



# Association of Direct Oral Anticoagulants vs. Vitamin K Antagonists With Fractures in Atrial Fibrillation Patients: A Systematic Review and Meta-Analysis

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**Background:** Current evidence regarding the application of direct oral anticoagulants (DOACs) vs. vitamin K antagonists (VKAs) on the fracture risk is inconsistent. Therefore, we conducted a meta-analysis to evaluate the fracture risk of DOACs vs. VKAs in patients with atrial fibrillation (AF).

**Methods:** The PubMed and Embase databases were systematically searched until June 2021 for all the studies that reported oral anticoagulants in AF patients. The random-effect model with an inverse variance method was selected to pool the risk ratios (RRs) and 95% confidence intervals (CIs).

**Results:** A total of 10 studies were included in this meta-analysis. Among AF patients receiving anticoagulants, DOAC users showed a reduced risk of any fracture compared to those with VKAs (RR = 0.80; 95% CI: 0.70–0.91) regardless of gender [males (RR = 0.79; 95% CI: 0.67–0.92) and females (RR = 0.71; 95% CI: 0.57–0.89)]. Apixaban (RR = 0.75; 95% CI: 0.60–0.92) and rivaroxaban (RR = 0.73; 95% CI: 0.61–0.88), but not dabigatran and edoxaban, were associated with a decreased risk of any fracture compared with VKAs. DOAC users had decreased risks of osteoporotic fractures (RR = 0.63; 95% CI: 0.47–0.84) and hip/pelvic fractures (RR = 0.88; 95% CI: 0.79–0.97) compared to those treated with VKAs.

**Conclusions:** Our meta-analysis suggested that the use of DOACs was associated with a reduced risk of any fracture compared with VKAs. Further studies should confirm our findings.

**Keywords:** atrial fibrillation, non-vitamin K antagonist oral anticoagulants, warfarin, fracture, meta

## INTRODUCTION

Atrial fibrillation (AF) is becoming an aging-related disease, and osteoporotic fractures are major health threats in the elderly. Oral anticoagulants are widely used for thromboprophylaxis in AF patients for decades. Vitamin K antagonists (VKAs) such as warfarin has been speculated to increase the risk of osteoporotic fracture. Warfarin interrupts the vitamin K-dependent calcium

balance and synergy with vitamin D bone-forming actions. Warfarin inhibits the  $\gamma$ -carboxylation of several osteoblast-specific proteins (1, 2), leading to low bone density and increased fracture risk (3). These observations propose a link between warfarin use and the risk of osteoporotic fractures (4, 5).

Direct oral anticoagulants (DOACs) including thrombin or Xa factor inhibitors (dabigatran, apixaban, rivaroxaban, and edoxaban) are recommended as the first-line drugs for thromboprophylaxis in AF patients. Data from both randomized controlled trials (RCTs) (4–7) and observational studies (8, 9) have shown that DOACs are at least non-inferior to warfarin for stroke prevention in AF patients. Additionally, DOACs might be associated with better outcomes in the elderly (10), as well as AF patients with complications [e.g., stroke (11), cancer, and peripheral artery disease (12)].

Since DOACs have no impact on osteocalcin, their effects on bone fracture have yet been undefined. A prior meta-analysis based on the RCTs (13) showed that DOACs were associated with a relatively lower fracture risk over warfarin in patients with AF or venous thromboembolism. However, there is a lack of consistent evidence regarding this issue in real-world settings. Several real-world studies found that there was no difference in the risk of bone fracture between DOACs and warfarin (14, 15), whereas other studies suggested that DOACs were associated with a lower risk of fracture compared to warfarin (16–18). Therefore, this meta-analysis was performed to compare the risk of fractures between DOACs vs. VKAs in AF patients.

## METHODS

The meta-analysis was performed under the recommendations of the Cochrane handbook for systematic reviews (19) and the Preferred Reporting Items for Reporting Systematic Reviews and Meta-analyses (20). The data of the current study are available from the corresponding author on reasonable requests. We did not provide ethical approval because only the published data were included.

### Eligibility Criteria

In this study, the following inclusion criteria were applied: (1) population (P)-nonvalvular AF patients; (2) intervention (I) and control (C)-DOACs vs. VKAs; (3) outcome (O)-bone fractures including any fracture, major osteoporotic fractures, vertebral, and humerus/forearm/wrist fractures and hip/pelvic fractures; and (4) study design-RCTs or observational studies. The effect estimates were propensity score-matched or adjusted risk ratios (RRs) and 95% confidence intervals (CIs). Studies with no data, such as reviews, case reports, case series, editorials, guidelines, and conference abstracts, were excluded.

