Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Fracture Risks in Patients Treated With Different Oral Anticoagulants: A Systematic Review and Meta-Analysis

Huei-Kai Huang, MD; Carol Chiung-Hui Peng, MD; Shu-Man Lin, MD; Kashif M. Munir, MD; Rachel Huai-En Chang, MD, MPH, MBA; Brian Bo-Chang Wu, MD; Peter Pin-Sung Liu, MS; Jin-Yi Hsu, MD; Ching-Hui Loh, MD, DrPH; Yu-Kang Tu, DDS, MSc, PhD

BACKGROUND: Evidence on the differences in fracture risk associated with non-vitamin K antagonist oral anticoagulants (NOAC) and warfarin is inconsistent and inconclusive. We conducted a systematic review and meta-analysis to assess the fracture risk associated with NOACs and warfarin.

METHODS AND RESULTS: We searched PubMed, Embase, Cochrane Library, Scopus, Web of Science, and ClinicalTrials.gov from inception until May 19, 2020. We included studies presenting measurements (regardless of primary/secondary/tertiary/safety outcomes) for any fracture in both NOAC and warfarin users. Two or more reviewers independently screened relevant articles, extracted data, and performed quality assessments. Data were retrieved to synthesize the pooled relative risk (RR) of fractures associated with NOACs versus warfarin. Random-effects models were used for data synthesis. We included 29 studies (5 cohort studies and 24 randomized controlled trials) with 388 209 patients. Patients treated with NOACs had lower risks of fracture than those treated with warfarin (pooled RR, 0.84; 95% CI, 0.77–0.91; $P<0.001$) with low heterogeneity ($I^2=38.9\%$). NOACs were also associated with significantly lower risks of hip fracture than warfarin (pooled RR, 0.89; 95% CI, 0.81–0.98; $P=0.023$). A nonsignificant trend of lower vertebral fracture risk in NOAC users was also observed (pooled RR, 0.74; 95% CI, 0.54–1.01; $P=0.061$). Subgroup analyses for individual NOACs demonstrated that dabigatran, rivaroxaban, and apixaban were significantly associated with lower fracture risks. Furthermore, the data synthesis results from randomized controlled trials and real-world cohort studies were quite consistent, indicating the robustness of our findings.

CONCLUSIONS: Compared with warfarin, NOACs are associated with lower risks of bone fracture.

Key Words: anticoagulant ■ fracture ■ meta-analysis ■ NOAC ■ warfarin

Oral anticoagulants (OACs) are commonly prescribed to prevent or treat thromboembolic events in patients with atrial fibrillation or venous thromboembolism.[1,2] Warfarin, a vitamin K antagonist, is a traditional OAC and has been a primary long-term treatment option for patients with atrial fibrillation or venous thromboembolism for decades. Recently, non-vitamin K antagonist oral anticoagulants (NOACs) have been approved as alternatives to vitamin K antagonists and have demonstrated similar or superior efficacy and safety compared with warfarin.[3,4] Because aging is one of the strongest risk factors for both atrial fibrillation and venous thromboembolism,[5,6] the prescription of OACs has gradually increased in the aging population worldwide.

Some previous studies have suggested that warfarin may increase fracture risks via its vitamin K antagonizing effect, which impairs bone mineralization; in contrast, NOACs are independent of mechanisms associated with vitamin K antagonists. However,

Correspondence to: Yu-Kang Tu, DDS, MSc, PhD, No 17, Xu-Zhou Road, Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan.E-mail: yukangtu@ntu.edu.tw

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.019618

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This systematic review and meta-analysis gathered data from 388 209 participants in 29 studies and showed that patients taking non-vitamin K antagonist oral anticoagulants had an overall 16% lower risk of developing fractures compared with those taking warfarin.
- Subgroup analyses for individual non-vitamin K antagonist oral anticoagulants demonstrated that dabigatran, rivaroxaban, and apixaban were significantly associated with lower fracture risks.
- The evidence from real-world cohort studies and randomized controlled trials is quite consistent, indicating the robustness of our findings.

What Are the Clinical Implications?

- This meta-analysis provided up-to-date evidence showing that non-vitamin K antagonist oral anticoagulants may be the preferred alternatives to warfarin for lowering fracture risks in patients requiring oral anticoagulant therapy.

Nonstandard Abbreviations and Acronyms

NOAC	non-vitamin K antagonist oral anticoagulant
OAC	oral anticoagulant

previous studies have provided conflicting evidence on the association between warfarin and fracture risks.[7–10] A previous cohort study published in 2017 was the first to compare the fracture risk associated with an NOAC (dabigatran) and warfarin, reporting a significantly lower fracture risk in dabigatran users.[11] Another cohort study in 2017 observed no significant difference in fracture risks among patients taking NOACs (both dabigatran and factor Xa inhibitors) and warfarin.[12] In 2018, a meta-analysis based on 12 randomized controlled trials (RCTs) showed that patients treated with NOACs had significantly lower risks of overall fracture, but not hip or vertebral fracture, than patients treated with warfarin.[13] However, all trials included in that meta-analysis considered fracture data as adverse events, and none of them were specifically designed to assess fracture risks. Moreover, the follow-up duration was ≤12 months in over half of these trials, which might yield insufficient statistical power for evaluating fracture events and the relatively low risks of fracture reported by these trials. Recently, several population-based cohort studies with larger sample sizes, longer follow-up durations, and greater statistical powers were conducted to evaluate the association between different OACs and fracture risks.[14–17] In addition, there is a growing number of RCTs comparing NOACs with warfarin. The relevant evidence regarding the fracture risks associated with OACs continues to accumulate.

Because osteoporosis and bone fractures pose major threats to the elderly and OACs are mainly prescribed to older adults who have multiple risk factors for fractures,[17,18] it is critically essential to determine whether a difference in fracture risks exists between NOACs and warfarin. Therefore, we conducted a systematic review and meta-analysis to compare the risk of bone fractures between patients treated with NOACs and those treated with warfarin. We searched for both clinical trials and observational studies to comprehensively evaluate the current evidence on this issue and compared the results from RCTs to real-world evidence.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files.

Data Sources and Literature Search

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[19] We searched PubMed, Embase, Cochrane Library, Scopus, Web of Science, and ClinicalTrials.gov for studies from their inception until May 19, 2020. We applied 2 search strategies. In brief, we initially searched articles using combinations of the following terms: “NOAC,” “dabigatran,” “rivaroxaban,” “apixaban,” “edoxaban,” “warfarin,” “vitamin K antagonist,” and “fracture” (search strategy 1). This search was conducted to identify articles that evaluated the fracture risk in patients treated with NOACs versus those treated with warfarin, regardless of the study design. However, this search could not identify RCTs, which may have reported fracture data as a part of adverse events only, available on websites for clinical trial registration (eg, ClinicalTrials.gov). Therefore, we conducted another search that used the following terms: “NOAC,” “dabigatran,” “rivaroxaban,” “apixaban,” “edoxaban,” and “clinical trial,” to identify all potential eligible trials related to NOACs (search strategy 2). These terms represent a simplified search concept; the full details and the combinations of search terms used in literature search strategies 1 and 2 are described in Data S1. Additionally, we examined the reference lists from relevant review articles and meta-analyses for additional articles to be included. The protocol registration application for this study was performed (PROSPERO

[International Prospective Register of Systematic Reviews] registration number: CRD42020182607). Institutional ethical approval was not required because this was a meta-analysis of data from published studies only.

Study Selection and Inclusion Criteria

We included studies if they (1) presented outcome measurements for any fracture in both NOAC and warfarin users, regardless of whether it was reported as primary/secondary/tertiary outcomes or referred to as an adverse/safety event in the articles or supplementary data or on online sites (such as the ClinicalTrials.gov website); and (2) compared and reported the relative risk (RR) of fracture between NOACs and warfarin, or it could be derived from the data in the study. No specific restrictions were set for study population, treatment indication, or treatment/follow-up duration. Clinical trials, cohort studies, and case–control studies that provided sufficient data were eligible. As observational studies (cohort and case–control) should report properly adjusted estimates by considering potential confounders (age and sex, at minimum), studies in which only unadjusted estimates were available were excluded. We excluded review articles, case reports, editorials, and letters to the editor that did not report original findings, and studies conducted in a laboratory or on animals. Three reviewers (H.-K.H., C.-C.P., and S.-M.L.) independently screened all titles and abstracts and evaluated the relevant articles. If a study was deemed eligible by any reviewer, that study was included for further full-text review. Two reviewers (H.-K.H. and C.-C.P.) then independently assessed the full texts of the studies, and any disagreement was resolved by consensus among members of the study team. We used Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) to manage our systematic review process, coordinating each author's work and enabling collaboration among the entire review team.

Study Outcomes

The primary outcome was any fracture event. The secondary outcomes were events of hip and vertebral fractures (the most common and quintessential osteoporotic fractures). Comparisons were made between all NOACs and warfarin, as well as between individual NOACs and warfarin.

Data Extraction and Quality Assessment

Two authors (H.-K.H. and C.-C.P.) independently extracted data using a prespecified standardized form, which included author names, trial name, publication year, study design, country, treatment indication, NOAC type, follow-up duration, mean age, sex, sample size, reported fracture sites, fracture risk estimates, and covariates adjusted in observational studies. A third author (S.-M.L.) then independently examined the extracted data and resolved any discrepancies. For observational studies, adjusted hazard ratios (HRs) or risk ratios along with standard errors were extracted. When a study reported estimates from covariate-adjusted models and propensity score matching/weighting models, we considered the latter less biased and preferred for inclusion in the meta-analysis.[15–17] In RCTs, we extracted fracture events and patient numbers in each treatment group. The total number of fracture events was the sum of any fracture site reported on the ClinicalTrials.gov website, because we were unable to obtain the exact number of patients developing fractures from the full texts of articles and trial registration websites.

Study quality was accessed independently by 3 reviewers (H.-K.H., R.H.-E.C., and B.B.-C.W.) using the Cochrane Collaboration's Risk of Bias tool for RCTs and the Newcastle–Ottawa Scale for observational studies.[20,21] Discrepancies were resolved via discussions among members of the study team.

Statistical Analysis

Risk ratios for fracture reported by RCTs and the adjusted HRs reported by observational studies were pooled together to calculate RRs in our meta-analysis. Between-study heterogeneity was evaluated using the I^2 and τ^2 statistics.[22,23] The heterogeneity was considered low, moderate, and high for I^2<50%, 50% to 75%, and >75%, respectively. The τ^2 was interpreted using the same units as the pooled effect (logarithm of RR). Considering the between-study heterogeneity, we calculated the pooled RR and respective 95% CIs using the DerSimonian and Laird random effects model.[24]

We conducted several predefined subgroup analyses to determine if the pooled estimates were influenced by different study-level factors. The subgroup analyses were conducted according to NOAC type (dabigatran, rivaroxaban, apixaban, or edoxaban), study design (RCT or cohort study), indication (atrial fibrillation or venous thromboembolism), mean follow-up period, mean age, sample size, and the geographic location of participants (North America, Europe, Asia, or multiple continents). We made efforts to contact the corresponding authors when additional information was required for subgroup analyses, but we did not receive any replies from the authors

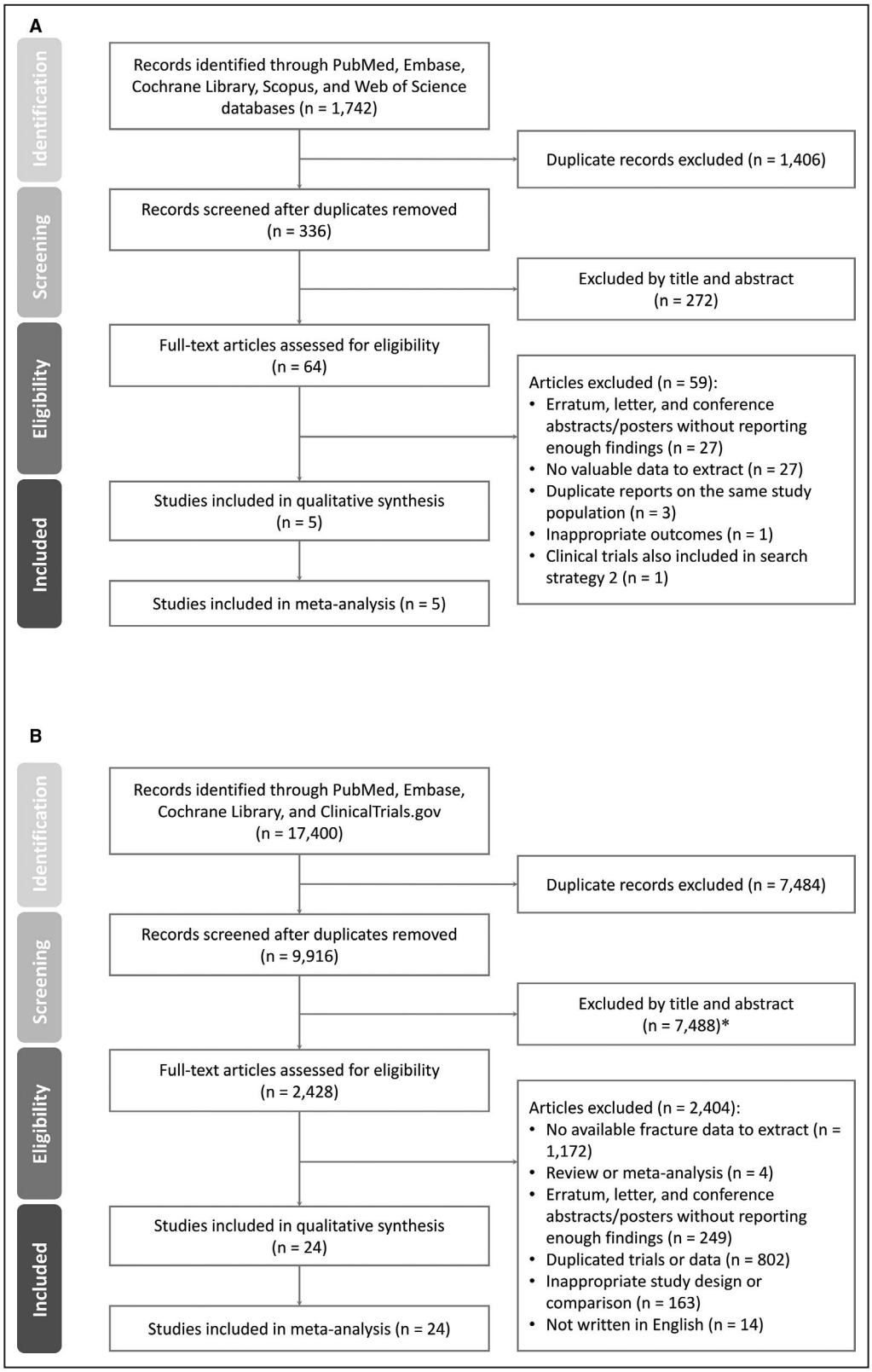


Figure 1. Flow diagram of literature search and article selection. (A) Search strategy 1. (B) Search strategy 2.

