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Review Article

Comparative risk of osteoporotic fractures with direct oral anticoagulants versus vitamin K antagonists in atrial fibrillation patients: a systematic review

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Abstract: Atrial fibrillation (AF) is increasingly prevalent in the elderly population and is associated with an elevated risk of osteoporotic fractures. This systematic review aimed to compare the risk of osteoporotic fractures between direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs), particularly warfarin, in patients with AF and to conduct head-to-head comparisons among different DOACs. We systematically searched literature published between January 2020 and October 2024 across multiple scientific databases. The included studies focused on adult patients with AF taking anticoagulants with fracture outcomes. We extracted and synthesized data on the fracture risk across different anticoagulant types. Our analysis revealed that DOACs, particularly rivaroxaban and apixaban, were associated with a lower fracture risk in AF patients than VKAs. Among the DOACs, apixaban appeared to have the most favorable profile for reducing hip fracture risk. Multiple studies have confirmed that DOACs are associated with decreased vertebral fracture risk compared to warfarin, with risk reductions ranging from 18-32% depending on the specific DOAC. DOACs appear to offer a safer alternative to VKAs in terms of fracture risk in patients with atrial fibrillation. This protective effect may be attributed to their lack of interference with vitamin K-dependent bone metabolism. Although evidence suggests that apixaban and rivaroxaban may have superior bone-protective profiles among DOACs, further research is needed to establish definitive comparisons between individual DOACs and elucidate their protective mechanisms.

Keywords: Atrial fibrillation, direct oral anticoagulants, non-vitamin K antagonist oral anticoagulants, vitamin K antagonists, warfarin, fracture, osteoporosis

Introduction

Atrial fibrillation (AF) is increasingly prevalent among the elderly and poses a significant risk of osteoporotic fractures [1]. The average lifetime incidence of AF in the United States is anticipated to surpass 12 million by 2030, with an estimated 1 in 3 to 1 in 5 individuals developing the condition [2]. Anticoagulant therapy, alongside rhythm and rate control, is a fundamental component of non-valvular AF management as it serves to prevent stroke and cardioembolic complications [3].

The relationship between AF and osteoporotic fractures is complex and mediated by shared risk factors and anticoagulant therapy effects. AF predominantly affects elderly populations, where age-related bone density decline and comorbidities, such as peripheral artery disease, increase fracture susceptibility. Additionally, vitamin K antagonists (VKAs), historically used for stroke prevention in AF, may accelerate bone loss by inhibiting osteocalcin carboxylation, a protein critical for bone mineralization [4]. Although AF itself is not a direct cause of osteoporotic fractures, its management strategies and associated age-related vulnerabilities create a clinically significant association. Several direct oral anticoagulants (DOACs) have replaced VKAs for various reasons. These include the direct thrombin inhibitor (dabigatran) and the direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban).

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Due to their relative efficacy and simplicity of administration compared to VKAs in preventing thromboembolism and significant bleeding, DOACs are utilized more frequently [5].

Osteoporosis and osteoporotic fractures become more common as people become older, especially among the elderly with AF [6]. Vitamin K is not only a cofactor in the formation of bone but also a crucial component associated with thrombosis. Osteocalcin, the primary noncollagenous protein in bone, is absorbed through vitamin K-dependent gamma-carboxylation. VKAs reduce the amount of osteocalcin used in the bone, which, in turn, reduces bone hardness. Reduced bone mineral quality is correlated with elevated concentrations of undercarboxylated osteocalcin in circulation. Nevertheless, there is no evidence to suggest that using VKAs is associated with a reduction in bone mineral density; instead, agents may influence bone structure independently of bone density [7, 8].

Contradictory findings from different studies make it unclear whether VKAs increase the risk of bone fracture. An additional conundrum pertains to whether DOACs exhibit a lower risk of osteoporotic fracture than VKAs [9]. An Asian study discovered that VKA users had a greater risk of osteoporotic fractures than dabigatran users [10]. A recent systematic review, on the other hand, found no increased risk of fracture among VKA users compared to control groups or DOAC users. Furthermore, no particular variation in fracture risk was observed among various categories of DOAC consumers [11]. Nevertheless, these studies failed to document the fracture risk associated with various anatomical sites or to account for the impact of DOAC dosage on fracture risk.