### Literature Search

The PubMed and Embase electronic databases were systematically searched from January 2009 (since the first available DOAC-dabigatran was applied to AF patients) to June 2021 for studies that compared the risk of any fracture between DOACs vs. VKAs in AF patients. The search strategy combined three kinds of search terms using the Boolean

operator “and”: (1) *atrial fibrillation* OR *atrial flutter*, AND (2) *non-vitamin K antagonist oral anticoagulants* OR NOACs OR *direct oral anticoagulants* OR DOACs OR *dabigatran* OR *rivaroxaban* OR *apixaban* OR *edoxaban*, AND (3) *vitamin K antagonists* OR *warfarin* OR *coumadin* OR *phenprocoumon* OR *acenocoumarol*, AND (4) *fracture* OR *bone fracture* OR *osteoporosis* OR *osteoporosis fracture*. There were no linguistic restrictions in the literature search. The literature search strategy is shown in **Supplementary Table 1**. To ensure a comprehensive literature search, the reference lists of the retrieved studies were screened to identify the additional reports.

### Study Selection and Data Extraction

All the retrieved studies were screened by two reviewers independently. Potential eligible studies were chosen after reviewing the titles and abstracts based on the established inclusion and exclusion criteria. The disputable issues were resolved by consensus, or by a discussion with the third author.

The following information was collected including the first author and publication year, country, data source, study design, baseline data of the participants (sample size, age, and the sex), inclusion period, type of DOACs, the follow-up time of DOAC users, and type of fractures.

### Risk of Bias Assessment

For the *post-hoc* analysis of RCTs, the bias risks were evaluated according to the Cochrane risk of bias assessment tool (19). The bias risk of each study was scored as “low,” “unclear,” or “high” risk in each section. The “low risk” was defined when three out of five biases were “low” (21). The Newcastle-Ottawa Scale (NOS) tool was applied to evaluate the methodological quality of observational studies. A study with a NOS score of <6 was defined as low quality (22).

### Statistical Analysis

In this meta-analysis, we performed all the statistical analyses using the Stata software (version 15.0, Stata Corp LP, College Station, TX) and the Review Manager 5.3 software (the Nordic Cochrane Center, Rigshospitalet, Denmark). The Cochrane Q test and  $I^2$  statistic were the most commonly reported statistical methods to assess the heterogeneity, where  $P < 0.1$  and  $I^2 > 50\%$  suggested substantial heterogeneity, respectively. The natural logarithms of RRs and standard errors of the included studies were calculated and then pooled by a random-effects model using an inverse variance method. The publication bias was assessed using the funnel plots, and further calculated using the Egger’s and Begg’s tests. The subgroup analyses were performed based on the DOAC types (dabigatran, apixaban, rivaroxaban, and edoxaban), the individual position of fractures (hip/pelvic fracture and osteoporosis fracture), gender (males vs. females), and length of the follow-up period ( $\geq 1$  vs.  $< 1$  year).

## RESULTS

### Study Selection

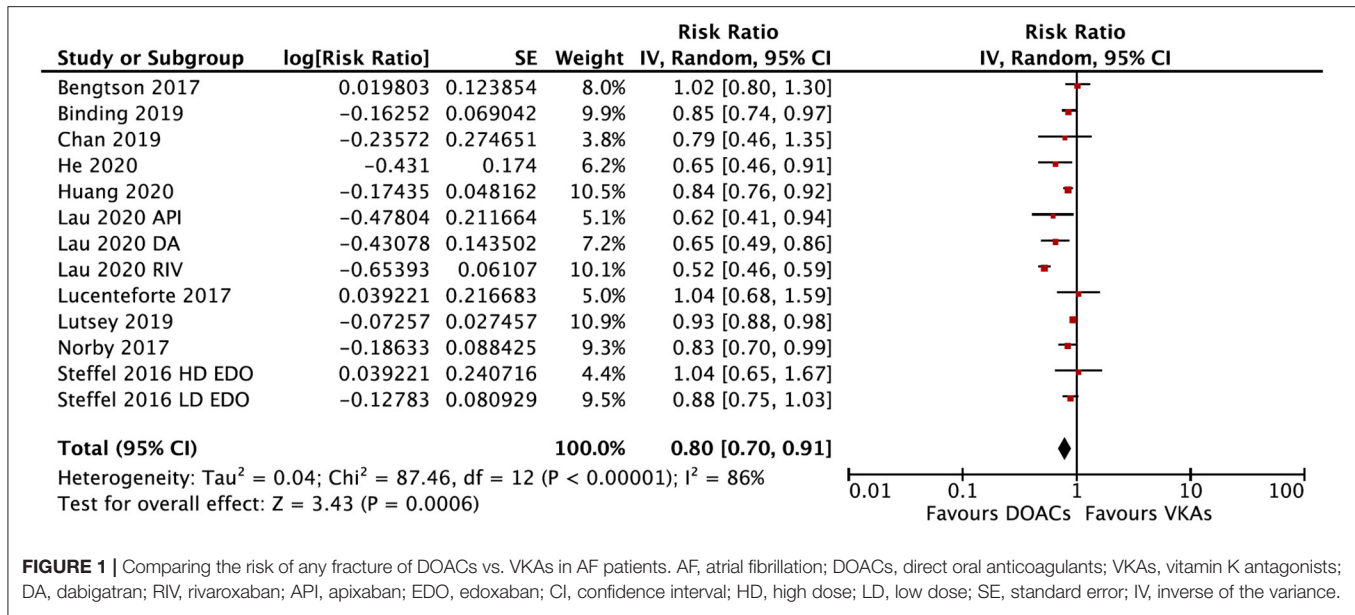
The process for electronic retrievals is shown in **Supplementary Figure 1**. A total of 10 studies [one sub-analysis

