

SYSTEMATIC REVIEW

Fracture risks in patients with atrial fibrillation treated with different oral anticoagulants: a meta-analysis and systematic review

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Abstract

Aims: evidence on the difference in fracture risks for patients with atrial fibrillation (AF) receiving direct oral anticoagulants (DOACs) versus warfarin remains controversial. We aim to compare the fracture risks between the DOAC and warfarin prescriptions among the AF patients.

Methods and Results: we systematically searched PubMed, EMBASE, the Cochrane Library and Web of Science up to 19 April 2021 for relevant studies. And the observational studies regarding the relationship between the DOAC versus warfarin prescriptions and fracture risks among the patients with AF were included in this meta-analysis. Two investigators independently screened the articles and extracted the relevant data. A random- or fixed-effect model was applied to calculate the pooled hazard ratio/relative ratios with 95% confidence intervals of fracture risks associated with the DOAC and warfarin prescriptions. Six studies comprising 351,208 patients and 9,424 fractures were included in this meta-analysis. Overall, the AF patients treated with DOACs tend to present a lower risk of any fracture compared with those treated with warfarin (relative ratio: 0.82, 95% confidence interval (CI): 0.74–0.91). Sub-analyses for each individual DOAC indicate that apixaban and rivaroxan are associated with lower risk of any fracture compared with warfarin (HR: 0.75, 95% CI: 0.60–0.92, and HR: 0.79, 95% CI: 0.71–0.88, respectively).

Conclusion: this meta-analysis suggests that DOAC users have a lower risk of fractures than the warfarin users. The results of this study may provide optimal anticoagulation opportunities for AF patients with high fracture risk factors.

Keywords: fracture, direct oral anticoagulant, warfarin, atrial fibrillation, meta-analysis, older people

Key Points

- Overall, patients with AF who treated with direct oral anticoagulants (DOACs) tended to be at lower risk of any fracture compared with warfarin.
 - For each DOAC, apixaban and rivaroxan initiation were associated with lower risk of any fracture compared with warfarin.
 - DOAC users showed a decreased risk of hip and vertebral fractures than warfarin users.
 - There was no statistically significant difference in the upper extremity fracture risks between the DOAC and the warfarin use.
 - Subgroup analyses indicated that DOAC had a lower risk of any fracture than warfarin in the female patients.
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Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia among older people. Vitamin K antagonists (VKAs) or non-vitamin-K-dependent direct oral anticoagulants (DOACs) are used for the prevention of stroke complications in patients with AF [1]. VKAs, including warfarin, have been a conventional and traditional treatment for thromboprophylaxis in patients with AF for decades. However, several studies reported that long-term warfarin treatment reduced bone mineral density (BMD) and increased the risks of osteoporotic fractures in patients with AF [2–4]. Furthermore, patients who are prescribed VKA should adhere to several dietary restrictions, which may also lead to a reduction in BMD. Large-scale population studies reported that the use of oral anticoagulants is associated with an increased risk of osteoporosis and consequent fractures compared with non-use [5, 6]. Osteoporotic fractures are associated with low quality of life, high risk of morbidity and mortality, and considerable burdens of health care cost [7–9] in older people. More recently, the approval of DOACs including dabigatran, apixaban and rivaroxaban has emerged as alternatives to warfarin. Dabigatran is a thrombin inhibitor. Apixaban and rivaroxaban are factor Xa inhibitors. DOACs are as efficacious as warfarin in preventing stroke for patients with AF and require less international normalised ratio monitoring [10–13]. Additionally, DOAC initiators are associated with lower risk of osteoporosis compared with warfarin initiators [14]. However, evidence on the difference in fracture risks for AF patients prescribed DOACs or warfarin is still limited and controversial. Recently, one meta-analysis including three current observational studies shows that DOAC use is associated with a lower risk of hip fractures compared with warfarin use [15]. Another meta-analysis including 12 randomised controlled trials (RCTs) also demonstrates a relatively lower risk of fractures in DOAC users compared with that in warfarin users, although the study population included not only patients with AF but also those with venous thromboembolism (VTE) and pulmonary embolism (PE) [16].

Therefore, we perform this comprehensive systematic review and meta-analysis via high-quality observational studies to determine the impact of DOACs and warfarin on the risk of fractures for AF patients, including hip and vertebral fractures. This study indicates that DOACs may provide preferable alternatives to warfarin for AF patients with high risk of fracture.

Methods and materials

This study conforms to the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement [17].