Due to the frequent use of DOACs by the elderly, it is crucial to evaluate the relative safety profiles of this drug class, particularly regarding fractures. Although recent studies have compared the fracture risks of various oral anticoagulants, the optimal DOAC remains unknown. Therefore, we conducted this systematic review to directly compare DOACs and their concurrent use with warfarin in terms of fracture risk. Furthermore, we compared our findings with those of other recent reviews.

Materials and methods

Search strategy

We have conducted a literature review comparing the risk of osteoporotic fracture among patients with AF treated with different DOACs versus VKAs. The research was performed in compliance with the PRISMA criteria, Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and the Flow Diagram is shown in **Figure 1**. The research was conducted in the PubMed, MEDLINE, Scopus, Web of Science, DOAJ, Science Direct, and Google Scholar databases between January 2020 and October 2024. It used the Advanced Search Builder, and the keywords were searched in [Title OR Abstract]. We have filtered only research articles published in the English language and using the combination of keywords and medical subject heading (MeSH), adjusted for each database, including: '(Atrial fibrillation OR AF) AND (Anticoagulant OR Direct oral anticoagulants OR DOACs OR Non-vitamin K antagonist oral anticoagulants OR Novel oral anticoagulants OR NOACs OR Dabigatran OR Rivaroxaban OR Apixaban OR Edoxaban) AND (Vitamin K antagonists OR VKAs OR Warfarin) AND (Fracture OR Bone fracture OR Osteoporotic fracture OR Osteoporosis OR Bone mineral density)'.

Inclusion and exclusion criteria

As described below, the population, intervention, comparison, and outcome (PICO) format was used as a guideline for the inclusion criteria. (P): non-valvular AF patients; (I) and (C): DOACs vs. VKAs (especially warfarin); (O): fractures occurring in various anatomical locations are classified as follows: (a) hip and/or pelvic fractures; (b) vertebral fractures; (c) fractures of the upper extremities (humerus, forearm, and wrist); (d) major osteoporotic fractures; and (e) any fracture requiring hospitalization. All included studies were randomized controlled trials (RCTs) or observational studies that reported the baseline characteristics of patients. We also included review articles that compared DOACs with warfarin in patients with AF. Furthermore, we excluded case studies, animal studies, and articles in which complete texts were unavailable in English.