**TABLE 1** | Baseline characteristics of the included studies of this study.

Included studies	Country	Study design	Number of participants	Age (y) /Male (%)	Study period	Data source	DOACs	Follow-up in DOAC users (months)	Controls	Outcomes	Quality assessment*
He-2020	Québec Canada	Observational study	25,663	75.6/50.3	2000–2014	Québec healthcare databases	DA; RIV; API	NA	VKAs	Any fracture, hip fracture, upper extremity fracture, vertebral fracture, Osteoporosis with pathological fracture	8
Lau-2020	Hong Kong China	Observational study	23,515	74.4/52.0	2010–2017	Clinical data analysis and reporting system	DA; RIV; API	14.1	warfarin	Osteoporotic fracture	8
Huang-2020	Taiwan China	Observational study	19,414	71.9/59.0	2012–2017	Taiwan's national health insurance research database	DA; RIV; API	28.8	warfarin	Hip, vertebral, and humerus/forearm/wrist fractures	8
Binding-2019	Danish	Observational study	37,350	NA/57.8	2013–2017	Danish national patient register	DOACs	24.0	warfarin	any fracture, major osteoporotic fractures, initiating osteoporotic medication, hip fractures	8
Lutsey-2019	United States	Observational study	167,275	68.9/62	2010–2015	MarketScan commercial claims and encounters and marketscan Medicare Supplemental and Coordination of Benefitsdatabases	DA; RIV; API	16.9	warfarin	Hip fractures, Inpatient fractures, All fractures	8
Chan YH-2019	Taiwan China	Observational study	24,338	74.6/56.8	2012–2017	National health insurance research database	EDO	>12.0	warfarin	Any fracture	8
Norby-2017	United States	Observational study	77,991	70.3/60.5	2010–2014	The truven health marketscan® commercial claims and encounters database and the medicare supplemental and coordination of benefits database	RIV	12.0	warfarin	Hip/pelvic fracture	8
Lucenteforte-2017	Denmark	Observational study	16,850	NA/51.1	2009–2015	Danish national prescription registry	DA	12.6	warfarin	Any fracture	8
Bengtson-2017	United States	Observational study	61,648	70.1/63.3	2009–2012	The truven health marketscan® commercial claims and encounters database and the medicare supplemental and coordination of benefits database	DA	15.0	warfarin	Hip/pelvic fracture	8
Steffel-2016	United States	Post-hoc analysis	20,205	72.0/62.4	NA	ENGAGE AF-TIMI 48 trial	EDO	NA	warfarin	Any fracture	Low risk

ENGAGE AF-TIMI 48, effective anticoagulation with factor xa next generation in atrial fibrillation-thrombolysis in myocardial infarction 48; DOACs, direct oral anticoagulants; DA, dabigatran; RIV, rivaroxaban; API, apixaban; EDO, edoxaban; VKAs, vitamin K antagonists; NOS, newcastle-ottawa scale; NA, not available.

\*The Newcastle-Ottawa Scale (NOS) items were used to evaluate the quality of the observational studies, which involve the selection of cohorts, the comparability of cohorts, and the assessment of the outcome).