Search strategy and selection criteria

Two independent reviewers (Xie and Liu) systematically searched PubMed, EMBASE, the Cochrane Library and

Web of Science databases for relevant studies until 19 April 2021 on the observational studies of the fracture risk of AF patients treated with DOACs or warfarin. The search terms include ‘non-vitamin K antagonist’, ‘direct oral anticoagulant’, ‘DOAC’, ‘apixaban’, ‘dabigatran’, ‘rivaroxaban’, ‘edoxaban’, ‘warfarin’, ‘vitamin K antagonist’, ‘VKA’, ‘AF’ and ‘fracture’. Our detailed search strategies are provided in [Supplementary Table S1](#). Two investigators (Xie and Liu) independently conducted literature screening by their titles and abstracts. When the information of the titles and abstracts was not enough, we reviewed the full text to complete the assessment before deciding to include or exclude the studies. The reference list of the included studies and existing reviews on the topic was screened to identify additional eligible studies. Any disagreement in the study selection process was resolved by a full discussion, and a third reviewer (Li) was consulted if a consensus could not be reached.

We included the studies according to the following inclusive criteria: (i) the study population was limited to patients who were newly diagnosed with AF and prescribed DOACs or warfarin for the first time; (ii) the studies presented outcome measurements of any fracture in patients with AF using DOACs and/or warfarin, regardless of whether the outcome was regarded as primary/secondary/tertiary; (iii) the studies reported the hazard ratio/relative ratios (HR/RRs) with corresponding 95% confidence intervals (CIs) of any fracture between DOAC and warfarin users and (iv) only observational studies were eligible. The primary outcomes are the incidence of any fracture in patients who were prescribed DOACs or warfarin. The secondary outcomes are the incidence of fractures at different sites/situations, including (i) hip fractures, (ii) vertebral fractures, (iii) upper extremity fractures (humerus/forearm/wrist fractures), (iv) hip and pelvic fractures; (v) major osteoporotic fracture and (vi) any fracture requiring hospitalisation. Major osteoporotic fracture was defined as a composite of hip, vertebral, forearm and proximal humerus fractures. Any fracture was defined with not only major osteoporotic fracture but also the femur, patella, tibia, fibula, ribs, pelvis, clavicle and scapula fractures [18].

We excluded the studies by the following exclusive criteria: (i) the studies only provided unadjusted HR/RRs of fractures for DOAC and/or warfarin users because observational studies should consider the potential confounders (gender and age, at minimum); (ii) the studies were duplicate articles and non-original research (letters, commentaries, editorials, reviews and meta-analyses) and (iii) the studies were case reports or animal experiments.

Data extraction and quality assessment

A pre-designed extraction form was used to extract the data. The extracted data included name of the first author, publication date, regions, study size, data resources, study design, study population, study exposures/comparisons, site of fractures, the evaluation method of fractures and the measure of

outcomes (adjusted HR/RRs with 95% CIs). Disagreements in data extraction were resolved by discussions among the two investigators (Xie and Liu), and a third reviewer (Li) was consulted if necessary. Subsequently, the two investigators independently evaluated the quality of the included articles according to the score of the Newcastle-Ottawa Scale (NOS) [19]. For cohort studies, the evaluation criteria include three aspects: selection, comparability and outcome assessment. A total score of at least eight points indicates high quality.

Data analysis

Our primary outcomes are risks of any fracture in patients with AF receiving the prescriptions of DOACs or warfarin. The adjusted HR/RRs with 95% CIs were used to examine the outcomes and calculate the pooled results. $P < 0.05$ indicates statistically significant. The between-study heterogeneity was assessed by employing the Q -statistic test. $P < 0.10$ for the Q -statistic indicates statistically significance [20]. The degree of inconsistency was evaluated using the I^2 index. $I^2 < 25\%$ is regarded as low degree of heterogeneity, and $I^2 \geq 75\%$ is considered as high heterogeneity [20]. A random- or fixed-effect model was used to pool the results according to the between-study heterogeneity. Subgroup analyses were performed based on patient characteristics, such as sex, age and history of osteoporosis. Sensitivity analyses were performed by removing each included study to examine the robustness of the results, and the publication bias was evaluated by Funnel plots, Begg's test and Egger's test. In case of a significant publication bias, we have adjusted it by using the 'trim and fill' algorithm to assess the fracture risk [21]. The statistical significance was defined as $P < 0.05$ in two-sided tests. The examination standard was defined as 0.017 ($0.05/3 = 0.017$) for each DOAC versus warfarin based on the Bonferroni method, where '3' refers to three comparisons: apixaban versus warfarin, dabigatran versus warfarin and rivaroxaban versus warfarin. Except that the 'trim and fill' algorithm was performed using the meta package of the R statistical software (version 4.0.3), all the other analyses were conducted with the STATA software (version 12.0).

Results

Literature search

There were 577 articles initially identified after database searching. Of which, 143 articles were removed due to duplication and 377 removed after screening their titles and abstracts. The remaining 58 articles were further screened for eligibility by reviewing their full text, and eventually, six articles that fulfilled the inclusion criteria were selected after examining the full text (Figure 1).