*In search strategy 2, we searched only for RCTs of NOACs; if the titles/abstracts were enough to help judge that the publications were not RCTs of NOACs or on an irrelevant topic, they were excluded in the title/abstract screening stage. NOAC indicates non-vitamin K antagonist oral anticoagulant; and RCT, randomized controlled trial.

of those studies.[11,12,17] Meta-regressions were further performed if sufficient studies (n≥10) were available. Egger's regression test and Begg's adjusted rank correlation test were conducted to determine publication bias.[25,26] If there were ≥10 studies included in the meta-analysis, we conducted a funnel plot analysis to assess publication bias or small study bias. A sensitivity analysis was conducted to evaluate the influence of each study on the overall pooled estimate (by omitting each study individually). All statistical tests were 2 sided, and results with $P<0.05$ were considered statistically significant. All statistical analyses were conducted using Stata version 15.1 (Stata Corporation, College Station, TX, USA).

RESULTS

Search Results

With search strategy 1, a total of 1742 studies were identified. After excluding duplicates and screening the titles and abstracts, 64 potentially relevant studies were retrieved for full-text review. Three studies, which were conducted by Lutsey et al,[15] Norby et al,[27] and Bengtson et al,[28] used the same databases (MarketScan Commercial Claims and Encounters and MarketScan Medicare Supplemental and Coordination of Benefits databases). The study by Lutsey et al was included in the final analysis because only this study declared fracture risks as the

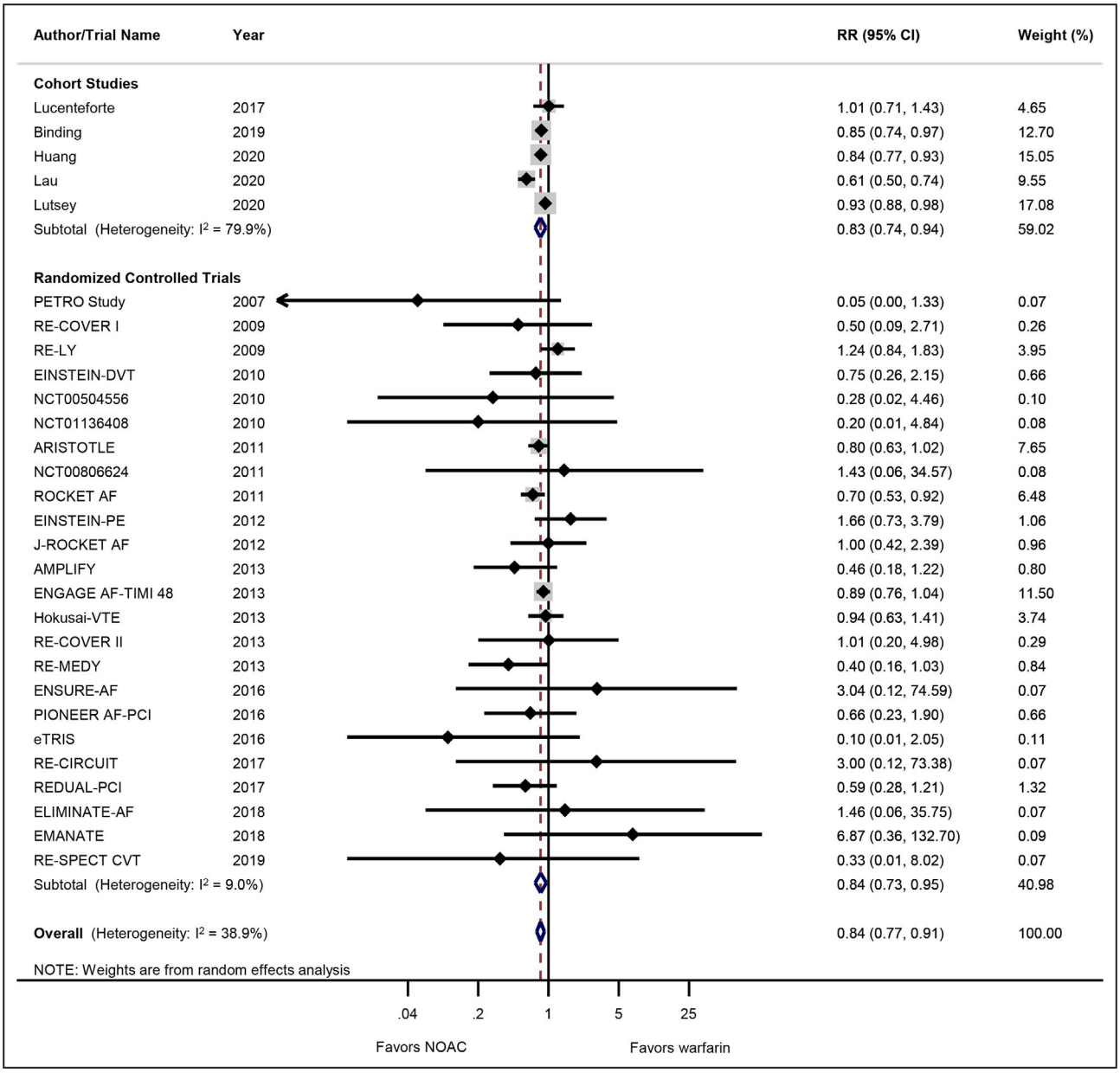


Figure 2. Forest plot of the relative risk of any fracture associated with NOACs compared with warfarin.[12,14–17,30–53]
NOAC indicates non-vitamin K antagonist oral anticoagulant; and RR, relative risk.

primary outcome and thus reported more comprehensive results.[15] In addition, Lau et al published 2 studies[11,17] using the same database (Clinical Data Analysis and Reporting System of the Hong Kong Hospital Authority); we included the data of only the latter[17] in the meta-analysis owing to its more comprehensive data and longer follow-up period. We excluded a cross-sectional study reporting the clinical signs of cranial fracture after a traumatic brain injury in patients using different anticoagulants.[29] With search strategy 2, a total of 17 400 relevant studies were identified. After excluding duplicates and screening the titles and abstracts, 2428 studies were retrieved for review of the full-text or trial registration. The search strategies for article selection are shown in Figure 1A and 1B.

After careful review, 29 studies met the eligibility criteria, including 5 cohort studies[12,14–17] and 24 RCTs[30–53] from search strategies 1 and 2, respectively. For cohort studies, we obtained the fracture data from the full-text articles. For RCTs, fracture data were obtained from the ClinicalTrial.gov website, because fracture was reported as an adverse event only in the included trials; no trial reported fracture events as a primary or secondary outcome.

In total, 388 209 participants were included in this meta-analysis. Except for RCTs, all included cohort studies had a large-scale population-based design. Additional information, such as age, sex, sample size, treatment indication, follow-up duration, NOAC type, and reported fracture sites, are summarized in Tables S1 and S2 (for cohort studies and RCTs, respectively). The results of the quality assessments are summarized in Table S3 (for cohort studies) and Table S4 (for clinical trials). The adjusted covariates for each cohort study are shown in Table S5.

Risk of Any Fracture Associated with All NOACs Versus Warfarin

All 29 studies reported at least 1 fracture site and were included in the analyses for any fracture. Patients treated with NOACs experienced a lower risk of any fracture than those treated with warfarin (pooled RR, 0.84; 95% CI, 0.77–0.91; $P<0.001$) with low heterogeneity ($I^2=38.9\%$) (Figure 2; Table 1). No evidence of publication bias was detected according to Egger's test ($P=0.149$) and Begg's test ($P=0.955$). The associated funnel plot is shown in Figure S1.

Risk of Any Fracture Associated with Individual NOACs Versus Warfarin

Compared with warfarin, a significantly lower risk of any fracture was found in patients taking dabigatran (pooled RR, 0.86; 95% CI, 0.75–0.99; $P=0.041$), rivaroxaban (pooled RR, 0.78; 95% CI, 0.69–0.87; $P<0.001$), and apixaban (pooled RR, 0.76; 95% CI, 0.65–0.89; $P=0.001$). A lower fracture risk was observed in patients taking edoxaban than in those taking warfarin, but the difference was not statistically significant (pooled RR, 0.89; 95% CI, 0.77–1.03; $P=0.122$) (Table 1).

Table 1. The Pooled Relative Risks of Any Fracture, Hip Fracture, and Vertebral Fracture in Patients Treated with NOACs as Opposed to Warfarin

Fracture Site	No. of Studies	Pooled RR (95%CI)	*P* Value	I^2 (%)
Any fracture				
NOAC overall	29	0.84 (0.77–0.91)	<0.001	38.9
Dabigatran	13	0.86 (0.75–0.99)	0.041	40.2
Rivaroxaban	8	0.78 (0.69–0.87)	<0.001	35.8
Apixaban	6	0.76 (0.65–0.89)	0.001	35.1
Edoxaban	7	0.89 (0.77–1.03)	0.122	0.0
Hip fracture				
NOAC overall	17	0.89 (0.81–0.98)	0.023	0.0
Dabigatran	7	1.00 (0.86–1.16)	0.958	0.0
Rivaroxaban	6	0.89 (0.76–1.03)	0.124	0.0
Apixaban	4	0.68 (0.52–0.89)	0.006	0.0
Edoxaban	3	0.89 (0.63–1.27)	0.535	0.0
Vertebral fracture				
NOAC overall	11	0.74 (0.54–1.01)	0.061	38.8
Dabigatran	3	0.82 (0.29–2.33)	0.711	63.9
Rivaroxaban	5	0.73 (0.63–0.85)	<0.001	0.0
Apixaban	3	0.47 (0.23–0.95)	0.035	49.1
Edoxaban	2	0.86 (0.60–1.23)	0.414	0.0

A pooled RR<1 indicates that NOAC is associated with a lower fracture risk than warfarin.

NA indicates not applicable; NOAC, non-vitamin K antagonist oral anticoagulants; and RR, relative risk.

Subgroup Analyses and Sensitivity Analyses for Any Fracture Event

All subgroup analyses consistently revealed lower risks of any fracture in patients taking NOACs than in those taking warfarin, irrespective of study design, treatment indications, mean follow-up period, mean age, sample size, and geographic location. Meta-regressions suggested no significant differences in the protective effects of NOACs between the subgroups (Table 2). The sensitivity analysis after omitting each study, in turn, demonstrated a robust pooled RR with only negligible differences (Figure S2).

We summarized the detailed results for each design subgroup, including the effect of each NOAC compared with warfarin. Overall, the evidence from real-world cohort studies and those from adverse events reported by RCTs are comparable (Table 3). The forest

Table 2. Subgroup and Heterogeneity Analyses of Pooled Relative Risks of Any Fracture in Patients Treated With NOACs as Opposed to Warfarin

Subgroups	No. of Studies	Pooled RR (95% CI)	*P* Value	I^2 (%)	Results of Meta-Regression		
					τ^2	I^2 Residual (%)	*P* Value
Overall	29	0.84 (0.77–0.91)	<0.001	38.9	0.014	NA	NA
Study design					0.018	40.2	0.989
Cohort study	5	0.83 (0.74–0.94)	0.004	79.9			
Randomized controlled trial	24	0.84 (0.74–0.95)	0.008	9.0			
Indication					0.016	40.7	0.754
Atrial fibrillation	20	0.84 (0.77–0.92)	<0.001	46.4			
Venous thromboembolism	9	0.76 (0.52–1.11)	0.150	20.3			
Mean follow-up period					0.015	40.9	0.592
<1 y	16	0.90 (0.65–1.24)	0.502	4.4			
≥1 y	13	0.83 (0.76–0.91)	<0.001	60.0			
Mean age					0.015	41.0	0.971
<65 y	13	0.83 (0.58–1.17)	0.276	10.2			
≥65 y	16	0.83 (0.76–0.92)	<0.001	53.7			
Sample size					0.014	39.9	0.527
n<5000	18	0.75 (0.54–1.04)	0.084	0.0			
n ≥5000	11	0.84 (0.77–0.92)	<0.001	64.4			
Geographic location					0.019	29.0	
North America	2	0.46 (0.06–3.51)	0.455	62.9			NA*
Europe	2	0.87 (0.77–0.99)	0.030	0.0			0.955
Asia	5	0.74 (0.57–0.96)	0.025	59.9			0.263
Multiple continents	20	0.84 (0.73–0.96)	0.012	12.5			0.610

A pooled RR<1 indicates that NOAC is associated with a lower fracture risk than warfarin.
NA indicates not applicable; NOAC, non-vitamin K antagonist oral anticoagulant; and RR, relative risk.
*Dummy variables were created for geographic location when performing meta-regression using North America as the reference group.

plots of the RR of any fracture associated with NOAC versus warfarin are shown in Figures S3 (for cohort studies) and S4 (for RCTs).

Risk of Hip Fractures

Seventeen studies (3 cohort studies and 14 trials) reported hip fracture events for data synthesis. Overall, patients on NOACs had a lower risk of hip fracture than those on warfarin (pooled RR, 0.89; 95% CI, 0.81–0.98; *P*=0.023) with minimal heterogeneity (I^2=0%) (Figure 3; Table 1). Egger's test (*P*=0.997) and Begg's test (*P*=0.592) demonstrated no evidence of publication bias, which is supported by the funnel plot shown in Figure S5. The subgroup analyses of individual NOACs demonstrated that the risk of hip fracture was significantly lower in patients taking apixaban (pooled RR, 0.68; 95% CI, 0.52–0.89; *P*=0.006) but not in patients taking other NOACs (Table 1).

Risk of Vertebral Fractures

Eleven studies (1 cohort study and 10 trials) reported vertebral fracture events for data synthesis. A lower, but not significant, risk of vertebral fracture was observed in NOAC users (pooled RR, 0.74; 95% CI, 0.54–1.01; *P*=0.061) with low heterogeneity (I^2=38.8%) (Figure 4; Table 1). No evidence of publication bias was found according to Egger's test (*P*=0.923) and Begg's test (*P*=0.640), and this was supported by the funnel plot shown in Figure S6. The subgroup analyses of individual NOACs demonstrated a significantly lower risk of vertebral fracture in patients treated with rivaroxaban (pooled RR, 0.73; 95% CI, 0.63–0.85; *P*<0.001) and apixaban (pooled RR, 0.47; 95% CI, 0.23–0.95; *P*=0.035) (Table 1).