**FIGURE 1** | Comparing the risk of any fracture of DOACs vs. VKAs in AF patients. AF, atrial fibrillation; DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists; DA, dabigatran; RIV, rivaroxaban; API, apixaban; EDO, edoxaban; CI, confidence interval; HD, high dose; LD, low dose; SE, standard error; IV, inverse of the variance.

of RCT (23) and nine observational studies (14–17, 24–28)] were included in this meta-analysis. To show the reliability of all the included studies, baseline information of the study participants is shown in **Table 1**. Six studies (15–17, 25–27) had a follow-up time of  $\geq 1$  year, 2 studies (14, 24) showed a follow-up time of  $< 1$  year, and two studies did not provide the specific follow-up time (23, 28).

We did the quality assessment and found that the sub-analysis of RCT (23) had a low risk of bias, and all of the included observational studies (14–17, 24–28) had an acceptable quality.

## DOACs vs. VKAs on the Risk of Fracture

The overall RRs and 95% CIs of fracture risks between DOACs vs. VKAs in AF patients are summarized in **Supplementary Table 2**. In the pooled analysis, compared with VKA use, the use of DOACs was associated with a decreased risk of any fracture (HR = 0.80, 95% CI 0.70–0.91) (**Figure 1**).

In the subgroup analysis based on the DOAC types, compared with VKAs, rivaroxaban (RR = 0.73; 95% CI: 0.61–0.88) and apixaban (RR = 0.75; 95% CI: 0.60–0.92), but not dabigatran (RR = 0.90; 95% CI: 0.80–1.01) and edoxaban (RR = 0.89; 95% CI: 0.77–1.03), were associated with a lower risk of any fracture (**Figure 2**). Compared with VKAs, the usage of DOACs acquired a lower risk of hip/pelvic fracture (RR = 0.88; 95% CI: 0.79–0.97) and osteoporosis fracture (RR = 0.63; 95% CI: 0.47–0.84) (**Figure 3**).

The subgroup analysis based on gender suggested that DOACs were associated with a lower risk of fractures in both males (RR = 0.79; 95% CI: 0.67–0.92) and females (RR: 0.71; 95% CI: 0.57–0.89) compared with VKAs ( $P_{interaction} = 0.48$ ; **Figure 4**). DOACs vs. VKAs were associated with a decreased risk of any fracture in patients with a follow-up of  $\geq 1$  year (RR = 0.76, 95% CI 0.63–0.91), but not in the group of  $< 1$  year (RR, 0.73, 95% CI 0.48–1.10), although the interaction was not significant between the two subgroups ( $P_{interaction} = 0.84$ ; **Figure 5**).

## Publication Bias

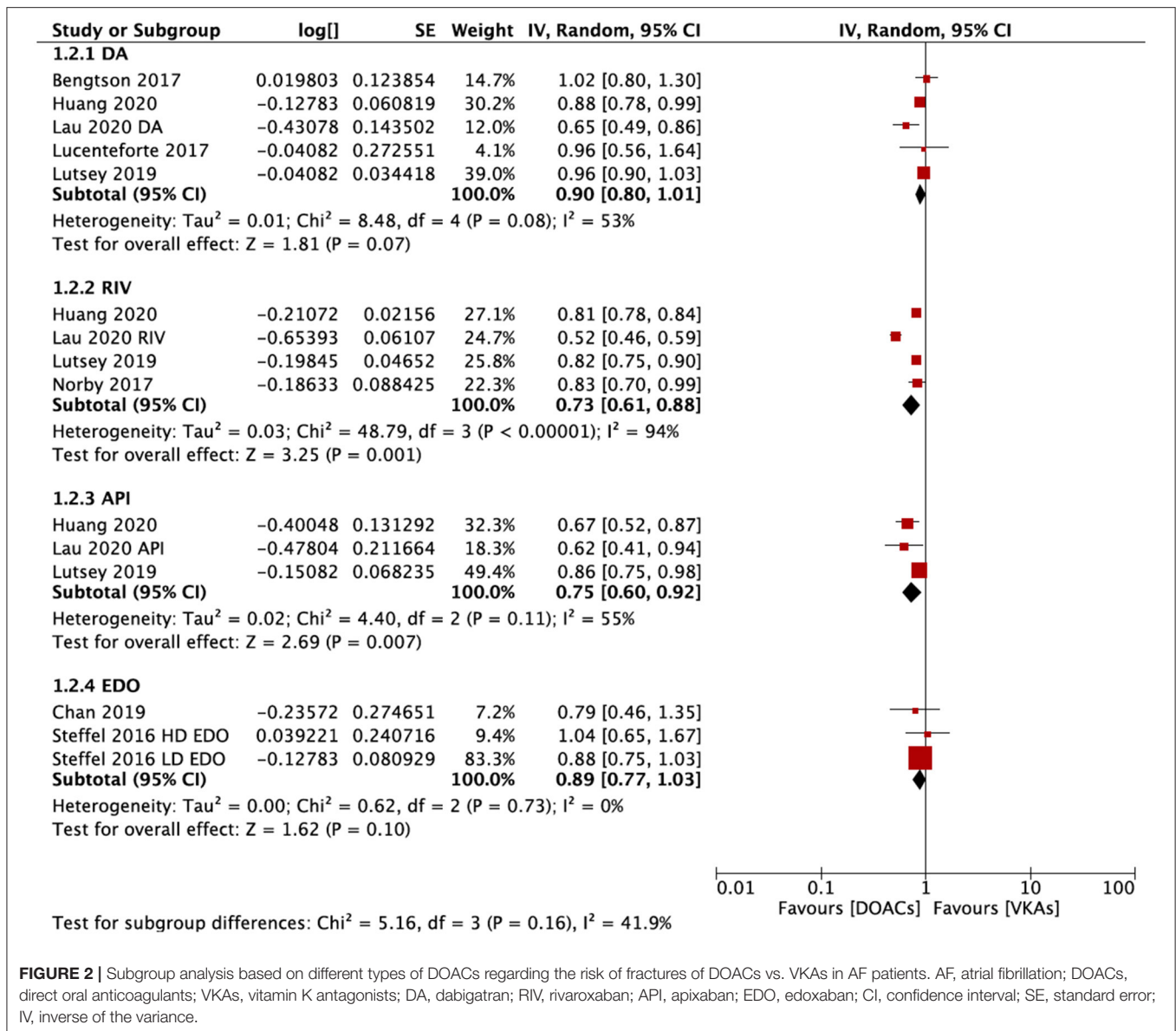
No potential publication biases were found checked by the funnel plots (**Supplementary Figure 2**) combined with the Egger's ( $P = 0.479$ , **Supplementary Figure 3**) and Begg's ( $p = 0.837$ ) tests.