Characteristics of the included studies

The six included studies [18, 22–26] in this meta-analysis were published between 2017 and 2020; they involved

participants from Northern America (three studies), Asia (two studies) and Europe (one study) and included a total of 351,208 patients with AF receiving the first prescription of DOACs or warfarin. The study characteristics are summarised in Table 1. These patients had undergone at least 90 days of anticoagulant treatment. Among the 351,208 participants, 9,424 developed fractures, of which 4,470 (2.5%) were DOAC users and 4,954 (2.8%) were warfarin users (Supplementary Table S2). In addition, the study period for each included study was ranging from 3 to 9 years. Fractures were considered the main outcome in all included studies, except for one [22] in which the fractures were regarded as the control outcome. All included studies adopted a retrospective cohort design. Additionally, all included studies used adjusted HR/RRs with 95% CIs to examine the outcomes. The population characteristics of the six included studies are shown in Supplementary Table S3. The mean age of the included participants ranges from 67 to 75 years old. The study populations of all the included studies were adjusted for confounding variables. The NOS scores ranging from eight to nine for the six included studies are interpreted as high quality (Supplementary Table S4).

Primary outcomes

For the six studies [18, 22–26] included in this data analysis, the results of meta-analysis showed the AF patients treated with DOACs were associated with a lower risk of any fracture when compared with those treated with warfarin (pooled RR: 0.82, 95% CI: 0.74–0.91, $P < 0.001$, I^2 : 72.1%) (Figure 2). Four studies reported fracture risks in patients with AF receiving individual DOACs versus warfarin [apixaban ($n = 3$ studies) [23–25], dabigatran ($n = 3$ studies) [23–25] and rivaroxaban ($n = 4$ studies) [22–25]]. Sub-analyses for each DOAC reveal that new users of apixaban and rivaroxaban tended to be at lower risk of any fracture compared with new users of warfarin (pooled HR: 0.75, 95% CI: 0.60–0.92, $P = 0.007$, I^2 : 54.5% and pooled RR: 0.79, 95% CI: 0.71–0.88, $P < 0.001$, I^2 : 55.2%, respectively). When comparing dabigatran with warfarin, there was some evidence of lower risk of any fracture (pooled HR: 0.87, 95% CI: 0.74–1.01, $P = 0.06$, I^2 : 74.6%), although the estimate was not statistically significant (Figure 3). All above results were pooled using the random-effect model because of $I^2 > 50\%$. Additionally, three studies [22–24] reported fracture risks between each individual DOAC, and the combined results show no significant difference in fracture risks between each individual DOAC (Supplementary Table S5).

Secondary outcomes

Hip fractures

Four of the included studies [18, 23, 25, 26] investigated the risk of hip fractures between DOAC and warfarin use in the AF patients. The combined result suggests that the DOAC users show a decreased risk of hip fractures than the warfarin users (pooled HR: 0.87, 95% CI: 0.79–0.97, $P = 0.01$,