DISCUSSION

In this large-scale meta-analysis involving 388 209 participants from 29 studies (with follow-up time ranging from 3 to 36 months), we found that patients treated with NOACs had an overall 16% and 11% lower relative risk of any fracture and hip fracture, respectively, than those treated with warfarin. The subgroup analyses showed that dabigatran, rivaroxaban, and apixaban were significantly associated with a lower fracture risk. The results from RCTs and real-world population-based

Table 3. The Pooled Relative Risks of Any Fracture, Hip Fracture, and Vertebral Fracture in Patients Treated with NOACs as Opposed to Warfarin Among Different Study Designs

Fracture Site	Cohort Studies				Randomized Controlled Trials			
	No. of Studies	Pooled RR (95%CI)	*P* Value	I^2 (%)	No. of Studies	Pooled RR (95%CI)	*P* Value	I^2 (%)
Any fracture								
NOAC overall	5	0.83 (0.74–0.94)	0.004	79.9	24	0.84 (0.73–0.95)	0.006	6.3
Dabigatran	4	0.88 (0.77–1.00)	0.054	62.0	9	0.69 (0.41–1.15)	0.155	33.1
Rivaroxaban	3	0.77 (0.67–0.89)	<0.001	69.6	5	0.79 (0.60–1.04)	0.096	6.3
Apixaban	3	0.75 (0.60–0.92)	0.007	54.5	3	0.76 (0.40–1.44)	0.393	38.0
Edoxaban	NA	NA	NA	NA	7	0.90 (0.78–1.03)	0.131	0.0
Hip fracture								
NOAC overall	3	0.89 (0.80–0.99)	0.036	0.0	14	0.90 (0.71–1.14)	0.403	0.0
Dabigatran	2	0.99 (0.85–1.15)	0.883	0.0	5	1.21 (0.52–2.82)	0.656	6.8
Rivaroxaban	2	0.89 (0.76–1.05)	0.156	0.0	4	0.88 (0.47–1.62)	0.672	3.2
Apixaban	2	0.62 (0.45–0.86)	0.004	0.0	2	0.85 (0.52–1.40)	0.528	0.0
Edoxaban	NA	NA	NA	NA	3	0.90 (0.63–1.27)	0.535	0.0
Vertebral fracture								
NOAC overall	1	0.75 (0.65–0.86)	<0.001	NA	10	0.74 (0.45–1.19)	0.226	43.6
Dabigatran	1	0.81 (0.68–0.95)	0.011	NA	2	0.66 (0.04–10.38)	0.764	79.4
Rivaroxaban	1	0.73 (0.62–0.85)	<0.001	NA	4	0.81 (0.38–1.73)	0.582	11.8
Apixaban	1	0.60 (0.41–0.88)	0.009	NA	2	0.37 (0.10–1.37)	0.137	41.8
Edoxaban	NA	NA	NA	NA	2	0.74 (0.46–1.20)	0.411	0.0

A pooled RR<1 indicates that NOAC is associated with a lower fracture risk than warfarin.
NA indicates not applicable; NOAC, non-vitamin K antagonist oral anticoagulant; and RR, relative risk.

cohort studies were quite consistent, indicating the robustness of our findings. We undertook separate meta-analyses for each type of NOAC as well as for different fractures sites, providing a comprehensive evaluation to address the knowledge gap.

Comparisons with Previous Studies

One previous meta-analysis, synthesizing data from 12 RCTs published before 2017, evaluated the differences in the risk of fracture associated with NOAC and warfarin.[13] All studies included in that meta-analysis reported fracture data as adverse events only online; none of them were specifically designed to assess fracture risks. That previous meta-analysis observed that patients taking NOACs showed a lower overall fracture risk than those taking warfarin (RR, 0.82; 95% CI, 0.73–0.93) but failed to demonstrate significant differences between NOAC and warfarin in the risk of hip fracture (RR, 0.99; 95% CI, 0.72–1.34) or of vertebral fracture (RR, 0.79; 95% CI, 0.59–1.06). In recent years, several real-world population-based cohort studies have provided data collected from routine clinical practice, with longer follow-up durations and higher statistical power, for evaluating the difference in fracture risk associated with NOACs and warfarin.[11,12,14–17] Additionally, a growing number of RCTs evaluating NOACs and warfarin have reported fractures as adverse events. Another recent meta-analysis, evaluating only hip fracture risk, showed that patients taking NOACs had a lower risk of hip fracture than those taking warfarin (HR, 0.89; 95% CI, 0.80–0.99);[54] however, this meta-analysis included only 3 observational studies. Our present meta-analysis used updated evidence, including 29 studies (5 large-scale cohort studies and 24 RCTs), and found a lower risk of any fracture in NOAC users (RR, 0.84; 95% CI, 0.77–0.91). The subgroup analyses identified a significantly lower risk of hip fracture (RR, 0.89; 95% CI, 0.81–0.98) in patients taking NOACs, by pooling the data of 17 studies. Pooled data from 11 studies also showed a lower, and almost significant, vertebral fracture risk with NOACs (RR, 0.74; 95% CI, 0.54–1.01). Furthermore, the present study provides novel information by evaluating individual NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) for all, hip, and vertebral fracture risks. Our results also showed that the risk estimates from real-world population-based cohort studies and RCTs (Table 3; Figures S3 and S4) were very similar, with a low between-study design heterogeneity. This indicates that the results of our meta-analyses were quite robust, and real-world evidence from cohort studies strengthens the evidence from RCTs on the protective effects of NOACs.

Possible Underlying Mechanisms

Although precise underlying mechanisms are still unclear, some factors might explain why NOACs are

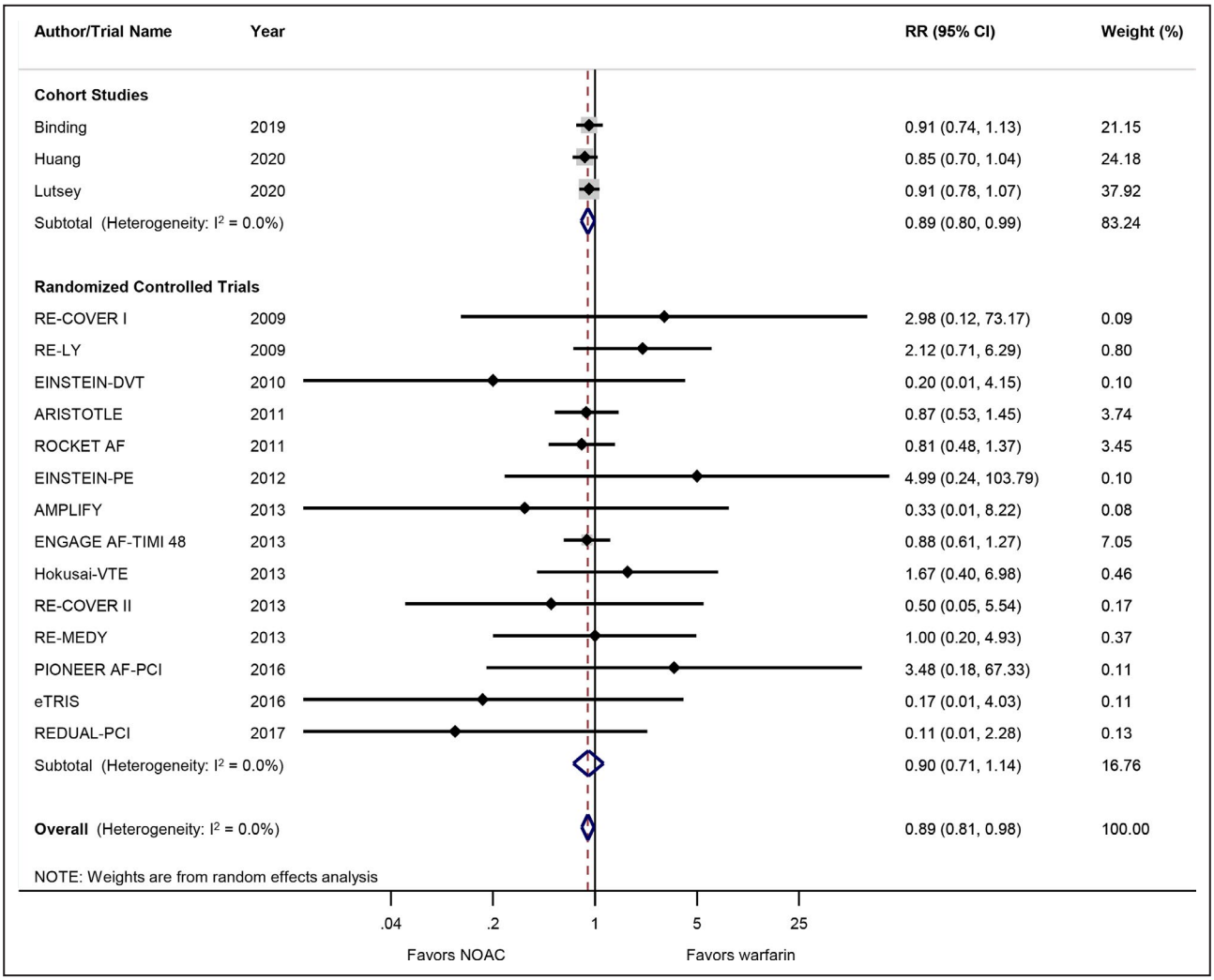


Figure 3. Forest plot of the relative risk of hip fracture associated with NOACs compared with warfarin.[14–16,31–33,36,38,39,41–45,47,48,50]
NOAC indicates non-vitamin K antagonist oral anticoagulant; and RR, relative risk.

associated with a lower fracture risk than warfarin. Warfarin, a vitamin K antagonist, may interfere with bone formation.[55] Warfarin antagonizes vitamin K-dependent processes and impairs the γ-carboxylation of osteocalcin and other bone matrix proteins, which are important in bone mineralization and formation.[9,55] NOACs are independent of the mechanisms related to antagonizing vitamin K and do not interfere with bone metabolism.[9] Previous animal studies revealed that NOACs have positive effects on bone biology, such as increased bone volume, decreased trabecular separation, and reduced bone turnover rate, increased bone mineral density of the fracture zone, and improved fracture healing, compared with those in the warfarin-treated or control groups.[56–58] Furthermore, possible positive effects of NOACs on bone health and the prevention of falls have been proposed recently.[59] Additional studies are needed to evaluate the underlying mechanisms of NOACs on bone health and fracture risks.

Clinical Implications

The lower risk of fractures in patients taking NOACs is an important finding. Osteoporotic fractures, especially hip and vertebral fractures, that occur more frequently in elderly people, cause significant morbidity, mortality, and socioeconomic burden. Previous studies have reported that atrial fibrillation, the most common indication for OAC treatment, is an important risk factor for osteoporotic fractures.[60,61] Many risk factors for osteoporotic fractures, such as old age and a history of diabetes mellitus and cardiovascular diseases, coexist in patients with atrial fibrillation.[11,62] Venous thromboembolism and fractures also share similar important risk factors, such as old age, immobilization, smoking, previous fracture, and malignancy.[63–65] As patients taking OACs are often at a higher risk of fractures, evidence regarding the differences in fracture risks associated with the use of different OACs is clinically useful. The use of anticoagulants also poses a challenge to anticoagulation

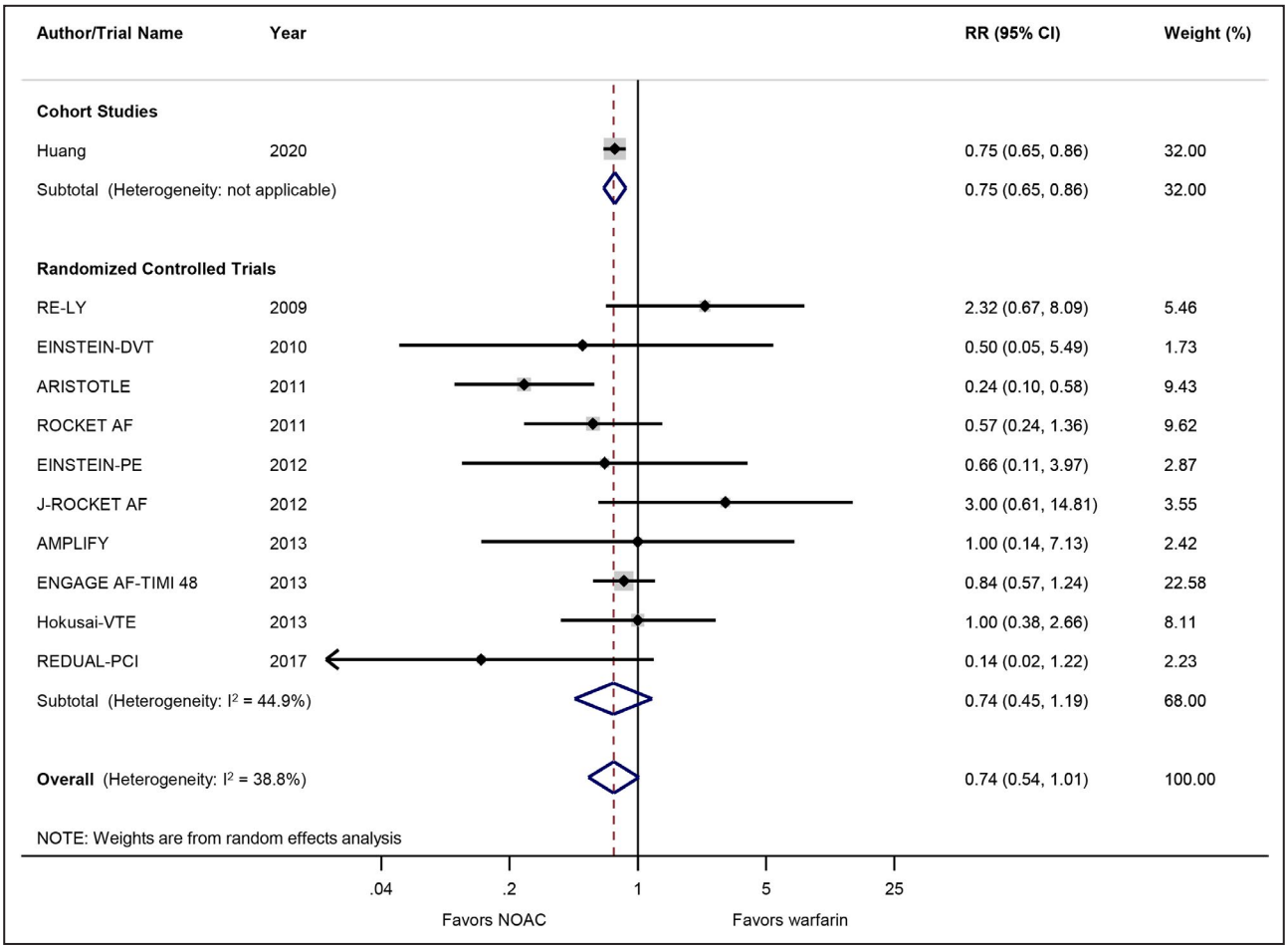


Figure 4. Forest plot of the relative risk of vertebral fracture associated with NOACs compared with warfarin.[16,32,33,36,38–43,50]
NOAC indicates non-vitamin K antagonist oral anticoagulant; and RR, relative risk.

during the surgical treatment of fractures.[66,67] This meta-analysis provides updated clinical evidence for the association between NOACs and lower fracture risk. Therefore, we suggest that when prescribing OAC treatment, the risk of fractures to patients should be carefully evaluated, and NOACs may be preferred over warfarin to lower fracture risks if both OAC types could be indicated. However, treatment decisions should consider all risks and benefits of NOACs versus warfarin for an individual patient.