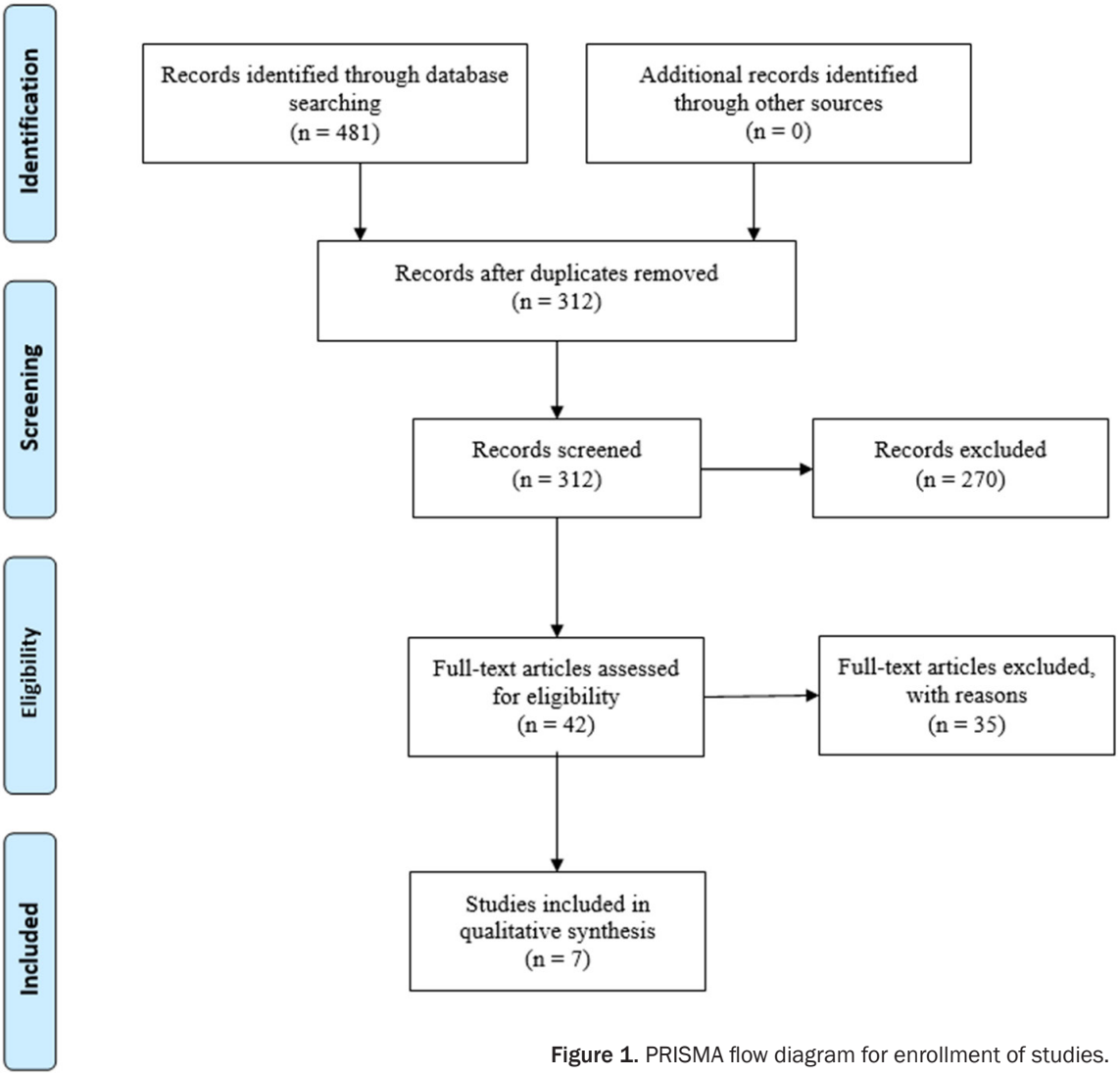

Figure 1. PRISMA flow diagram for enrollment of studies.

Data extraction and quality evaluation

The titles and abstracts were reviewed by A.M. After implementing the inclusion and exclusion criteria, data from the studies were extracted based on the survey requirements.

Relevant studies were included after scanning the references in previously published review articles. Seven eligible published research articles were obtained in their final versions. For some, we chose to include only the main findings that fit the purpose of this review (**Figure 1**).

Results

Study selection

Following our systematic search, 481 articles published between January 2020 and October 2024 were obtained. After removing duplicate articles (n = 169), the titles and abstracts of 312 studies were screened. Two hundred and seventy studies were excluded, and the 42 remaining studies were qualified to assess their full texts. Seven studies were included in the systematic review. **Figure 1** illustrates the study-selection process. The data extracted from the six eligible articles are summarized in **Table 1**.

Study characteristics and outcomes

In the present study, we evaluated 7 retrospective cohort studies with 165863 participants with a mean age of ≥ 70 (**Table 1**).

The included studies used various measures to evaluate the relationship between anticoagulant use (DOACs versus VKA/warfarin) and frac-