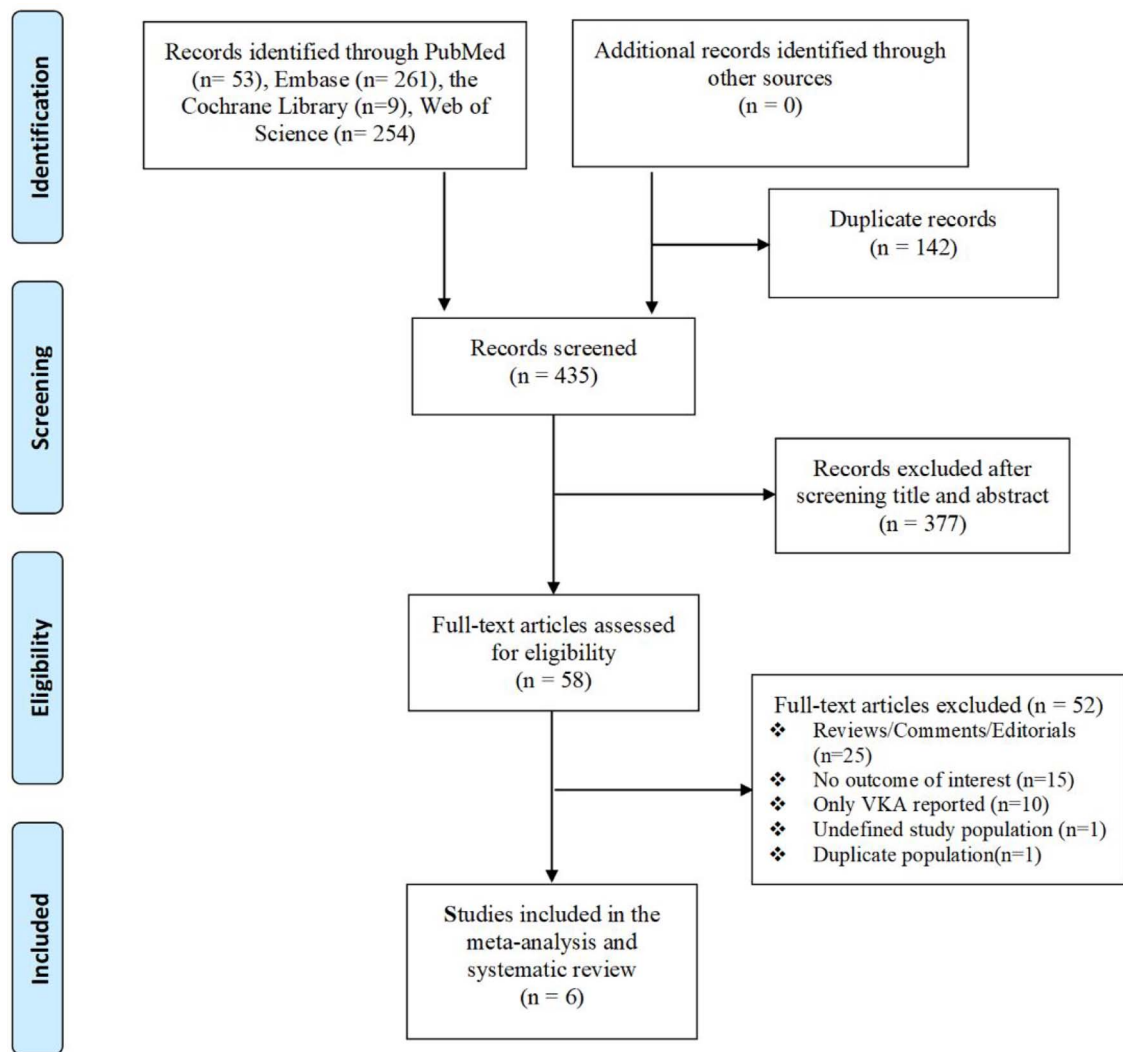


Figure 1. Flowchart of study selection in this systematic review and meta-analysis.

I^2 : 36.8%) (Supplementary Figure S1). Sub-analyses for each DOAC reveal that apixaban tended to present a lower risk of hip fractures compared with warfarin (pooled HR: 0.62, 95% CI: 0.45–0.86, $P = 0.004$, I^2 : 0.0%). However, compared with the warfarin, dabigatran and rivaroxaban are not associated with a lower risk of hip fracture (Table 2). A fixed-effect model was used to pool the above results due to the low heterogeneity ($I^2 < 50\%$ and $P > 0.10$).

Vertebral fractures

Two of the selected studies [25, 26] reported the vertebral fracture risks among the DOAC and the warfarin initiators. The pooled result suggests that the DOAC initiators have a reduced risk of vertebral fractures compared with the warfarin initiators (pooled HR: 0.75, 95% CI: 0.65–0.86, $P < 0.001$, I^2 : 0.0%). The results were pooled using a fixed-effect model because of the low heterogeneity ($I^2 < 50\%$ and $P > 0.05$). Moreover, Huang *et al.* [25] found a significant association between individual DOACs and a lower risk of vertebral fractures when compared with warfarin (Table 2).

Upper extremity fractures: humerus/forearm/wrist fractures

Two selected studies [25, 26] compared the risk of upper extremity fractures among the DOAC and the warfarin users. The results were pooled using a fixed-effect model ($I^2 > 50\%$ and $P > 0.10$). There is no statistically significant difference in the upper extremity fracture risks between the DOAC and the warfarin use. Huang *et al.* [25] showed a lower risk of humerus/forearm/wrist fractures in the rivaroxaban users compared with that of the warfarin users, but no significant difference in the humerus/forearm/wrist fracture risks was found for the apixaban and dabigatran users (Table 2).

The 2-year absolute standardised risk

The 2-year absolute standardised risk of any fracture was 3.09% (95% CI: 2.85–3.33%) for the DOAC users and 3.77% (95% CI: 3.37–4.19%) for the warfarin users [18]. The absolute risk of the DOAC users is 0.68% lower than that of the warfarin users. For each DOAC [24], the 2-year absolute standardised risk of any fracture is higher with the