Study Limitations

In this systematic review and meta-analysis, we provided comprehensive and updated evidence on the protective effects of NOACs on fracture compared with warfarin. However, there are several limitations worth addressing. First, similar to the meta-analysis mentioned previously,[13] the data of fracture events from included RCTs were reported as only one of the adverse events in ClinicalTrials.gov. None of the included trials were explicitly designed to assess fracture risks; therefore, detailed assessment methods for identifying fracture events remain unclear. In addition, the follow-up duration was relatively short (≤12 months) in over half of the included trials; the proportion of fracture events to the number of patients was also low. Furthermore, we calculated the number of any fracture events by summing up the events of each fracture site, which may not be equal to the exact number of patients with fractures because a patient might have experienced more than 1 fracture. However, this method of calculating outcome events was not different between the NOAC and warfarin groups; thus, the bias in RRs we obtained from these RCTs was likely minimal. Second, despite the considerably larger sample size of real-world observational studies than that of RCTs, the real-world observational data may be biased owing to unknown or unmeasured confounders. The claim-based retrospective cohort studies may have a problem in accurately capturing diseases with codes, as medical information/histories are not adjudicated or captured systematically. The mean follow-up time of the included real-world cohort studies was also short (range from<12 to 29.2 months; Table S1). However,

in our meta-analysis, the results from studies with 2 different study designs were comparable, indicating that such a bias was likely not of great concern. Third, the results from some of our subgroup analyses were not statistically significant (eg, the analysis of edoxaban), although their point estimates were similar to those of statistical significance (Table 1). This may be because of insufficient statistical power in the subgroup of different NOACs, especially in the analyses of specific fracture sites (hip and vertebral). It should also be noted that none of the subgroups of individual NOACs or fracture sites reached statistical significance in the analyses focusing on only RCTs (Table 3). The statistical power of these subgroup analyses was low, because these RCTs were not designed for evaluating fracture events and tended to have a relatively short follow-up duration. More studies, especially RCTs and high-quality prospective studies with longer follow-up, are needed to evaluate the effect of individual NOACs on each specific fracture site.

CONCLUSIONS

This systematic review and meta-analysis gathered data of 388 209 participants involved in 29 studies and revealed that patients taking NOACs had a 16% lower risk of developing fractures than those taking warfarin. The subgroup analyses demonstrated a similar effect on lower fracture risk for individual NOACs (dabigatran, rivaroxaban, and apixaban) than for warfarin. Based on current evidence, NOACs may be preferred over warfarin to lower fracture risks in patients with indications for OAC therapy. Future studies are necessary to investigate the mechanisms underlying the associations between different OACs and bone health.

ARTICLE INFORMATION

Received October 6, 2020; accepted February 11, 2021.

Affiliations

From the Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan (H.H., Y.T.); Departments of Family Medicine and Medical Research, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan (H.H.); Department of Internal Medicine, University of Maryland Medical Center Midtown Campus, Baltimore, MD (C.C.P.); Department of Physical Medicine and Rehabilitation, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan (S.L.); School of Medicine, Tzu Chi University, Hualien, Taiwan (S.L., J.H., C.L.); Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine, Baltimore, MD (K.M.M.); The Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD (R.H.C.); School of Medicine, College of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan (B.B.W.); Center for Aging and Health, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan (P.P.L., J.H., C.L.); Department of Dentistry, National Taiwan University Hospital and School of Dentistry, National Taiwan University, Taipei, Taiwan (Y.T.); and Research Center of Big Data and Meta-analysis, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan (Y.T.).

Acknowledgments

We thank Carrie Price, MLS, and Katie Lobner, MLIS, at Johns Hopkins University for their expert reference searches.

Sources of Funding

None.

Disclosures

None.

Supplementary Material

Data S1. Detailed Search Strategies
Tables S1–S5
Figures S1–S6

REFERENCES

1. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American heart association task force on practice guidelines and the heart rhythm society. *Circulation*. 2014;130:2071–2104. DOI: 10.1161/CIR.0000000000000040.
2. Witt DM, Nieuwlaat R, Clark NP, Ansell J, Holbrook A, Skov J, Shehab N, Mock J, Myers T, Dentali F, et al. American society of hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv*. 2018;2:3257–3291. DOI: 10.1182/bloodadvances.2018024893.
3. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2011;4:14–21. DOI: 10.1161/CIRCOUTCOMES.110.958108.
4. Chao TF, Lip GYH, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, et al. Age threshold for the use of non-vitamin k antagonist oral anticoagulants for stroke prevention in patients with atrial fibrillation: Insights into the optimal assessment of age and incident comorbidities. *Eur Heart J*. 2019;40:1504–1514. DOI: 10.1093/eurheartj/ehy837.
5. Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, et al. Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study. *Circulation*. 2018;138:37–47. DOI: 10.1161/CIRCULATIONAHA.117.031658.
6. Engbers MJ, van Hylckama VA, Rosendaal FR. Venous thrombosis in the elderly: Incidence, risk factors and risk groups. *J Thromb Haemost*. 2010;8:2105–2112. DOI: 10.1111/j.1538-7836.2010.03986.x.
7. Gage BF, Birman-Deych E, Radford MJ, Nilasena DS, Binder EF. Risk of osteoporotic fracture in elderly patients taking warfarin: results from the national registry of atrial fibrillation 2. *Arch Intern Med*. 2006;166:241–246. DOI: 10.1001/archinte.166.2.241.
8. Rejnmark L, Vestergaard P, Mosekilde L. Fracture risk in users of oral anticoagulants: a nationwide case-control study. *Int J Cardiol*. 2007;118:338–344. DOI: 10.1016/j.ijcard.2006.07.022.
9. De Caterina R, Mundi S, Fusaro M. Vitamin k antagonists and osteoporotic fractures: insights from comparisons with the NOACs. *Eur Heart J*. 2020;41:1109–1111. DOI: 10.1093/eurheartj/ehaa077.
10. Fiordellisi W, White K, Schweizer M. A systematic review and meta-analysis of the association between vitamin k antagonist use and fracture. *J Gen Intern Med*. 2019;34:304–311. DOI: 10.1007/s11606-018-4758-2.
11. Lau WC, Chan EW, Cheung CL, Sing CW, Man KK, Lip GY, Siu CW, Lam JK, Lee AC, Wong IC. Association between dabigatran vs warfarin and risk of osteoporotic fractures among patients with nonvalvular atrial fibrillation. *JAMA*. 2017;317:1151–1158. DOI: 10.1001/jama.2017.1363.
12. Lucenteforte E, Bettiol A, Lombardi N, Mugelli A, Vannacci A. Risk of bone fractures among users of oral anticoagulants: an administrative database cohort study. *Eur J Intern Med*. 2017;44:e30–e31. DOI: 10.1016/j.ejim.2017.07.022.
13. Gu ZC, Zhou LY, Shen L, Zhang C, Pu J, Lin HW, Liu XY. Non-vitamin k antagonist oral anticoagulants vs. Warfarin at risk of fractures: a systematic review and meta-analysis of randomized controlled trials. *Front Pharmacol*. 2018;9:348. DOI: 10.3389/fphar.2018.00348.

14. Binding C, Bjerring Olesen J, Abrahamsen B, Staerk L, Gislason G, Nissen BA. Osteoporotic fractures in patients with atrial fibrillation treated with conventional versus direct anticoagulants. *J Am Coll Cardiol*. 2019;74:2150–2158. DOI: 10.1016/j.jacc.2019.08.1025.
15. Lutsey PL, Norby FL, Ensrud KE, MacLehose RF, Diem SJ, Chen LY, Alonso A. Association of anticoagulant therapy with risk of fracture among patients with atrial fibrillation. *JAMA Intern Med*. 2020;180:245–253. DOI: 10.1001/jamainternmed.2019.5679.
16. Huang HK, Liu PP, Hsu JY, Lin SM, Peng CC, Wang JH, Loh CH. Fracture risks among patients with atrial fibrillation receiving different oral anticoagulants: a real-world nationwide cohort study. *Eur Heart J*. 2020;41:1100–1108. DOI: 10.1093/eurheartj/ehz952.
17. Lau WCY, Cheung CL, Man KKC, Chan EW, Sing CW, Lip GYH, Siu CW, Lam JKY, Lee ACH, Wong ICK. Association between treatment with apixaban, dabigatran, rivaroxaban, or warfarin and risk for osteoporotic fractures among patients with atrial fibrillation. *Ann Intern Med*. 2020;173:1–9. DOI: 10.7326/M19-3671.
18. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet*. 2002;359:1761–1767. DOI: 10.1016/S0140-6736(02)08657-9.
19. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264–269. DOI: 10.7326/0003-4819-151-4-200908180-00135.
20. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. DOI: 10.1136/bmj.d5928.
21. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The newcastle-ottawa scale (nos) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute website. 2019.
22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560. DOI: 10.1136/bmj.327.7414.557.
23. Rucker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on i(2) in assessing heterogeneity may mislead. *BMC Med Res Methodol*. 2008;8:79. DOI: 10.1186/1471-2288-8-79.
24. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011.
25. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088–1101. DOI: 10.2307/2533446.
26. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634. DOI: 10.1136/bmj.315.7109.629.
27. Norby FL, Bengtson LGS, Lutsey PL, Chen LY, MacLehose RF, Chamberlain AM, Rapson I, Alonso A. Comparative effectiveness of rivaroxaban versus warfarin or dabigatran for the treatment of patients with non-valvular atrial fibrillation. *BMC Cardiovasc Disord*. 2017;17:238. DOI: 10.1186/s12872-017-0672-5.
28. Bengtson LGS, Lutsey PL, Chen LY, MacLehose RF, Alonso A. Comparative effectiveness of dabigatran and rivaroxaban versus warfarin for the treatment of non-valvular atrial fibrillation. *J Cardiol*. 2017;69:868–876. DOI: 10.1016/j.jjcc.2016.08.010.
29. Galliazzo S, Bianchi MD, Virano A, Trucchi A, Donadini MP, Dentali F, Bertu L, Grandi AM, Ageno W. Intracranial bleeding risk after minor traumatic brain injury in patients on antithrombotic drugs. *Thromb Res*. 2019;174:113–120. DOI: 10.1016/j.thromres.2018.12.015.
30. Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, Pedersen KE, Lionetti DA, Stangier J, Wallentin L. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO study). *Am J Cardiol*. 2007;100:1419–1426. DOI: 10.1016/j.amjcard.2007.06.034.
31. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361:2342–2352. DOI: 10.1056/NEJMoa0906598.
32. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151. DOI: 10.1056/NEJMoa0905561.
33. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363:2499–2510. DOI: 10.1056/NEJMoa1007903.
34. Weitz JI, Connolly SJ, Patel I, Salazar D, Rohatagi S, Mendell J, Kastrissios H, Jin J, Kunitada S. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. *Thromb Haemost*. 2010;104:633–641. DOI: 10.1160/TH10-01-0066.
35. Ingelheim B. A dose response study of dabigatran etexilate(bibr 1048) in pharmacodynamics and safety in patients with non-valvular atrial fibrillation in comparison to warfarin. Nct01136408. 2014; 2020.
36. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992. DOI: 10.1056/NEJMoa1107039.
37. Chung N, Jeon HK, Lien LM, Lai WT, Tse HF, Chung WS, Lee TH, Chen SA. Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. *Thromb Haemost*. 2011;105:535–544. DOI: 10.1160/TH10-07-0451.
38. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891. DOI: 10.1056/NEJMoa1009638.
39. Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366:1287–1297. DOI: 10.1056/NEJMoa1113572.
40. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, Izumi T, Koretsune Y, Kajikawa M, Kato M, et al. Rivaroxaban vs. Warfarin in Japanese patients with atrial fibrillation - the J-rocket AF study. *Circ J*. 2012;76:2104–2111. DOI: 10.1253/circj.CJ-12-0454.
41. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369:799–808. DOI: 10.1056/NEJMoa1302507.
42. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104. DOI: 10.1056/NEJMoa1310907.
43. Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwocho L, Segers A, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369:1406–1415. DOI: 10.1056/NEJMoa1306638.
44. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, Christiansen AV, Friedman J, Le Maulf F, Peter N, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129:764–772. DOI: 10.1161/CIRCULATIONAHA.113.004450.
45. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, Kvamme AM, Friedman J, Mismetti P, Goldhaber SZ. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med*. 2013;368:709–718. DOI: 10.1056/NEJMoa1113697.
46. Goette A, Merino JL, Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, Mercuri MF, Grosso MA, Fernandez V, Al-Saady N, et al. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *Lancet*. 2016;388:1995–2003. DOI: 10.1016/S0140-6736(16)31474-X.
47. Piazza G, Mani V, Goldhaber SZ, Grosso MA, Mercuri M, Lanz HJ, Schussler S, Hsu C, Chinigo A, Ritchie B, et al. Magnetic resonance venography to assess thrombus resolution with edoxaban monotherapy versus parenteral anticoagulation/warfarin for symptomatic deep vein thrombosis: a multicenter feasibility study. *Vasc Med*. 2016;21:361–368. DOI: 10.1177/1358863X16645853.
48. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Ianus J, Burton P, van Eickels M, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med*. 2016;375:2423–2434. DOI: 10.1056/NEJMoa1611594.
49. Calkins H, Willems S, Gerstenfeld EP, Verma A, Schilling R, Hohnloser SH, Okumura K, Serota H, Nordaby M, Guiver K, et al. Uninterrupted dabigatran versus warfarin for ablation in atrial fibrillation. *N Engl J Med*. 2017;376:1627–1636. DOI: 10.1056/NEJMoa1701005.

50. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S, et al. Dual antithrombotic therapy with Dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017;377:1513–1524. DOI: 10.1056/NEJMoa1708454.
51. Hohnloser SH, Camm J, Cappato R, Diener HC, Heidbuchel H, Lanz HJ, Mont L, Morillo CA, Smolnik R, Yin OQP, et al. Uninterrupted administration of edoxaban vs vitamin K antagonists in patients undergoing atrial fibrillation catheter ablation: rationale and design of the ELIMINATE-AF study. *Clin Cardiol*. 2018;41:440–449. DOI: 10.1002/clc.22918.
52. Ezekowitz MD, Pollack CV Jr, Halperin JL, England RD, VanPelt NS, Spahr J, Sudworth M, Cater NB, Breazna A, Oldgren J, et al. Apixaban compared to heparin/vitamin k antagonist in patients with atrial fibrillation scheduled for cardioversion: the emanate trial. *Eur Heart J*. 2018;39:2959–2971. DOI: 10.1093/eurheartj/ehy148.
53. Ferro JM, Coutinho JM, Dentali F, Kobayashi A, Alasheev A, Canhão P, Karpov D, Nagel S, Posthuma L, Roriz JM, et al. Safety and efficacy of dabigatran etexilate vs dose-adjusted warfarin in patients with cerebral venous thrombosis: a randomized clinical trial. *JAMA Neurol*. 2019;76:1457–1465. DOI: 10.1001/jamaneurol.2019.2764.
54. Huang H-K, Yeh J-I, Loh C-H. Hip fracture risk in patients with atrial fibrillation receiving oral anticoagulants: a meta-analysis based on current observational studies. *Eur Heart J*. 2020;41:2919–2920. DOI: 10.1093/eurheartj/ehaa361.
55. Sugiyama T, Kugimiya F, Kono S, Kim YT, Oda H. Warfarin use and fracture risk: an evidence-based mechanistic insight. *Osteoporos Int*. 2015;26:1231–1232. DOI: 10.1007/s00198-014-2912-1.
56. Fusaro M, Dalle Carbonare L, Dusso A, Arcidiacono MV, Valenti MT, Aghi A, Pasho S, Gallieni M. Differential effects of dabigatran and warfarin on bone volume and structure in rats with normal renal function. *PLoS One*. 2015;10:e0133847. 10.1371/journal.pone.0133847.
57. Kluter T, Weuster M, Bruggemann S, Menzdorf L, Fitschen-Oestern S, Steubesand N, Acil Y, Pufe T, Varoga D, Seekamp A, et al. Rivaroxaban does not impair fracture healing in a rat femur fracture model: an experimental study. *BMC Musculoskelet Disord*. 2015;16:79. DOI: 10.1186/s12891-015-0502-9.
58. Morishima Y, Kamisato C, Honda Y, Furugohri T, Shibano T. The effects of warfarin and edoxaban, an oral direct factor Xa inhibitor, on gamma-carboxylated (Gla-osteocalcin) and undercarboxylated osteocalcin (uc-osteocalcin) in rats. *Thromb Res*. 2013;131:59–63. DOI: 10.1016/j.thromres.2012.08.304.
59. Sugiyama T. Osteoporotic fractures associated with Dabigatran vs Warfarin. *JAMA*. 2017;318:90–91. DOI: 10.1001/jama.2017.6908.
60. Wong CX, Gan SW, Lee SW, Gallagher C, Kinnear NJ, Lau DH, Mahajan R, Roberts-Thomson KC, Sanders P. Atrial fibrillation and risk of hip fracture: a population-based analysis of 113,600 individuals. *Int J Cardiol*. 2017;243:229–232. DOI: 10.1016/j.ijcard.2017.05.012.
61. Kim D, Yang PS, Kim TH, Uhm JS, Park J, Pak HN, Lee MH, Joung B. Effect of atrial fibrillation on the incidence and outcome of osteoporotic fracture- a nationwide population-based study. *Circ J*. 2018;82:1999–2006. DOI: 10.1253/circj.CJ-17-1179.
62. Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. *BMJ*. 2009;339:b4229. DOI: 10.1136/bmj.b4229.
63. Schulman S, Ageno W, Konstantinides SV. Venous thromboembolism: past, present and future. *Thromb Haemost*. 2017;117:1219–1229. DOI: 10.1160/TH16-10-0823.
64. Gregson J, Kaptoge S, Bolton T, Pennells L, Willeit P, Burgess S, Bell S, Sweeting M, Rimm EB, Kabrhel C, et al. Cardiovascular risk factors associated with venous thromboembolism. *JAMA Cardiol*. 2019;4:163–173. DOI: 10.1001/jamacardio.2018.4537.
65. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. Frax and the assessment of fracture probability in men and women from the UK. *Osteoporos Int*. 2008;19:385–397. DOI: 10.1007/s00198-007-0543-5.
66. Kaatz S, Mahan CE, Nakhle A, Gunasekaran K, Ali M, Lavender R, Paje DG. Management of elective surgery and emergent bleeding with direct oral anticoagulants. *Curr Cardiol Rep*. 2017;19:124. DOI: 10.1007/s11886-017-0930-2.
67. Croci DM, Dalolio M, Guzman R, Mariani L, Schaeren S, Kamenova M, Soleman J. Direct oral anticoagulants in patients undergoing spine surgery. *World Neurosurg*. 2019;125:e1034–e1041. DOI: 10.1016/j.wneu.2019.01.236.

SUPPLEMENTAL MATERIAL

Data S1.

Detailed Search Strategies

Search Strategy 1

PubMed:

("NOACs"[tw] OR "NOAC"[tw] OR "DOACs"[tw] OR "DOAC"[tw] OR "new oral anticoagulant" [tw] OR "new oral anti coagulant"[tw] OR "novel oral anticoagulant"[tw] OR "new oral anti coagulant"[tw] OR "new oral anticoagulants"[tw] OR "new oral anti coagulants"[tw] OR "novel oral anticoagulants"[tw] OR "new oral anti coagulants"[tw] OR "non-vitamin K antagonist oral anticoagulants"[tw] OR "non-vitamin K antagonist oral anticoagulant"[tw] OR "novel oral anticoagulants"[tw] OR "new oral anticoagulants"[tw] OR "direct oral anticoagulants"[tw] OR "direct oral anticoagulant"[tw] OR "direct oral anti coagulant"[tw] OR "direct oral anti coagulants"[tw] OR "factor Xa inhibitors"[tw] OR "factor IIa inhibitors"[tw] OR "direct thrombin inhibitor"[tw] OR "direct thrombin inhibitors"[tw] OR "factor xa inhibitor"[tw] OR "factor IIa inhibitor"[tw] OR "dabigatran"[tw] OR "Pradaxa"[tw] OR "rivaroxaban"[tw] OR "Xarelto"[tw] OR "apixaban"[tw] OR "Eliquis"[tw] OR "eliques"[tw] OR "edoxaban"[tw] OR "Savaysa"[tw] OR "roteas"[tw] OR “Lixiana” [tw] OR “betrixaban”[tw] OR “Bevyxxa”[tw] OR "edoxaban" [Supplementary Concept] OR "apixaban" [Supplementary Concept] OR "Dabigatran"[Mesh] OR "Rivaroxaban"[Mesh] OR "betrixaban" [Supplementary Concept] OR (("new oral"[tw] OR "novel"[tw] OR "non vitamin k"[tw]) AND (anticoagulant*[tw] OR anti coagulant*[tw])))

AND

("warfarin" OR "vitamin k" OR "Coumadin" OR "acenocoumarol" OR "acenocoumarol"[mh] OR "phenprocoumon"[mh] OR "phenprocoumon" OR "Vitamin K/antagonists and inhibitors"[Mesh] OR "jantoven")

AND

("fracture" OR "fractures" OR "fractures, bone"[mh])

Limit: English

EMBASE:

('NOACs' OR 'NOAC' OR 'DOACs' OR 'DOAC' OR 'new oral anticoagulant' OR 'new oral anti coagulant' OR 'novel oral anticoagulant' OR 'new oral anti coagulant' OR 'new oral anticoagulants' OR 'new oral anti coagulants' OR 'novel oral anticoagulants' OR 'new oral anti coagulants' OR 'non-vitamin K antagonist oral anticoagulants' OR 'non-vitamin K antagonist oral anticoagulant' OR 'novel oral anticoagulants' OR 'new oral anticoagulants' OR 'direct oral anticoagulants' OR 'direct oral anticoagulant' OR 'direct oral anti coagulant' OR 'direct oral anti coagulants' OR 'factor Xa inhibitors' OR 'factor IIa inhibitors' OR 'direct thrombin inhibitor' OR 'direct thrombin inhibitors' OR 'factor xa inhibitor' OR 'factor IIa inhibitor' OR 'dabigatran' OR 'Pradaxa' OR 'rivaroxaban' OR 'Xarelto' OR 'apixaban' OR 'Eliquis' OR 'eliques' OR 'edoxaban' OR 'Savaysa' OR 'roteas' OR 'Lixiana' OR 'betrixaban' OR 'Bevyxxa' OR 'edoxaban'/exp OR 'apixaban'/exp OR 'Dabigatran'/exp OR 'Rivaroxaban'/exp OR 'betrixaban'/exp OR (('new oral' OR 'novel' OR 'non vitamin k') AND (anticoagulant* OR anti coagulant*)))

AND

('warfarin' OR 'vitamin k' OR 'Coumadin' OR 'acenocoumarol' OR 'acenocoumarol'/exp OR 'phenprocoumon'/exp OR 'phenprocoumon' OR 'antivitamin K'/exp OR 'jantoven')

AND

('fracture' OR 'fractures' OR 'fracture'/exp)

Limit: English

Cochrane Library:

("NOACs":ti,ab,kw OR "NOAC":ti,ab,kw OR "DOACs":ti,ab,kw OR "DOAC":ti,ab,kw OR "new oral anticoagulant":ti,ab,kw OR "new oral anti coagulant":ti,ab,kw OR "novel oral anticoagulant":ti,ab,kw OR "new oral anti coagulant":ti,ab,kw OR "new oral anticoagulants":ti,ab,kw OR "new oral anti coagulants":ti,ab,kw OR "novel oral anticoagulants":ti,ab,kw OR "new oral anti

coagulants":ti,ab,kw OR "non vitamin K antagonist oral anticoagulants":ti,ab,kw OR "non vitamin K antagonist oral anticoagulant":ti,ab,kw OR "novel oral anticoagulants":ti,ab,kw OR "new oral anticoagulants":ti,ab,kw OR "direct oral anticoagulants":ti,ab,kw OR "direct oral anticoagulant":ti,ab,kw OR "direct oral anti coagulant":ti,ab,kw OR "direct oral anti coagulants":ti,ab,kw OR "factor Xa inhibitors":ti,ab,kw OR "factor IIa inhibitors":ti,ab,kw OR "direct thrombin inhibitor":ti,ab,kw OR "direct thrombin inhibitors":ti,ab,kw OR "factor xa inhibitor":ti,ab,kw OR "factor IIa inhibitor":ti,ab,kw OR "dabigatran":ti,ab,kw OR "Pradaxa":ti,ab,kw OR "rivaroxaban":ti,ab,kw OR "Xarelto":ti,ab,kw OR "apixaban":ti,ab,kw OR "Eliquis":ti,ab,kw OR "eliques":ti,ab,kw OR "edoxaban":ti,ab,kw OR "Savaysa":ti,ab,kw OR "roteas":ti,ab,kw OR "Lixiana":ti,ab,kw OR "betrixaban":ti,ab,kw OR "Bevyxxa":ti,ab,kw OR [mh "dabigatran"] OR [mh "rivaroxaban"] OR [mh "apixaban"] OR [mh "edoxaban"] OR [mh "betrixaban"] OR (("new oral":ti,ab,kw OR "novel":ti,ab,kw OR "non vitamin k":ti,ab,kw) AND (anticoagulant*:ti,ab,kw OR anti coagulant*:ti,ab,kw)))

AND

("vitamin K antagonists":ti,ab,kw OR "warfarin":ti,ab,kw OR "Coumadin":ti,ab,kw OR "Acenocoumarol":ti,ab,kw OR "Phenprocoumon":ti,ab,kw OR "Phenprocoumon":ti,ab,kw)

AND

("Fracture":ti,ab,kw)

Scopus:

TITLE-ABS-KEY(({NOACs} OR {NOAC} OR {DOACs} OR {DOAC} OR {new oral anticoagulant} OR {new oral anti coagulant} OR {novel oral anticoagulant} OR {new oral anti coagulant} OR {new oral anticoagulants} OR {new oral anti coagulants} OR {novel oral anticoagulants} OR {new oral anti coagulants} OR {non-vitamin K antagonist oral anticoagulants} OR {non-vitamin K antagonist oral anticoagulant} OR {novel oral anticoagulants} OR {new oral anticoagulants} OR {direct oral anticoagulants} OR {direct oral

anticoagulant} OR {direct oral anti coagulant} OR {direct oral anti coagulants} OR {factor Xa inhibitors} OR {factor IIa inhibitors} OR {direct thrombin inhibitor} OR {direct thrombin inhibitors} OR {factor xa inhibitor} OR {factor IIa inhibitor} OR {dabigatran} OR {Pradaxa} OR {rivaroxaban} OR {Xarelto} OR {apixaban} OR {Eliquis} OR {eliques} OR {edoxaban} OR {Savaysa} OR {roteas} OR {Lixiana} OR {betrixaban} OR {Bevyxxa} OR (({new oral} OR {novel} OR {non vitamin k}) AND (anticoagulant* OR anti coagulant*)))

AND

({warfarin} OR {vitamin k} OR {Coumadin} OR {acenocoumarol} OR {phenprocoumon} OR {jantoven})

AND

({fracture} OR {fractures}))

Limit: English

Web of Science:

TS=(("NOACs" OR "NOAC" OR "DOACs" OR "DOAC" OR "new oral anticoagulant" OR "new oral anti coagulant" OR "novel oral anticoagulant" OR "new oral anti coagulant" OR "new oral anticoagulants" OR "new oral anti coagulants" OR "novel oral anticoagulants" OR "new oral anti coagulants" OR "non-vitamin K antagonist oral anticoagulants" OR "non-vitamin K antagonist oral anticoagulant" OR "novel oral anticoagulants" OR "new oral anticoagulants" OR "direct oral anticoagulants" OR "direct oral anticoagulant" OR "direct oral anti coagulant" OR "direct oral anti coagulants" OR "factor Xa inhibitors" OR "factor IIa inhibitors" OR "direct thrombin inhibitor" OR "direct thrombin inhibitors" OR "factor xa inhibitor" OR "factor IIa inhibitor" OR "dabigatran" OR "Pradaxa" OR "rivaroxaban" OR "Xarelto" OR "apixaban" OR "Eliquis" OR "eliques" OR "edoxaban" OR "Savaysa" OR "roteas" OR "Lixiana" OR "betrixaban" OR "Bevyxxa" OR (("new oral" OR "novel" OR "non vitamin k") AND (anticoagulant* OR anti coagulant*)))

AND

("warfarin" OR "vitamin k" OR "Coumadin" OR "acenocoumarol" OR "phenprocoumon" OR "jantoven")

AND

("fracture" OR "fractures"))

Limit: English

Search Strategy 2

PubMed:

("NOACs"[tw] OR "NOAC"[tw] OR "DOACs"[tw] OR "DOAC"[tw] OR "new oral anticoagulant" [tw] OR "new oral anti coagulant"[tw] OR "novel oral anticoagulant"[tw] OR "new oral anti coagulant"[tw] OR "new oral anticoagulants"[tw] OR "new oral anti coagulants"[tw] OR "novel oral anticoagulants"[tw] OR "new oral anti coagulants"[tw] OR "non-vitamin K antagonist oral anticoagulants"[tw] OR "non-vitamin K antagonist oral anticoagulant"[tw] OR "novel oral anticoagulants"[tw] OR "new oral anticoagulants"[tw] OR "direct oral anticoagulants"[tw] OR "direct oral anticoagulant"[tw] OR "direct oral anti coagulant"[tw] OR "direct oral anti coagulants"[tw] OR "factor Xa inhibitors"[tw] OR "factor IIa inhibitors"[tw] OR "direct thrombin inhibitor"[tw] OR "direct thrombin inhibitors"[tw] OR "factor xa inhibitor"[tw] OR "factor IIa inhibitor"[tw] OR "dabigatran"[tw] OR "Pradaxa"[tw] OR "rivaroxaban"[tw] OR "Xarelto"[tw] OR "apixaban"[tw] OR "Eliquis"[tw] OR "eliques"[tw] OR "edoxaban"[tw] OR "Savaysa"[tw] OR "roteas"[tw] OR “Lixiana” [tw] OR “betrixaban”[tw] OR “Bevyxxa”[tw] OR "edoxaban" [Supplementary Concept] OR "apixaban" [Supplementary Concept] OR "Dabigatran"[Mesh] OR "Rivaroxaban"[Mesh] OR "betrixaban" [Supplementary Concept] OR (("new oral"[tw] OR "novel"[tw] OR "non vitamin k"[tw]) AND (anticoagulant*[tw] OR anti coagulant*[tw])))
AND
(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR randomised [tiab] OR placebo [tiab] OR randomly [tiab] OR trial [tiab]) NOT (“animals”[mesh] NOT (“animals”[mesh] AND “humans”[mesh]))
Limits: English

EMBASE:

('NOACs':ti,ab,kw OR 'NOAC':ti,ab,kw OR 'DOACs':ti,ab,kw OR 'DOAC':ti,ab,kw OR 'new oral anticoagulant':ti,ab,kw OR 'new oral anti coagulant':ti,ab,kw OR 'novel oral anticoagulant':ti,ab,kw OR 'new oral anti coagulant':ti,ab,kw OR 'new oral

anticoagulants':ti,ab,kw OR 'new oral anti coagulants':ti,ab,kw OR 'novel oral anticoagulants':ti,ab,kw OR 'new oral anti coagulants':ti,ab,kw OR 'non-vitamin K antagonist oral anticoagulants':ti,ab,kw OR 'non-vitamin K antagonist oral anticoagulant':ti,ab,kw OR 'novel oral anticoagulants':ti,ab,kw OR 'new oral anticoagulants':ti,ab,kw OR 'direct oral anticoagulants':ti,ab,kw OR 'direct oral anticoagulant':ti,ab,kw OR 'direct oral anti coagulant':ti,ab,kw OR 'direct oral anti coagulants':ti,ab,kw OR 'factor Xa inhibitors':ti,ab,kw OR 'factor IIa inhibitors':ti,ab,kw OR 'direct thrombin inhibitor':ti,ab,kw OR 'direct thrombin inhibitors':ti,ab,kw OR 'factor xa inhibitor':ti,ab,kw OR 'factor IIa inhibitor':ti,ab,kw OR 'dabigatran':ti,ab,kw,de OR 'Pradaxa':ti,ab,kw,de OR 'rivaroxaban':ti,ab,kw,de OR 'Xarelto':ti,ab,kw,de OR 'apixaban':ti,ab,kw,de OR 'Eliquis':ti,ab,kw,de OR 'eliques':ti,ab,kw,de OR 'edoxaban':ti,ab,kw,de OR 'Savaysa':ti,ab,kw,de OR 'roteas':ti,ab,kw,de OR 'Lixiana':ti,ab,kw,de OR 'betrixaban':ti,ab,kw,de OR 'Bevyxxa':ti,ab,kw,de OR (('new oral':ti,ab,kw OR 'novel':ti,ab,kw OR 'non vitamin k':ti,ab,kw) AND (anticoagulant*:ti,ab,kw OR anti coagulant*:ti,ab,kw)))

AND

('randomized controlled trial'/de OR 'controlled clinical trial'/de OR randomized:ti,ab OR randomised:ti,ab OR placebo:ti,ab OR randomly:ti,ab OR trial:ti,ab) NOT ('animal'/exp NOT ('animal'/exp AND 'human'/exp))

Limits: English

Cochrane Library:

("NOACs":ti,ab,kw OR "NOAC":ti,ab,kw OR "DOACs":ti,ab,kw OR "DOAC":ti,ab,kw OR "new oral anticoagulant":ti,ab,kw OR "new oral anti coagulant":ti,ab,kw OR "novel oral anticoagulant":ti,ab,kw OR "new oral anti coagulant":ti,ab,kw OR "new oral anticoagulants":ti,ab,kw OR "new oral anti coagulants":ti,ab,kw OR "novel oral anticoagulants":ti,ab,kw OR "new oral anti coagulants":ti,ab,kw OR "non vitamin K antagonist oral anticoagulants":ti,ab,kw OR "non vitamin K antagonist oral anticoagulant":ti,ab,kw OR "novel oral anticoagulants":ti,ab,kw OR "new oral anticoagulants":ti,ab,kw OR "direct oral

anticoagulants":ti,ab,kw OR "direct oral anticoagulant":ti,ab,kw OR "direct oral anti coagulant":ti,ab,kw OR "direct oral anti coagulants":ti,ab,kw OR "factor Xa inhibitors":ti,ab,kw OR "factor IIa inhibitors":ti,ab,kw OR "direct thrombin inhibitor":ti,ab,kw OR "direct thrombin inhibitors":ti,ab,kw OR "factor xa inhibitor":ti,ab,kw OR "factor IIa inhibitor":ti,ab,kw OR "dabigatran":ti,ab,kw OR "Pradaxa":ti,ab,kw OR "rivaroxaban":ti,ab,kw OR "Xarelto":ti,ab,kw OR "apixaban":ti,ab,kw OR "Eliquis":ti,ab,kw OR "eliques":ti,ab,kw OR "edoxaban":ti,ab,kw OR "Savaysa":ti,ab,kw OR "roteas":ti,ab,kw OR "Lixiana":ti,ab,kw OR "betrixaban":ti,ab,kw OR "Bevyxxa":ti,ab,kw OR [mh "dabigatran"] OR [mh "rivaroxaban"] OR [mh "apixaban"] OR [mh "edoxaban"] OR [mh "betrixaban"] OR (("new oral":ti,ab,kw OR "novel":ti,ab,kw OR "non vitamin k":ti,ab,kw) AND (anticoagulant*:ti,ab,kw OR anti coagulant*:ti,ab,kw)))

ClinicalTrials.gov:

"new oral anticoagulant" OR "novel oral anticoagulant" OR "non vitamin K antagonist oral anticoagulant" OR "direct oral anticoagulant" OR “NOAC” OR “DOAC” OR "dabigatran" OR "apixaban" OR "edoxaban" OR "rivaroxaban" OR "betrixaban"

Table S1. Summary of the included cohort studies in the present meta-analysis

Author name	Year	Design	Country	Treatment indication	NOAC type	Mean Follow-up (months)	Mean age (years)	Female (%)	Study sample size (n)	Reported fracture sites
Lucenteforte[12]	2017	Retrospective cohort study	Italy	Not specified	Dabigatran and direct Xa inhibitors (combined rivaroxaban and apixaban)	<12*	Not provided‡	48.9	16,850	Hip or vertebral fracture
Binding[14]	2019	Retrospective cohort study	Denmark	AF	Dabigatran, rivaroxaban, apixaban, and edoxaban (all combined)	24	72.7	42.2	37,350	Any fracture; major osteoporotic fracture; hip fracture
Huang[16]	2020	Retrospective cohort study	Taiwan	AF	Dabigatran, rivaroxaban, and apixaban	29.2†	71.9	41.0	28,776§	Hip; vertebral; and humerus/forearm/wrist fractures
Lau[17]	2020	Retrospective cohort study	Hong Kong	AF	Dabigatran, rivaroxaban, and apixaban	14.1	74.4	48.0	23,515	Hip or vertebral fracture
Lutsey[15]	2020	Retrospective cohort study	USA	AF	Dabigatran, rivaroxaban, and apixaban	16.9	68.9	38.0	167,275§	Hip fracture and all clinical fractures

* no report of the actual mean follow-up time.

† Median.

‡ 67.2% patients ≥75 years old; 32.8% patients <75 years old.

§ Overall study sample size before head-to-head propensity score matching.

Abbreviations: AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant

Table S2. Summary of the included randomized controlled trials in the present meta-analysis

Trial name	Year	Country	Treatment indication	NOAC type	Follow-up duration (months)	Mean age (years)	Female (%)	Study sample size (n)	Reported fracture sites
PETRO Study[30]	2007	4 (Denmark, Netherlands, Sweden, and USA)	AF	Dabigatran	3	69.7	18.1	502	Radius
RE-COVER I[31]	2009	29 countries	VTE	Dabigatran	6	54.7	41.6	2,539	Femur; hip; lower limb; radius; rib; tibia
RE-LY[32]	2009	44 countries	AF	Dabigatran	24*	71	36.4	18,040	Ankle; cervical vertebral; clavicle; compression; facial bones; femoral neck; femur; fibula; foot; forearm; hand; hip; humerus; lower limb; lumbar vertebral; multiple; patella; pelvic; pubic rami; radius; rib; scapula; skull; spinal compression; spinal; sternal; thoracic vertebral; tibia; upper limb; wrist; pathological; unspecified
EINSTEIN-DVT‖[33]	2010	35 countries	VTE	Rivaroxaban	3, 6, or 12†	56.1	43.2	3,429	Ankle; clavicle; femoral neck; femur; humerus; radius; rib; spinal compression; ulna; thoracic vertebral; pathological
NCT00504556‡[34]	2010	12 countries	AF	Edoxaban	4	65	37.9	1,143	Clavicle; upper limb
NCT01136408‡[35]	2010	1 (Japan)	AF	Dabigatran	3	67.8	12.3	166	Femur
ARISTOTLE[36]	2011	39 countries	AF	Apixaban	21.6*	Median 70	35.3	18,140	Hand; periprosthetic; upper limb; foot; spinal compression; facial bones; open; tibia; acetabulum; ankle; clavicle; femoral neck; pelvic; scapula; skull; wrist; cervical vertebral; femur; hip; lower limb; patella; thoracic vertebral; pubis; spinal; sternal; fibula; forearm; unspecified; humerus; rib; traumatic; lumbar vertebral; radius; ulna; pathological
NCT00806624‡[37]	2011	4 (Taiwan, South Korea, Hong Kong, and Singapore)	AF	Edoxaban	3	65.1	34.6	234	Unspecified fracture
ROCKET AF[38]	2011	45 countries	AF	Rivaroxaban	23.6*	Median 73	39.7	14,236	Ankle; avulsion; cervical vertebral; clavicle;

									compression; facial bones; femoral neck; femur; fibula; foot; unspecified; hand; hip; humerus; lower limb; lumbar vertebral; multiple; patella; pelvic; pubis; radius; rib; skull; spinal compression; spinal; thoracic vertebral; tibia; traumatic; upper limb; wrist; pathological
EINSTEIN-PE[‖][39]	2012	38 countries	VTE	Rivaroxaban	3, 6, or 12[†]	57.7	47.1	4,817	Ankle; facial bones; femoral neck; femur; fibula; foot; hip; humerus; rib; spinal compression; sternal; tibia; traumatic; cervical vertebral; lumbar vertebral; thoracic vertebral; upper limb
J-ROCKET AF[40]	2012	1 (Japan)	AF	Rivaroxaban	16.2*	71.1	19.4	1,278	Femur; fibula; patella; radius; rib; spinal compression; tibia; ulna; skull
AMPLIFY[41]	2013	28 countries	VTE	Apixaban	at least 6	56.9	41.3	5,365	Ankle; cervical vertebral; facial bones; femur; hip; humerus; lower limb; lumbar vertebral; pelvic; radius; spinal compression; upper limb; wrist; pathological
ENGAGE AF-TIMI 48[42]	2013	46 countries	AF	Edoxaban	33.6*	Median 72	38.1	21,026	Femur; hip; rib; humerus; spinal compression; femoral neck; lower limb; lumbar vertebral; facial bones; pelvic; fibula; thoracic vertebral; ankle; pubis; cervical vertebral; foot; forearm; patella; radius; ulna; wrist; acetabulum; sacrum; hand; periprosthetic; spinal; tibia; upper limb; clavicle; compression; jaw; multiple; scapula; skull; unspecified; coccyx; ischium; skull; sternal; osteoporotic; pathological
Hokusai-VTE[43]	2013	37 countries	VTE	Edoxaban	12	55.8	42.8	8,240	Femur; rib; spinal compression; femoral neck; tibia; acetabulum; hip; jaw; radius; spinal; ankle; clavicle; compression; fibula; foot; sacrum; hand; humerus; lower limb; pelvic; pubis; thoracic vertebral; upper limb; wrist; facial bones; forearm; lumbar vertebral; multiple; traumatic
RE-COVER II[44]	2013	31 countries	VTE	Dabigatran	6	54.9	39.4	2,568	Femoral neck; hip; humerus; multiple; upper limb
RE-MEDY[45]	2013	33 countries	VTE	Dabigatran	6-36	54.7	39	2,856	Acetabulum; ankle; femoral neck; femur; fibula; foot; hand; hip; humerus; lower limb; radius; tibia; upper limb
ENSURE-AF[46]	2016	19 countries	AF	Edoxaban	2	64.2	34.4	2,149	Ankle

eTRIS[47]	2016	1 (USA)	VTE	Edoxaban	4	54.8	26.2	84	Femoral neck; rib
PIONEER AF-PCI[48]	2016	14 countries	AF	Rivaroxaban	12	70.1	25.5	2,099	Compression; femoral neck; hip; humerus; lower limb; pubis; radius; rib; traumatic; upper limb
RE-CIRCUIT[49]	2017	11 countries	AF	Dabigatran	3-4	59.2	25.2	676	Acetabulum
REDUAL-PCI[50]	2017	41 countries	AF	Dabigatran	14.0[§]	70.8	24	2,678	Ankle; clavicle; femoral neck; femur; hand; hip; lumbar vertebral; multiple; pelvic; periprosthetic; pubis; rib; skull; spinal compression; sternal; upper limb; wrist
ELIMINATE-AF[‖][51]	2018	11 countries	AF	Edoxaban	5	59.5	28.1	602	Foot
EMANATE[52]	2018	12 countries	AF	Apixaban	1-4	64.6	33.2	1,456	Femur; radius
RE-SPECT CVT[53]	2019	9 countries	VTE	Dabigatran	6	45.2	55	120	Upper limb

*****Median.

[†]Depended on the intended duration of treatment.