## DISCUSSION

In the present meta-analysis, compared with VKAs, the use of DOACs (mainly rivaroxaban and apixaban) was associated with a lower fracture risk among long-term AF patients. There was no significant different interaction between male and female patients. Overall, DOACs might be a safe alternative among AF patients in terms of decreasing the fracture risks compared with VKAs regardless of gender.

The potential increased risk of fracture with warfarin is coherent with the mechanism of anticoagulation. By regulating vitamin K, warfarin inhibits the  $\gamma$ -carboxylation of osteocalcin, which is associated with a low bone mineral density. Two prior meta-analyses assessed the risk of fracture associated with DOACs compared with VKAs (13, 29). One meta-analysis comprising 89,549 patients of 12 RCTs demonstrated that rivaroxaban and apixaban showed a lower fracture risk when compared to warfarin (13), consistent with our current findings. An *in vivo* study indicated that dabigatran has a better bone safety profile than warfarin because warfarin could interrupt bone by reducing the trabecular size and increasing bone turnover (30). Nevertheless, dabigatran has non-inferiority or superiority to warfarin in terms of reducing the fracture risk in the real-world population. Lutsey et al. found that the estimates between dabigatran and warfarin were near the null for hip and all clinical fractures (17). They only found some evidence of a lower risk of fractures requiring hospitalization associated with dabigatran (17). Lucenteforte et al. also presented no significant