Fracture risks in patients with AF treated with different oral anticoagulants

Table 1. Basic characteristics of included studies

Author (Year)	Regions	Sample size	Source of data	Study design (S)	Study population (P)	Exposure/Comparison (I/C)	Outcome (O)	Measures	Method to ascertain fractures
Norby <i>et al.</i> (2017) [22]	America	150,679	MarketScan databases	Retrospective cohort study	Non-valvular AF	(1) Rivaroxaban versus warfarin (2) Rivaroxaban versus dabigatran (first-prescription)	Hip/pelvic fracture (control outcomes)	aHR	ICD-9-CM codes
Binding <i>et al.</i> (2019) [18]	Denmark	37,350	The Danish National Patient Register	Retrospective cohort study	Non-valvular AF	DOAC versus VKA (first-prescription)	(1) Hip fracture (2) major osteoporotic fracture (3) any fracture (4) initiation of osteoporosis medication (5) a combined endpoint.	aHR	ICD-10
Lutsey <i>et al.</i> (2019) [23]	America	167,275 after matching*	MarketScan databases	Retrospective cohort study	Non-valvular AF	DOACs (dabigatran, rivaroxaban, apixaban) versus warfarin (first-prescription)	(1) Hip fracture (2) fracture requiring hospitalisation (3) all clinical fractures	aHR	ICD-9-CM codes
Lau <i>et al.</i> (2020) [24]	Hong Kong	23,515 after matching	The Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority	Retrospective cohort study	Non-valvular AF	DOACs (dabigatran, rivaroxaban, apixaban) versus warfarin (first-prescription)	A composite of hip and vertebral fractures	aHR	ICD-9-CM codes
Huang <i>et al.</i> (2020) [25]	Tai Wan	19,414 after matching	Taiwan's National Health Insurance Research Database (NHIRD)	Retrospective cohort study	AF	DOACs (dabigatran, rivaroxaban, apixaban) versus warfarin (first-prescription)	(1) Hip fractures (2) vertebral fractures (3) humerus/forearm/wrist fractures	aHR	ICD-9-CM codes
He <i>et al.</i> (2020) [26]	Canada	25,663 after matching	Healthcare databases from the Canadian province of Québec: RAMQ, MED-ECHO and ISQ	Retrospective cohort study	Non-valvular AF	DOAC versus VKA (first-prescription)	(1) A diagnosis of fracture (admission or primary diagnosis) (2) a composite of hip fracture (3) vertebral fracture (4) upper extremity fracture (humerus, forearm, or wrist fracture) (5) osteoporosis with pathologic fracture	aHR	ICD-10 codes

*The sample size is derived from matching method. **Abbreviations:** ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10, International Classification of Diseases, Tenth Revision; aHR, adjusted hazard ratio.

use of warfarin than that with the use of apixaban, dabigatran and/or rivaroxaban (0.88% [95% CI: 0.21–1.66%], 0.81% [95% CI: 0.23–1.34%] and 1.13% [95% CI: 0.53–1.67%], respectively) (Supplementary Table S6).

Subgroup analyses

Subgroup analyses were conducted for gender and age groups. Four of the selected studies [18, 23, 25, 26] show fracture risks between the DOACs use and the warfarin use