[‡]Named by clinical trial registry number.

[§]Median.

[‖]The control group in these studies contained both warfarin and acenocoumarol users; the present meta-analysis included them in the warfarin group.

Abbreviations: AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; VTE, venous thromboembolism

Table S3. Quality assessment of the included cohort studies using the Newcastle–Ottawa Scale

Author	Year	Selection				Comparability		Outcome			Total Quality Score
		Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	The outcome of interest was not present at the start of the study	Adjusted for age	Adjusted for sex	Assessment of outcome	Follow-up length	Loss to follow-up rate	
Lucenteforte	2017	1	1	0	1	1	1	1	0	0	**6**
Binding	2019	1	1	1	1	1	1	1	1	1	**9**
Huang	2020	1	1	1	1	1	1	1	1	1	**9**
Lau	2020	1	1	1	1	1	1	1	1	1	**9**
Lutsey	2020	1	1	1	1	1	1	1	1	1	**9**

Selection:

1) Representativeness of exposed cohort: 1, truly or somewhat representative of a community/population-based study; 0, selected group of users or no description of the derivation of the cohort.

2) Selection of non-exposed cohort: 1, drawn from the same community as the exposed cohort; 0, drawn from a different source or no description of the derivation of the non-exposed cohort.

3) Ascertainment of exposure: 1, validation of oral anticoagulant use with a secure record or structured interview; 0, written self-report or no description of validation of oral anticoagulant use.

4) Demonstration that outcome of interest was not present at the start of the study: 1, yes; 0, no.

Comparability:

1) Study adjusted for age: 1, yes; 0, no.

2) Study adjusted for sex: 1, yes; 0, no.

Outcome:

1) Assessment of outcome: 1, independent blind assessment, confirmed by medical records or record linkage; 0, self-reported or no description.

2) Was follow-up long enough for outcomes to occur: 1, duration of follow-up ≥ 1 year; 0, duration of follow-up < 1 year.

3) Loss to follow-up rate: 1, complete follow-up or loss to follow up rate ≤20%; 0, loss to follow up rate >20% or no statement.

Table S4. Quality assessment of the included randomized controlled trials using the Cochrane risk of bias tool

Trial name	Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting	Other biases
PETRO Study	2007	U	U	H	L	L	L	L
RE-COVER I	2009	L	L	L	L	L	L	L
RE-LY	2009	L	L	H	L	L	L	L
EINSTEIN-DVT	2010	L	L	H	L	L	L	L
NCT00504556	2010	L	L	H	L	L	L	L
NCT01136408	2010	L	U	H	U	U	L	U
ARISTOTLE	2011	L	L	L	L	L	L	L
NCT00806624	2011	L	L	H	L	L	L	L
ROCKET AF	2011	L	L	H	L	L	L	L
EINSTEIN-PE	2012	L	L	H	L	L	L	L
J-ROCKET AF	2012	U	U	L	L	U	L	L
AMPLIFY	2013	L	L	L	L	L	L	L
ENGAGE AF-TIMI 48	2013	L	L	L	L	L	L	L
Hokusai-VTE	2013	L	L	L	L	L	L	L
RE-COVER II	2013	L	L	L	L	L	L	L
RE-MEDY	2013	L	L	L	L	U	L	L
ENSURE-AF	2016	L	L	H	L	L	L	L
eTRIS	2016	L	L	H	L	U	L	L
PIONEER AF-PCI	2016	L	L	H	U	L	L	L
RE-CIRCUIT	2017	L	L	H	L	L	L	L
REDUAL-PCI	2017	L	L	H	L	L	L	L
ELIMINATE-AF	2018	L	L	H	L	L	L	L

EMANATE	2018	L	L	H	U	L	L	L
RE-SPECT CVT	2019	L	L	H	L	L	L	L

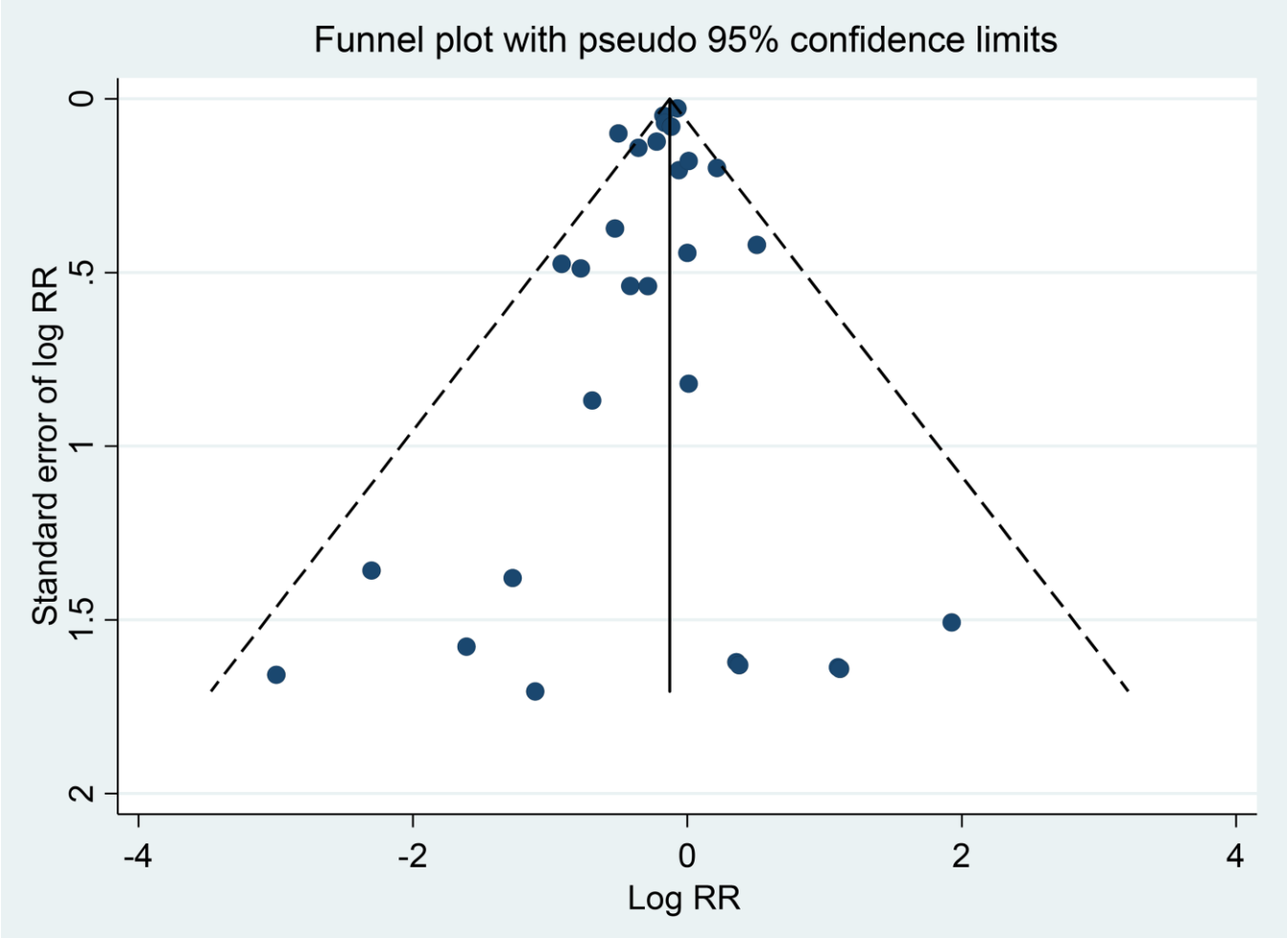
L: low risk; U: unclear risk; H: high risk

Table S5. Covariates adjusted in each cohort study included in the present meta-analysis

Author	Year	Age	Sex	HTN	DM	COPD	CAD/MI	Heart failure	CKD	Stroke	Dementia	Osteoporosis/ BMD	Medication use	Other variables
Lucenteforte	2017	●	●											The pattern of OAC use (incident or non-incident)
Binding	2019	●	●		●	●		●		●			Hormone replacement therapy, antidepressant drugs, glucocorticoid medication, statin	Previous syncope, liver disease, inflammatory polyarthritis, alcohol
Huang	2020	●	●	●	●	●	●	●	●	●	●	●	Corticosteroids, diuretics, NSAID, statins, PPI, antiepileptics, antiparkinsonian, antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants, thyroxine, antithyroid drugs, antiosteoporotic drugs	Thyroid disease, rheumatoid arthritis, malignancy, income level, time from AF diagnosis to OAC prescription, hospital level, hospital region, physician specialty, Charlson comorbidity index, cirrhosis, depression, parkinsonism, epilepsy, cataract, CHA2DS2-VASc score
Lau	2020	●	●	●	●	●		●	●	●		●	ACEI, ARB, β-Blockers, PPI, bisphosphonates, antidepressants, systemic glucocorticoids	Previous fall, previous fracture, rheumatoid arthritis, liver disease, inflammatory polyarthropathies
Lutsey	2020	●	●	●	●	●	●	●	●	●	●	●	Digoxin, clopidogrel, antiplatelets, ACEI, ARB, β-blockers, calcium channel blockers, antiarrhythmic agents, statins, diabetes medications, osteoporosis medications	Previous fracture, peripheral artery disease, liver disease, depression, hematological disorders, GI tract bleeding, other bleeding, frailty, malignancy, prior procedures (cardiac, vascular, GI tract, and neurological), alcohol, CHA2DS2-VASc score

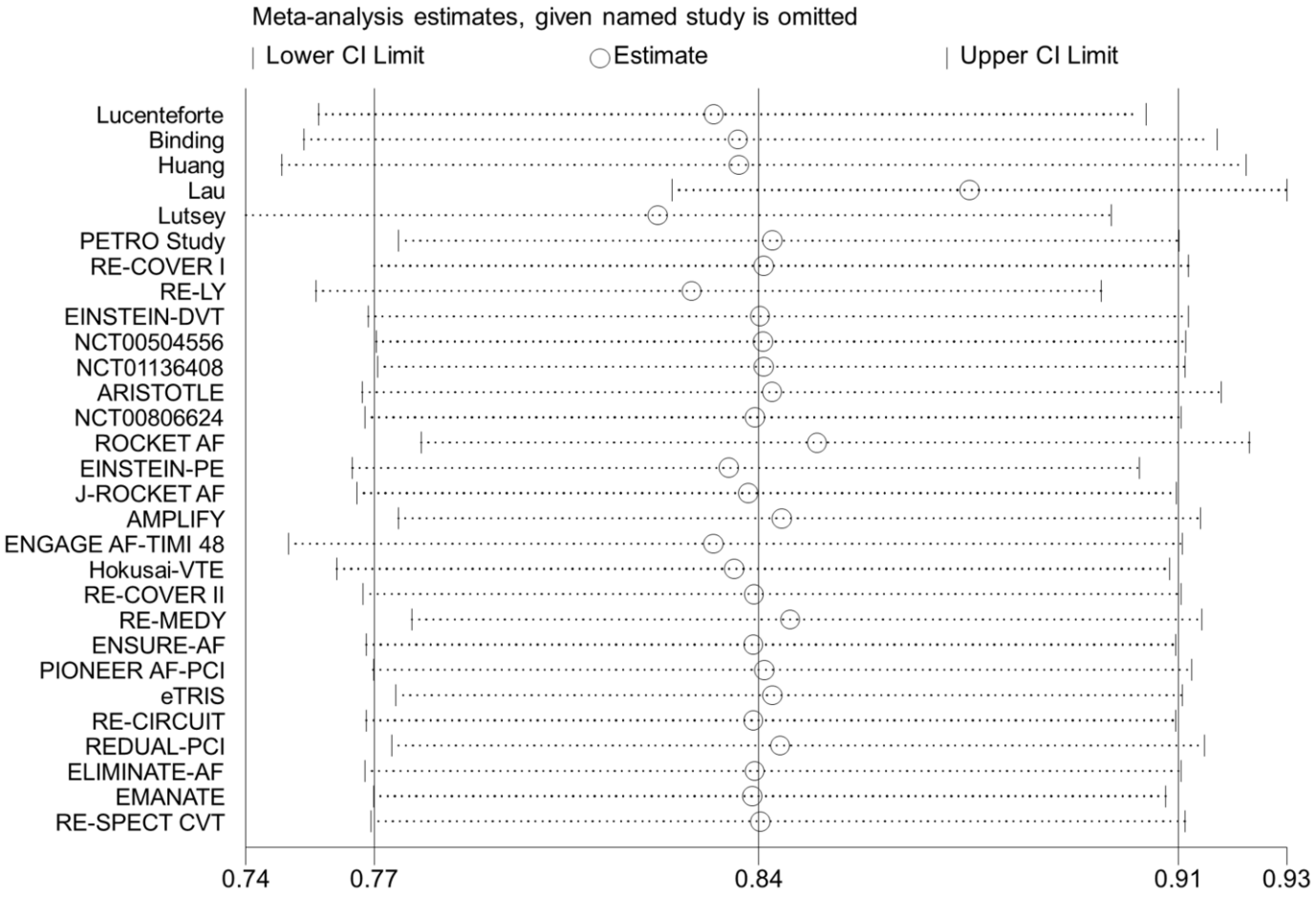
Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; AF, atrial fibrillation; BMD, bone mineral density; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; GI, gastrointestinal; HTN, hypertension; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drugs; OAC, oral anticoagulants; PPI, proton-pump inhibitors

Figure S1. Funnel plot for the publication bias in studies comparing any fracture risk between NOACs and warfarin