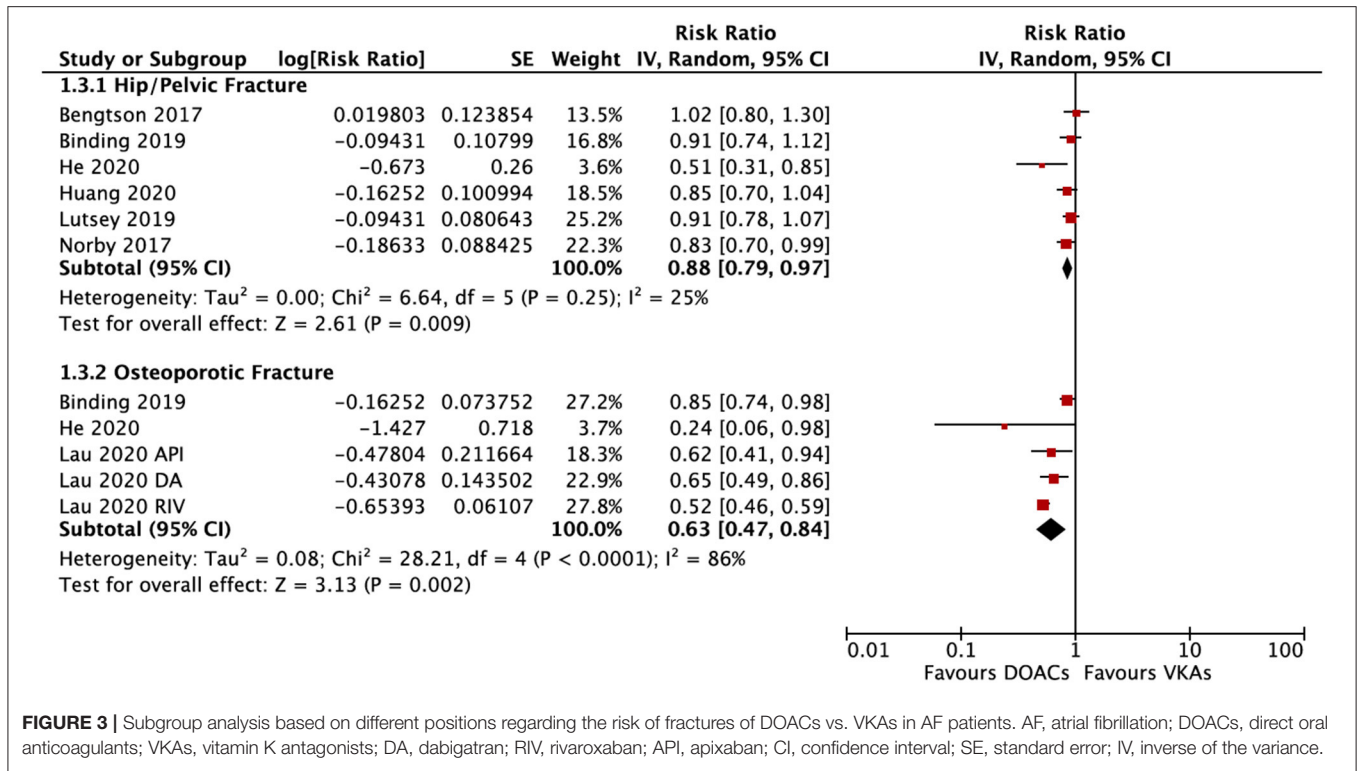


difference in the fracture risk between dabigatran with warfarin (25). In contrast, a retrospective cohort study published in 2020 reported a significantly lower risk of osteoporotic fractures associated with the use of dabigatran among AF patients (26). One potential explanation for the discrepancies across the studies may be the different definitions of fracture and the duration of oral anticoagulants. The biological effect of warfarin on bone metabolism is cumulative and chronic. Lucenteforte et al. restricted cohort eligibility to patients who had been continuously exposed to oral anticoagulants within 1 year, which might lead to an underestimation of fracture risk in warfarin users (25).