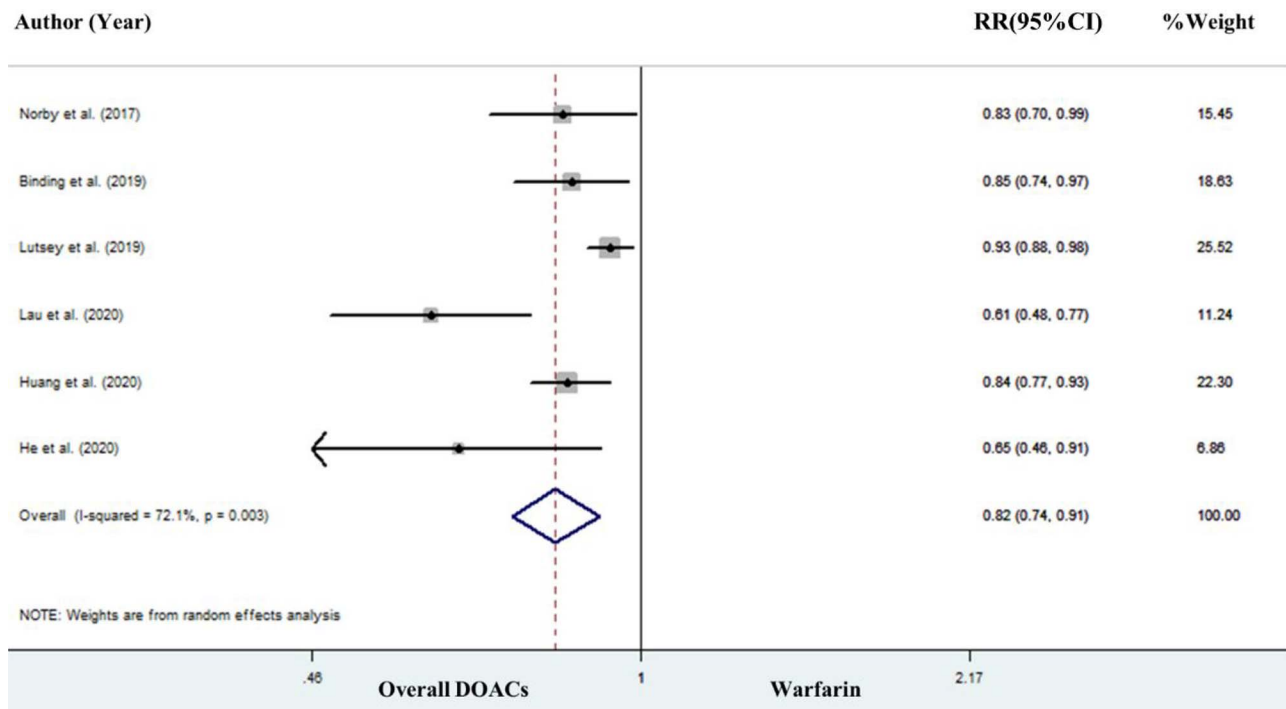


Figure 2. Risk of any fracture with overall DOACs versus warfarin.

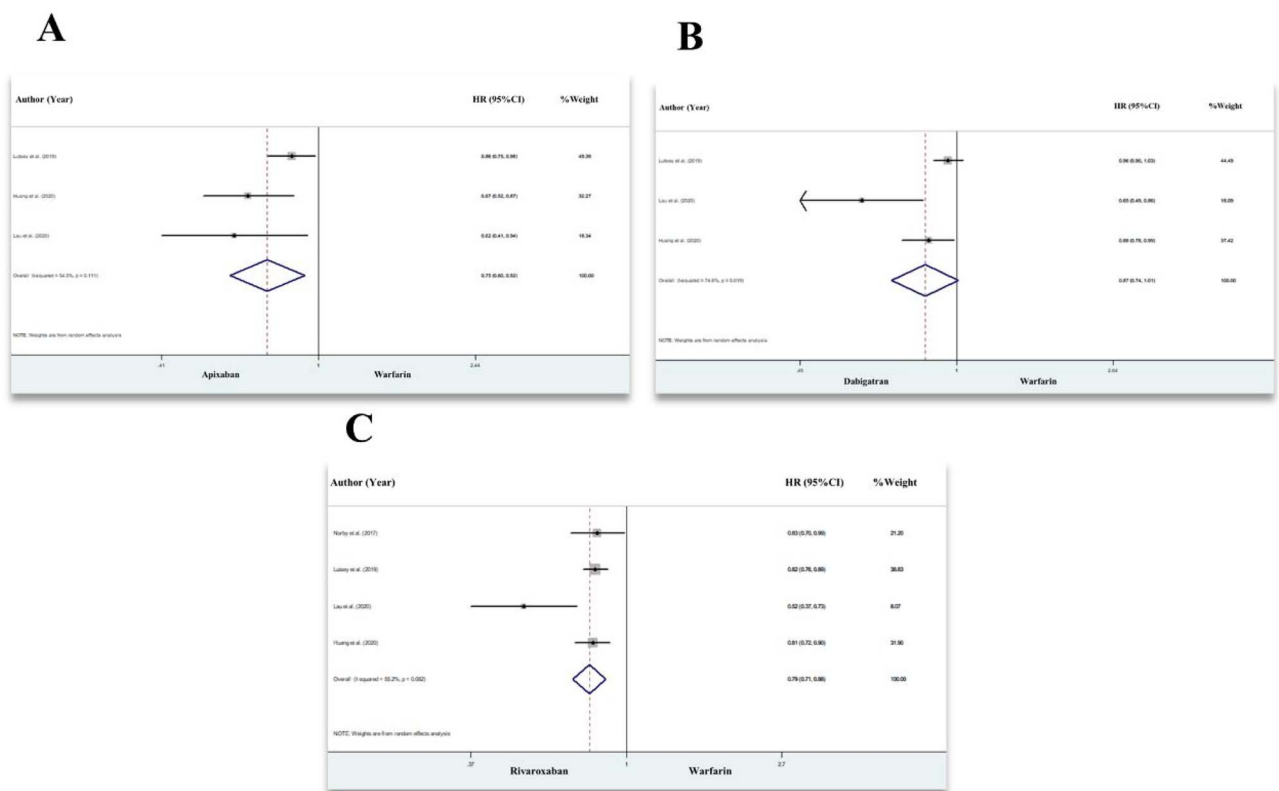


Figure 3. Risk of any fracture with individual DOACs versus warfarin. (A) Apixaban versus warfarin, (B) dabigatran versus warfarin and (C) rivaroxaban versus warfarin.