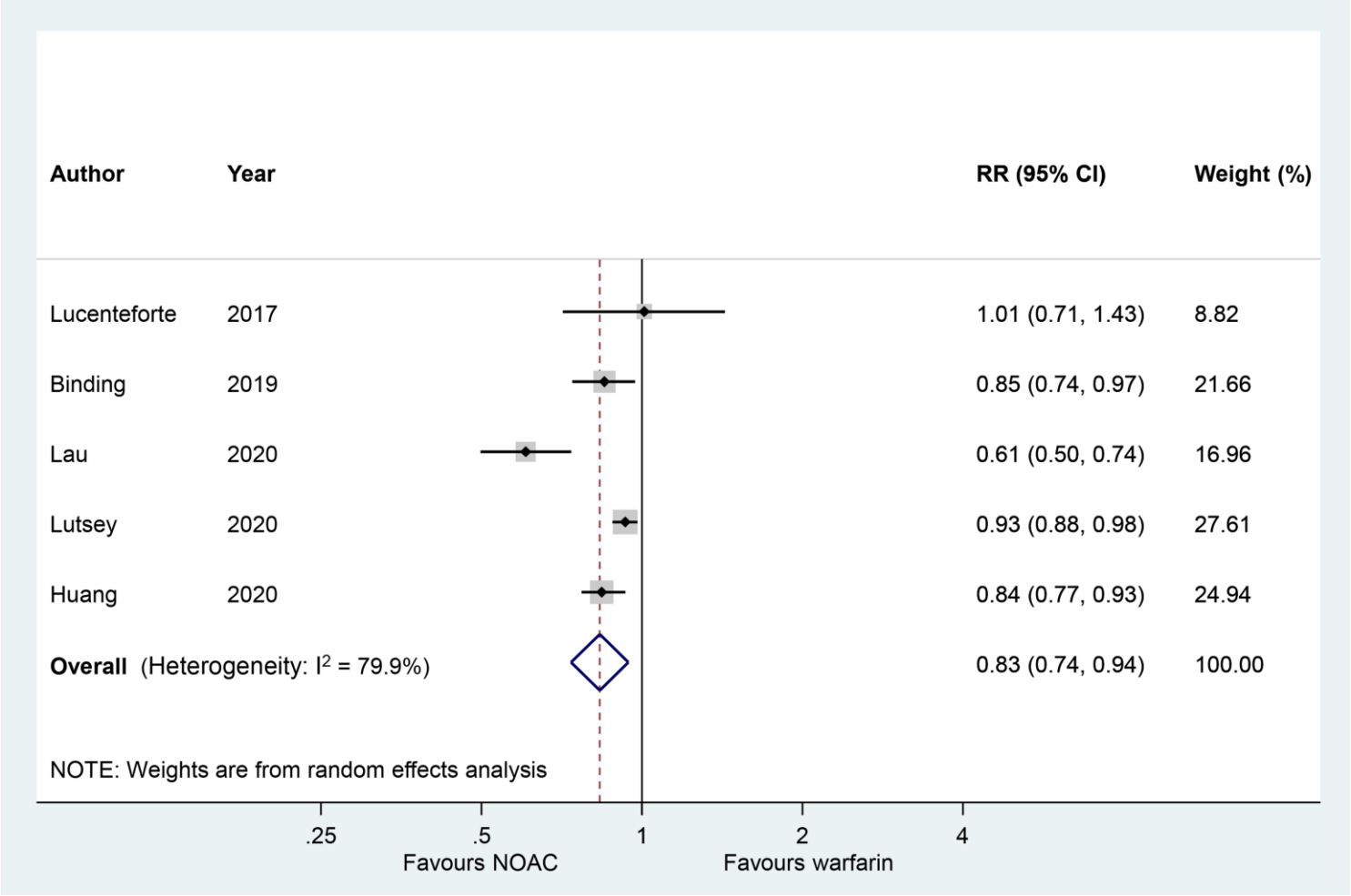
Abbreviations: RR, relative risk

Figure S2. Sensitivity analysis of the meta-analysis of studies comparing any fracture risk between NOACs and warfarin with each study omitted individually one at a time



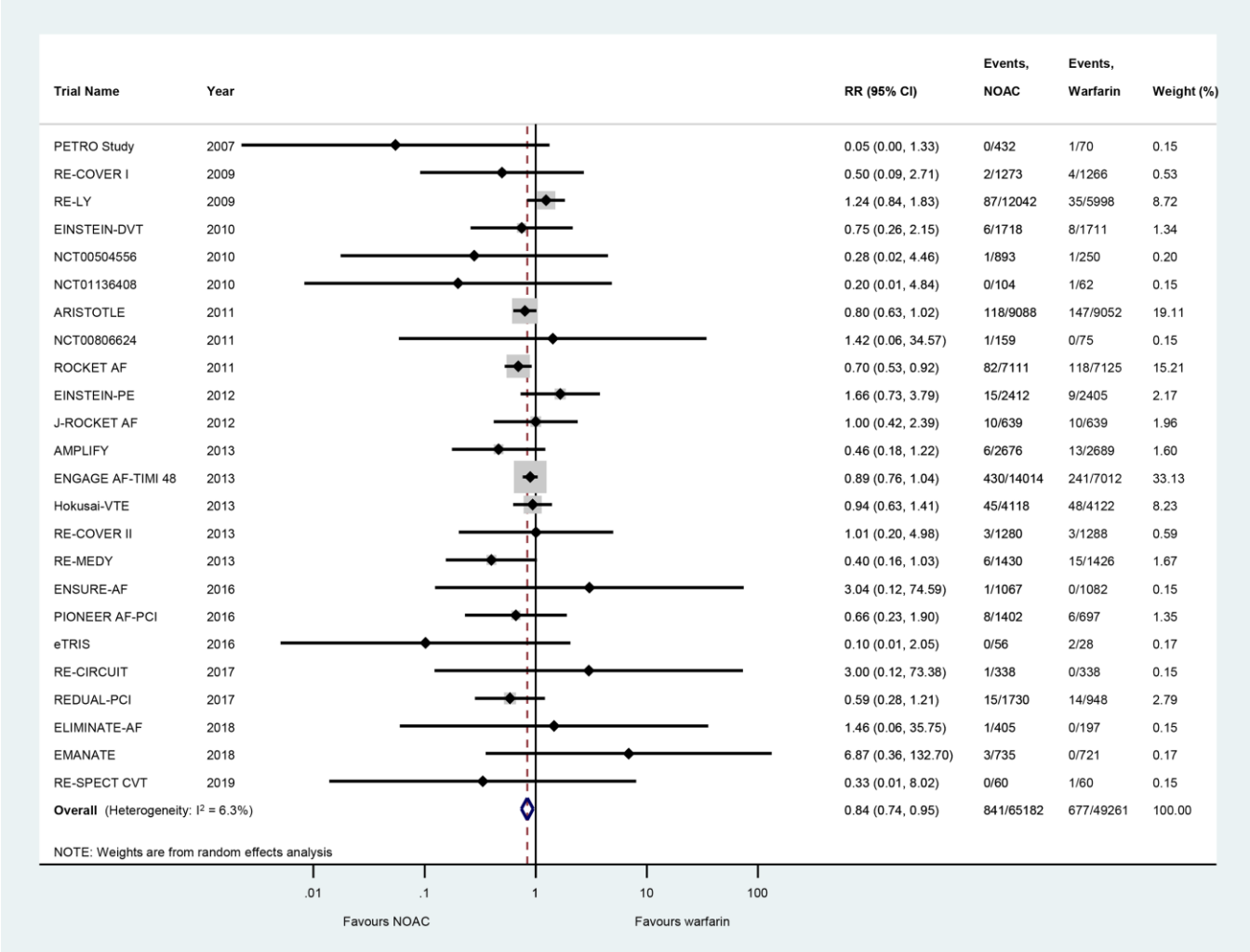
Abbreviations: CI, confidence interval

Figure S3. Forest plot of the relative risk of any fracture associated with NOACs compared to warfarin in the cohort studies subgroup



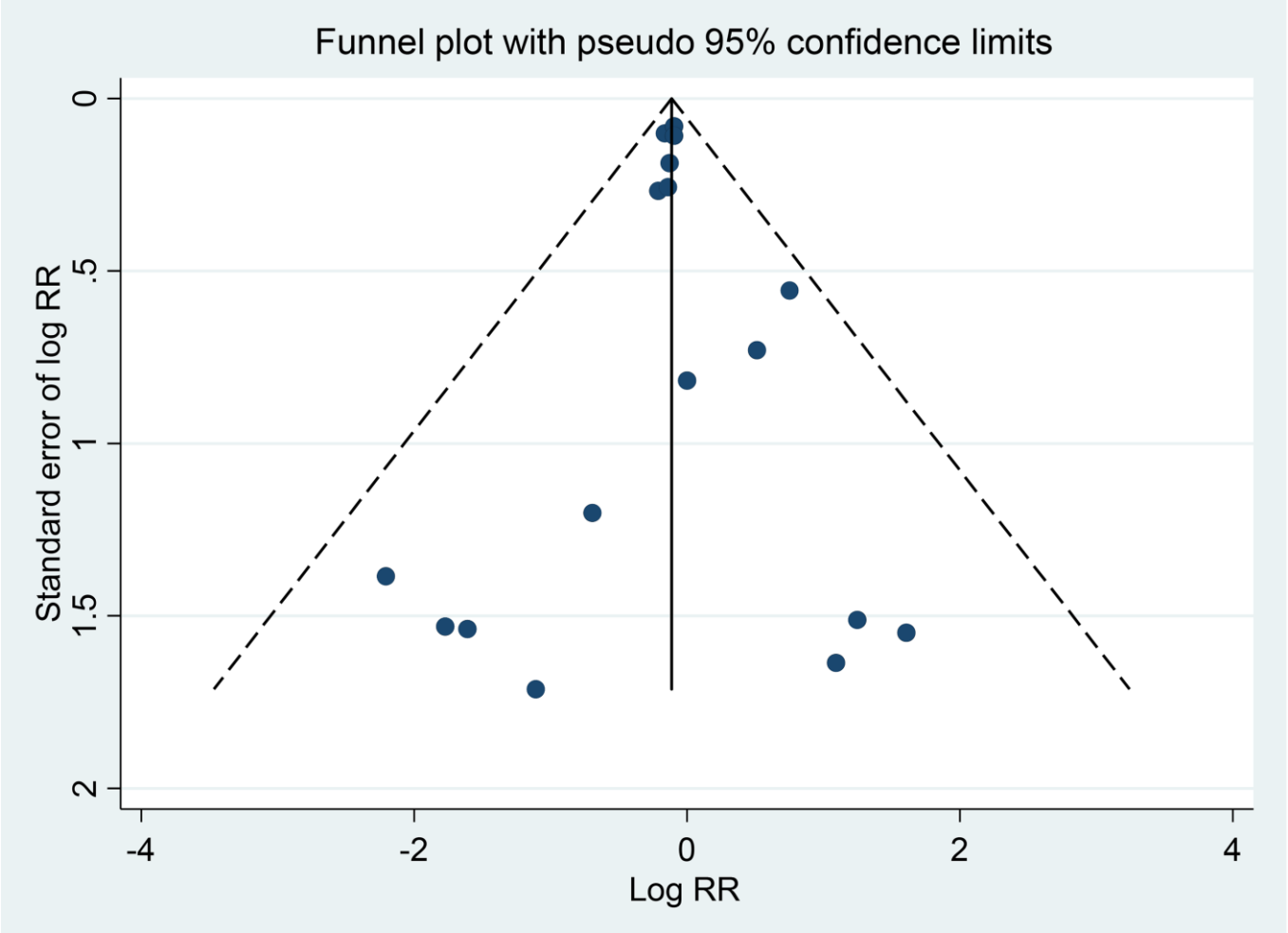
Abbreviations: CI, confidence interval; RR, relative risk

Figure S4. Forest plot of the relative risk of any fracture associated with NOACs compared to warfarin in the randomized controlled trials subgroup



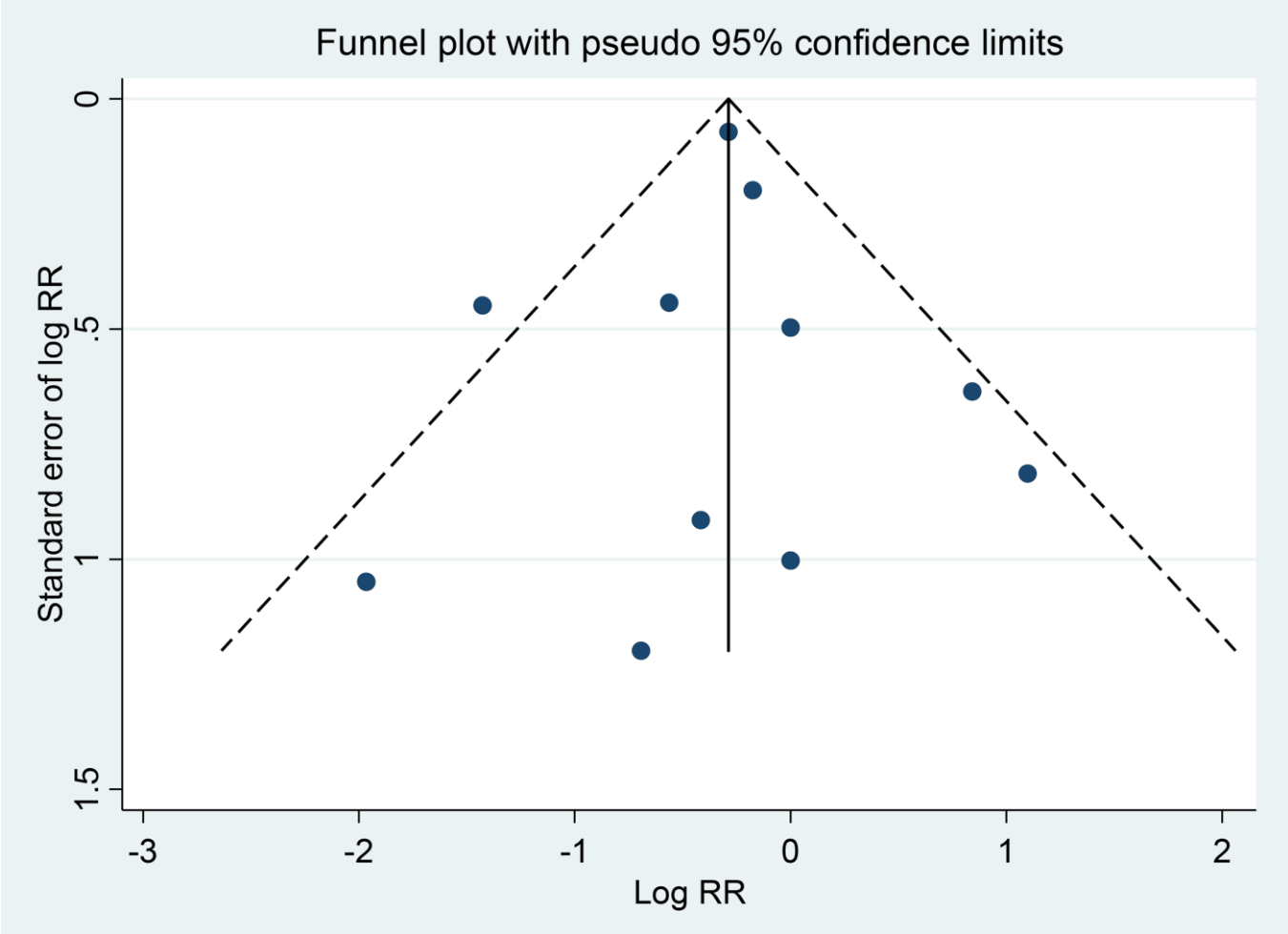
Abbreviations: CI, confidence interval; RR, relative risk

Figure S5. Funnel plot for the publication bias in studies comparing hip fracture risk between NOACs and warfarin



Abbreviations: RR, relative risk

Figure S6. Funnel plot for the publication bias in studies comparing vertebral fracture risk between NOACs and warfarin



Abbreviations: RR, relative risk