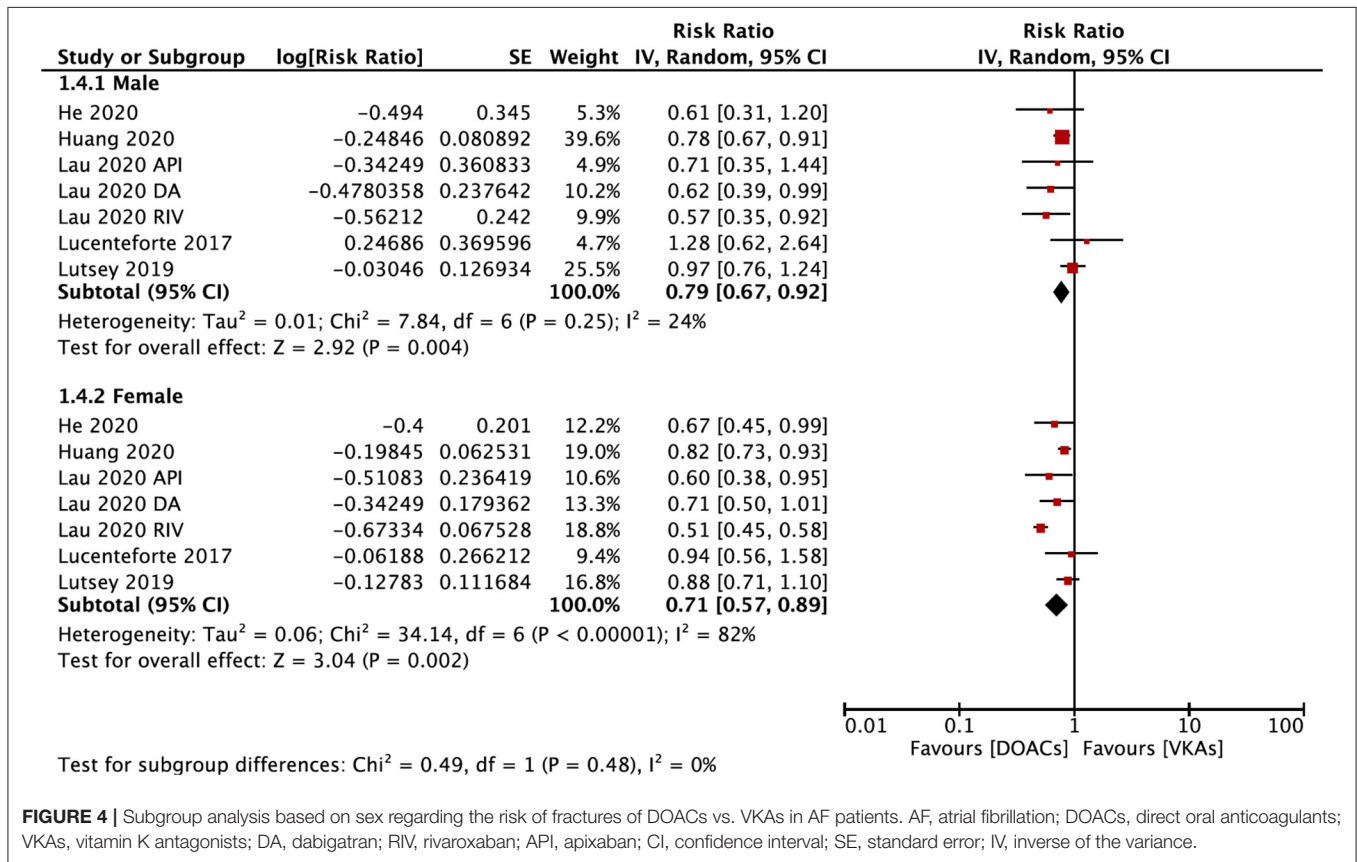
Edoxaban has no effects on the production of Gla-osteocalcin; and thus may have a lower risk of adverse effects on bone health in the rats (31). Although there are still no experiments on humans, evidence of the fracture

risk with edoxaban use is limited. A *post-hoc* analysis from the ENGAGE AF-TIMI 48 trial showed that edoxaban has a comparable risk of fracture with warfarin irrespective of the dosage (23). Given the limited number of edoxaban-associated studies included in the meta-analysis, further study should confirm the fracture risk of edoxaban vs. warfarin in AF patients.

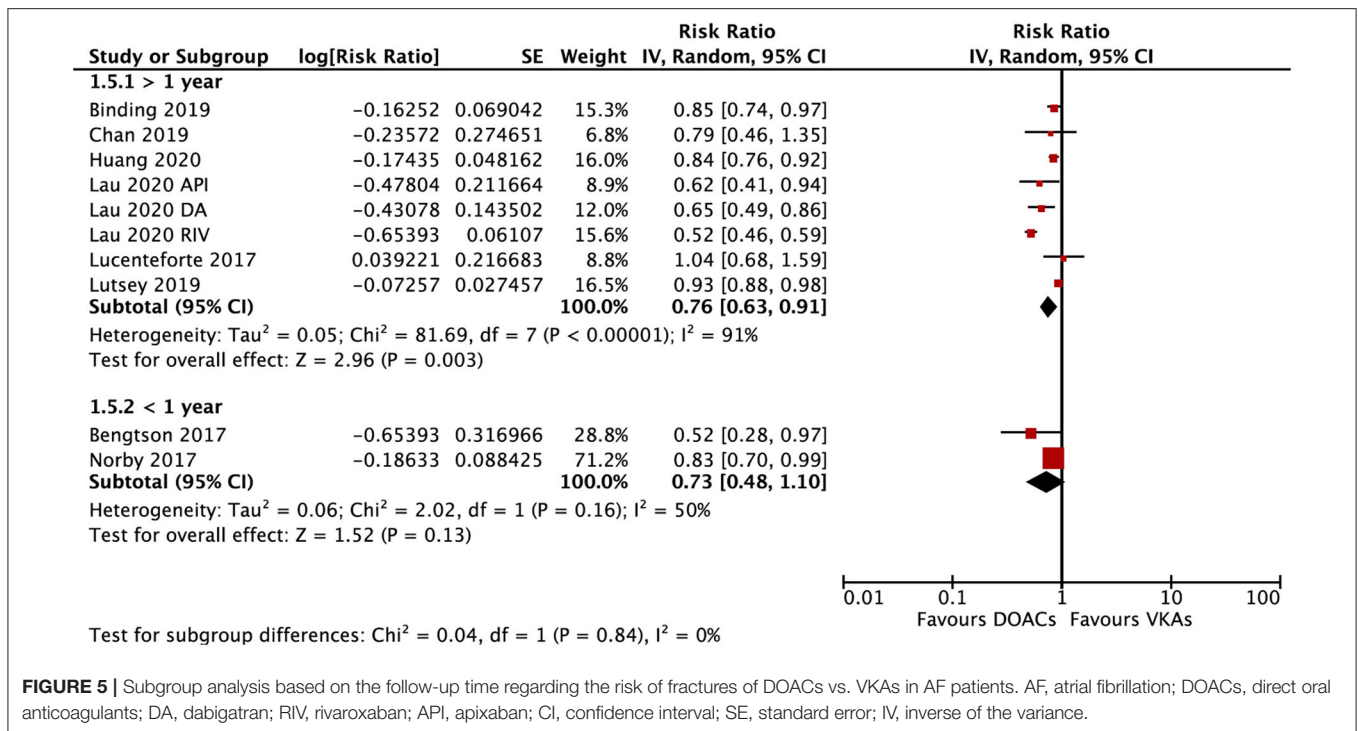
In the current meta-analysis, DOACs were showed a decreased risk of overall fracture events comparing with VKAs. Particularly, rivaroxaban and apixaban are showed reduced risks of fracture events. Although Lau et al. (26) did comparisons between dabigatran and rivaroxaban regarding the osteoporotic fractures risk in AF patients, no significant difference was detected. Lutsey et al. (17) yielded no statistically significant differences in the incidence of fracture between DOAC and DOAC among patients with AF. Further studies should confirm



