice-and extrapolation from the trial data may be erroneous. We used the same definition for "mortality related to venous thromboembolism" which were used in individual trials and these definitions might vary to some extent (Table 4). Few of our results showed wide confidence intervals and a high degree of statistical heterogeneity; however the clinically important outcomes such as the analysis for the primary efficacy outcome compared to placebo, and all-cause mortality did not show any heterogeneity. We were unable to perform subgroup analysis according to the etiology of venous thromboembolism because of the lack of patient-level data. Another large trail (Hokusai-VTE study) with a different NOAC edoxaban is not yet published; hence we were unable to include that data.

5 Conclusion

The findings of NOACs significantly reducing the risk of recurrent venous thromboembolism or thromboembolism related death compared to placebo is of likely significance for clinical practice. All three new agents (apixaban, rivaroxaban, and dabigatran) individually as well as together, were effective compared to placebo-and thus represent a viable alternative to warfarin. Use of NOACs was not associated with higher risk of major bleeding, however dabigatran and rivaroxaban were found to be associated with higher risk of major or clinically relevant bleeding compared to placebo, reiterating the need for close clinical vigilance in patients on these medications.

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Authorship Partha Sardar had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors had access to the data and a role in study design, interpretation and writing of the manuscript.

Disclosure None.

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