Table 1. Characteristics of the included articles in our study

Study	Year	Study type	Regions	Sample size	Study population	Age, year	Type of Anticoagulant	Fracture location	Mean of follow-up	Conclusion
Bezabhe et al.	2022	Retrospective study	Australia	18454	AF	73.2	DOACs (rivaroxaban, apixaban, or dabigatran) and warfarin	All osteoporotic fractures	841 days	DOACs were related to lower fracture risk in AF patients than warfarin.
Zhou et al.	2022	Retrospective study	Hong Kong	5014	Non-valvular AF	70	Edoxaban versus warfarin	Hip fracture	637.5 days	Edoxaban reduces hip fracture risks.
Kuo et al.	2021	Retrospective study	Taiwan	56795	Non-valvular AF	Mean of 75-76 in all groups	Rivaroxaban, dabigatran, apixaban	Osteoporotic, hip, or spine fracture	2 years	Different DOACs didn't affect AF patients' risk of osteoporotic fracture.
He et al.	2021	Retrospective study	Canada	25663	Non-valvular AF	Mean of 75-78 in all groups	Rivaroxaban, apixaban, or dabigatran	Upper extremity fracture (humerus, forearm, or wrist fracture), hip fracture, vertebral fracture, and osteoporosis with pathologic fracture	≥ 180 days and < 180 days	DOACs reduce fracture risk compared to VKAs.
Lau et al.	2020	Retrospective study	Hong Kong	23515	Non-valvular AF	74.4 ± 10.8	DOACs (rivaroxaban, dabigatran, apixaban) and warfarin	Hip and vertebral fractures	423 days	DOACs may reduce osteoporotic fracture risk in AF patients compared to warfarin.
Huang et al.	2020	Retrospective study	Taiwan	19414	Non-valvular AF	71	DOACs (rivaroxaban, apixaban, or dabigatran) and warfarin	Vertebral, hip, and humerus/forearm/wrist fractures	2.4 years	DOACs were related to lower fracture risk in AF patients than warfarin.
Huang et al.	2020	Retrospective study	Taiwan	17008	AF	~71	DOACs (rivaroxaban, apixaban, or dabigatran) and warfarin	Low-impact fractures of all upper and lower extremities	2.1 years	Patients with AF had a significantly lower risk of osteoporosis when taking rivaroxaban or apixaban compared to warfarin.

AF: Atrial fibrillation, DOACs: Direct oral anticoagulants, VKAs: Vitamin K antagonists.

ture risk. The primary outcome measure across these studies was the incidence of fractures, although this was examined with different levels of specificity. Most studies have assessed individual fracture types, such as hip, vertebral, spine, osteoporotic, and upper extremity fractures (including humerus, forearm, and wrist fractures). He et al. [12] specifically investigated osteoporosis with pathological fractures in conjunction with specific anatomical fracture sites. Zhou et al. [13] concentrated on hip fractures, while also considering the incidence of medically attended falls and all-cause mortality as additional outcomes.

In 2020, He et al. [12] conducted a retrospective cohort study to compare DOACs versus VKAs' effects on fracture risk in patients with non-valvular AF. There were 15357 new users of VKAs and 10306 new users of DOACs in the study population. In this trial, long-term use of DOACs (≥ 180 days) was related to a 35% lower incidence of fracture than long-term use of VKAs. Based on fracture type, using DOACs for 180 days or more was associated with a decreased rate of osteoporosis with pathologic fractures and hip fractures compared with VKAs. However, there were no significant differences between DOACs and VKAs in terms of the risk of vertebral fracture or upper extremity fracture. Also, shorter DOAC usage duration (less than 180 days) did not affect the fracture rate compared to VKA use.

In 2022, Zhou et al. [13] conducted a study on a Chinese population to compare the effects of edoxaban versus warfarin on the risk of hip fracture. A total of 5014 patients were enrolled, including 579 edoxaban users and 4435 warfarin users, with a mean follow-up of 637.5 days. This study showed that the edoxaban users had a significantly decreased incidence of medically attended falls, new-onset hip fractures, and all-cause deaths in the matched sample ($P < 0.001$).

In 2021, Kuo et al. [14] conducted a study to evaluate the risk of fracture in patients with non-valvular AF that used DOACs. A total of 56,795 patients were entered into this study. Dabigatran, rivaroxaban, and apixaban were administered to 24,597, 26,968, and 5,230 patients, respectively. After 2 years of follow-up, there was no statistically significant difference in the incidence of osteoporotic, hip, or spine fractures among individuals who received apixaban, rivaroxaban, or dabigatran. This study demonstrated that patients who received dabigatran had a higher incidence of hip and osteoporotic fractures than those receiving apixaban and rivaroxaban in cases with a history of hip fracture or concomitant peripheral artery disease (PAD). When compared with rivaroxaban and apixaban, users of dabigatran had a lower incidence of spine fracture and osteoporotic fracture in individuals receiving standard-dosage DOACs. On the other hand, users of dabigatran had a higher incidence of hip fractures when the drug was supplied at a low dose. However, this study has some limitations regarding osteoporosis diagnostic accuracy and loss of control over confounding factors.