**FIGURE 3 |** Subgroup analysis based on different positions regarding the risk of fractures of DOACs vs. VKAs in AF patients. AF, atrial fibrillation; DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists; DA, dabigatran; RIV, rivaroxaban; API, apixaban; CI, confidence interval; SE, standard error; IV, inverse of the variance.



**FIGURE 4 |** Subgroup analysis based on sex regarding the risk of fractures of DOACs vs. VKAs in AF patients. AF, atrial fibrillation; DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists; DA, dabigatran; RIV, rivaroxaban; API, apixaban; CI, confidence interval; SE, standard error; IV, inverse of the variance.



**FIGURE 5** | Subgroup analysis based on the follow-up time regarding the risk of fractures of DOACs vs. VKAs in AF patients. AF, atrial fibrillation; DOACs, direct oral anticoagulants; DA, dabigatran; RIV, rivaroxaban; API, apixaban; CI, confidence interval; SE, standard error; IV, inverse of the variance.

the association of DOAC with another DOAC in the risk of fracture.

The incidence of fracture position is an important factor that should be taken into consideration. Loss of bone quality due to aging and high incidence of osteoporotic fractures (especially hip and vertebral fractures) are the major threats to the elderly, causing significant morbidity, mortality, as well as high socioeconomic burdens (32, 33). AF itself is a risk factor for osteoporotic fractures. Overlapped risk factors such as older age, diabetes mellitus, and stroke are often shared by AF and osteoporotic fractures in patients, and they are also the risk factors for stroke (18). Thus, AF patients who take anticoagulants should be considered to be vulnerable to fractures. Our data suggested that DOACs usage is associated with a reduced incidence of overall fracture events. In addition, the benefits were also confirmed after patients were classified by the types of hip/pelvic fracture and the osteoporosis fracture rates, consistent with the results of the previous studies (24, 27).

## Limitations

We acknowledged that there are some limitations of this study. First, although we only included studies with the propensity score-matched or adjusted RRs, the quality of our meta-analysis was inherently limited because the potential unmeasured residual confounders would still exist due to the nature of real-world data. The high heterogeneity in this study might affect the reliability of findings, and further prospective studies should confirm our results. Second, only one study (23) provided the time within the therapeutic range value of warfarin users, which would underestimate the efficacy of warfarin. Third, the evaluation was limited to the AF patients treated with anticoagulants

due to the limited data regarding patients with deep vein thrombosis or pulmonary vein thrombosis. Fourth, the age-related classifications of participants were also should be analyzed in this item's identification in further studies. Finally, due to the limited data of comparisons between DOAC vs. DOAC, we could not provide a choice of prescribing the most populated DOACs to AF patients especially those who are at a high risk of fractures.

## CONCLUSION

Our meta-analysis suggested that the use of DOACs was associated with a reduced risk of any fracture compared with VKAs. Further prospective studies should confirm these findings.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fcvm.2021.713187/full#supplementary-material>

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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