for the sex group. The combined results suggest that the DOAC-treated patients with AF have a lower risk of any fracture compared with the warfarin-treated patients among

the female group (pooled HR: 0.87, 95% CI: 0.83–0.93, I^2 : 13.0%). But there is no significant difference in the risk of any fracture between the DOACs use and the warfarin

Table 2. Primary and secondary outcomes for overall and individual DOACs versus warfarin

Outcomes	No. of studies	HR/RR(95%CI)	P-value	Heterogeneity		
				χ^2	P-value	I^2 index
Any fracture						
DOACs	6 (18, 22–26)	0.82(0.74–0.91)	<0.001	17.94	0.003	72.1%
Apixaban	3 (23–25)	0.75(0.60–0.92)	0.007	4.40	0.111	54.5%
Dabigatran	3 (23–25)	0.87(0.74–1.01)	0.061	7.88	0.019	74.6%
Rivaroxaban	4 (22–25)	0.79(0.71–0.88)	0.000	6.69	0.082	55.2%
Hip fractures						
DOACs	4 (18, 23, 25, 26)	0.87(0.79–0.97)	0.010	4.75	0.191	36.8%
Apixaban	2 (23, 25)	0.62(0.45–0.86)	0.004	0.44	0.506	0.0%
Dabigatran	2 (23, 25)	0.99(0.85–1.15)	0.883	0.02	0.898	0.0%
Rivaroxaban	2 (23, 25)	0.89(0.76–1.05)	0.156	0.00	1.000	0.0%
Vertebral fractures						
DOACs	2 (25, 26)	0.75(0.65–0.86)	<0.001	0.19	0.661	0.0%
Apixaban	1 (25)	0.60(0.41–0.88)	0.009	–	–	–
Dabigatran	1 (25)	0.81(0.68–0.95)	0.011	–	–	–
Rivaroxaban	1 (25)	0.73(0.62–0.85)	<0.001	–	–	–
Upper extremity fractures (humerus/forearm/wrist fractures)						
DOACs	2 (25, 26)	0.91(0.76–1.10)	0.313	1.75	0.186	42.8%
Apixaban	1 (25)	1.04(0.63–1.74)	0.869	–	–	–
Dabigatran	1 (25)	0.96(0.76–1.20)	0.694	–	–	–
Rivaroxaban	1 (25)	0.78(0.62–0.98)	0.030	–	–	–

Abbreviations: HR, hazard ratio; RR, relative ratio; CI, confident interval.

use among the male group. In addition, compared with the warfarin use, no statistically significant association between the DOAC use and the lower fracture risks is observed in patients of <75 and ≥75 years old. Our sub-analyses demonstrate that DOACs are associated with lower risks of fractures compared with warfarin in the AF patients with a history of osteoporosis, but not in those without a history of osteoporosis (Supplementary Table S7).

Sensitivity analyses

Sensitivity analyses were conducted to examine the stability of the results. After removing each individual study at a time, the fracture risks in the DOAC users compared with the warfarin users generally keep constant and stable in this meta-analysis (Supplementary Table S8 and Supplementary Figure S2).

Publication bias

In this meta-analysis, the publication bias was not statistically significant based on Begg’s test ($P = 0.12$), but significant based on Egger’s test ($P = 0.01$). The funnel plot was shown in Supplementary Figure S3. After adjusted for the publication bias by means of the trim and filled analysis (Supplementary Figure S4), the adjusted results show that the DOAC use has a lower risk of fractures compared with the warfarin use (pooled RR: 0.89, 95% CI: 0.80–0.99, $P = 0.027$, I^2 : 76.3%). Thus, the adjusted pooled results keep stable after adding three ‘missing’ studies.

Discussion

This systematic review and meta-analysis based on the previous observational studies demonstrates that the DOAC use represents lower risk of any fracture in patients with AF compared with the warfarin use. These main pooled results are based on moderate heterogeneity (I^2 : 72.1%). Additionally, the sub-analyses for each individual DOAC reveal that new users of apixaban and rivaroxan tend to be at lower risk of any fracture compared with new users of warfarin. However, there is no statistically significant difference in the fracture risks between individual DOACs. It is worth mentioning that the DOAC use is associated with a lower risk of hip fracture when compared with the warfarin use with a low degree of heterogeneity (I^2 : 36.8%). This result is consistent with a recent meta-analysis including three observational studies conducted by Huang *et al.* [15]. The pooled results also suggest that the risk of vertebral fractures is lower among the DOAC users when compared with the warfarin users with minimal heterogeneity (I^2 : 0.0%).

Although the exact mechanisms are not well clarified, some evidence may explain why lower risk of fractures is found in the DOAC users rather than the warfarin ones. Warfarin as a vitamin K inhibitor can interfere with γ -carboxylation and antagonise vitamin-K-dependent processes. It not only suppresses proteins in the coagulation cascade but also reduces the γ -carboxylation form of bone proteins, including osteocalcin and periostin, leading to abnormal bone mineralisation and formation [27–30]. Previous study found that long-term warfarin treatments could weaken cortical bone quality hardness of rib and vertebra due to a decreased osteocalcin content in rat [31].

Besides, warfarin decreases the activity of osteoblasts and increases the activity of osteoclasts, leading to bone loss and a decrease in bone strength of rat femurs [32]. These are the reasons why warfarin treatments are deleterious to normal bone metabolism and increase the risk of fractures. Conversely, DOACs produce their anticoagulant effects through a vitamin-K-independent process, and therefore, theoretically, do not affect bone metabolism. Switching to rivaroxaban from warfarin in patients with AF increases the level of bone formation markers (osteopontin and bone alkaline phosphatase) compared with baseline [33]. Moreover, an experimental study demonstrated that the treatment of rivaroxaban does not decline fracture healing in rats with femur fractures but significantly increases the volume of bone tissue in the fracture zones [34]. However, an *in vitro* study using human osteoblastic cell line Saos2 indicated that the treatment of rivaroxaban inhibits the first stage of bone formation, though not in any later stages [35]. Although the detailed mechanism has not been elucidated yet, these results indicate that DOACs may have potential positive effects on bone health. Further studies are needed to evaluate the mechanism of how DOACs affect bone metabolism and fracture risks.

Another recent meta-analysis including 12 RCTs revealed a relatively lower fracture risk in the DOAC use compared with the warfarin use. However, the study population includes not only patients with AF but also patients with VTE and PE [16]. Recently, Huang *et al.* [15] performed a meta-analysis including three current observational studies and suggest that the DOAC use has a lower risk of hip fractures compared with the warfarin use, which is in line with our result indicating the association between the DOAC use, rather than the warfarin use, and the lower risk of hip fractures. However, it is worth noting that the prescription of whether DOACs or warfarin in older patients with AF should generally depend on the evaluation of the risk of ischemic stroke, hemorrhage, monitoring and affordability rather than the risk of osteoporotic fractures [36]. Furthermore, a comprehensive and integrated approach to AF management based on the 'Atrial fibrillation Better Care' (ABC) pathway has been recognised in recent years [37–39], and the choice of anticoagulation is not the only consideration. The ABC pathway refers to (A) 'Avoid stroke (with Anticoagulants)', (B) 'Better symptom management' and (C) 'Cardiovascular and Comorbidity management'. The recent meta-analysis demonstrated that compliance with such a holistic approach is associated with mitigating the risk of major adverse outcomes (all-cause death cardiovascular death, stroke and major bleeding) [40]. Therefore, the older patients with AF receiving warfarin or DOACs still need physical activities and dietary supplementation of vitamin D and calcium to prevent osteoporotic fractures [41, 42].

This study has several strengths. Firstly, we included the most recent relevant studies in this meta-analysis and compared the effects of DOACs and warfarin use on fracture risks based on our pooled results. In addition, we further analysed the fracture risks for individual DOACs and fractures at different sites. Secondly, this meta-analysis included

high-quality observational studies using the real-world data with large-scale patients included. Besides, the included studies have a longitudinal study period (ranging from three to nine years) for the development of fractures, and therefore, HR as a measure of outcomes is extracted from each included study to obtain the synthesised results.

However, this meta-analysis also has a few limitations. Firstly, although sophisticated analysis methods such as propensity score matching and incorporating multivariable Cox regression models were applied, unmeasured confounders could still remain due to the lack of granular data on clinical characteristics, such as BMD, serum calcium and vitamin D levels. Moreover, the included studies relied on health records, which were not extracted for the purpose of investigating fractures. On this occasion, the outcome assessment of fractures was only based on administrative diagnosis codes which contributed to potential misclassification bias. Secondly, this meta-analysis has significant publication bias according to Egger's test. This might be due to the small number of studies included in this meta-analysis because we have difficulties in obtaining other potential unpublished studies. But our primary pooled results have sustained stable through the trim and filled methods. Thirdly, the result of primary outcomes was pooled with a moderate degree of heterogeneity. Sub-analyses reveal that individual DOACs, gender and fracture site might be potential factors for the heterogeneity. Therefore, our study cannot fully establish the causality between the prescription of DOACs versus warfarin and the fracture risks, thus the finding here should be interpreted cautiously and further RCTs are needed to confirm this causality.

Conclusion

This meta-analysis based on the real-world evidence suggests that the DOAC use have a lower risk of fractures than the warfarin use for older patients with AF. For each individual DOAC, only apixaban and rivaroxaban uses are associated with a significantly lower risk of any fracture compared with the warfarin use. This study may provide optimal anticoagulation opportunities for AF patients with high fracture risk factors.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflict of Interest: None.

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