In 2020, Lau et al. compared the risk for osteoporotic fracture between different anticoagulants. Among 23515 patients with AF, DOACs and warfarin were prescribed for 13974 and 9541 cases, respectively. Over a median follow-up of 423 days, 401 fractures were identified (apixaban: 53, dabigatran: 95, rivaroxaban: 57, and warfarin: 196). After 24-month follow-up, DOAC use was associated with a lower risk for fracture than warfarin use. Also, at the end of 24 months, no significant differences were observed in the comparisons between DOACs ($P > 0.001$). Finally, they concluded that DOAC use is associated with a lower risk of osteoporotic fracture compared to warfarin use. They also found no difference in fracture risk between different DOACs among patients with AF.

In 2020, Haung et al. [15] performed a head-to-head comparison of DOACs and also compared DOACs with warfarin usage on the fracture risk. Among 19414 patients with AF, 9707 cases were entered into the DOAC and warfarin groups. Sub-analyses revealed that each DOAC, namely dabigatran ($P = 0.027$), rivaroxaban ($P < 0.001$), and apixaban ($P = 0.003$), associated with a lower risk of vertebral fracture in AF patients compared to warfarin. However, the analyses for hip fracture revealed that only apixaban was significantly associated with a lower hip fracture risk ($P = 0.029$). With regard to humerus/forearm/wrist fractures, only rivaroxaban was significantly associated with a lower risk of these fractures ($P = 0.030$).

An additional investigation carried out by similar authors assessed the risk of osteoporosis

among individuals with AF who were administered DOACs or warfarin [16]. Out of 17008 patients who presented with AF, 8504 were classified as DOAC and warfarin-treated. In general, DOACs were associated with a reduced incidence of osteoporosis in comparison to warfarin. Additionally, the subgroups treated with rivaroxaban ($P < 0.001$) and apixaban ($P < 0.001$) exhibited considerably reduced risks of osteoporosis compared to the dabigatran subgroup ($P = 0.698$).

In 2022, Bezabhe et al. [17] evaluated the risk of osteoporotic fractures among AF patients who received DOACs versus warfarin. Out of 18454 patients with AF, 1714, 5871, 5248, and 5621 patients received dabigatran, rivaroxaban, apixaban, and warfarin, respectively. Overall, DOAC use was associated with a significantly lower risk of a new diagnosis of osteoporosis than warfarin use ($P < 0.001$). Also, the use of each DOAC was correlated with a significantly lower risk of osteoporosis compared with warfarin ($P < 0.001$ for rivaroxaban; $P < 0.001$ for apixaban; $P = 0.044$ for dabigatran). In a head-to-head comparison of DOACs, they found that osteoporosis was significantly lower in patients treated with rivaroxaban than dabigatran ($P < 0.01$). Nevertheless, no statistically significant differences were observed in the osteoporosis risk between patients who received apixaban and those who received dabigatran or rivaroxaban.

Discussion

The present study aimed to identify fracture risks among patients prescribed DOACs and warfarin. In this systematic review, DOACs, particularly rivaroxaban and apixaban, were associated with a lower fracture risk among patients with AF than VKAs. Although DOACs might be a safe alternative in decreasing fracture risks, the best choice among DOACs is not completely clear.

Our findings have important clinical implications for anticoagulant selection in patients with AF, especially those with an elevated fracture risk. The consistent pattern across multiple large observational studies strongly suggests that the choice of anticoagulants influences bone health outcomes. This protective effect is particularly relevant for elderly patients with AF who often have concurrent osteoporosis risk factors. Based on our analysis, we believe that clinicians should consider this bone-protective advantage when selecting anticoagulation for AF patients with elevated fracture risk, particularly favoring DOACs over VKAs.

Physiologically, the difference in fracture risk between DOACs and VKAs may be attributed to pharmacologic bone mineral density (BMD). Vitamin K is necessary for carboxylation of numerous proteins contributing to bone metabolism, such as matrix Gla protein and osteocalcin, while VKAs like warfarin can inhibit vitamin K. Osteocalcin, which is dependent on vitamin K, is essential for binding calcium to the bone. VKAs can diminish osteocalcin efficacy by blocking its carboxylation, which lowers BMD and reduces calcium binding, thereby increasing fracture risk. Moreover, by altering osteoblast and osteoclast activity, VKAs may upset the regular balance of bone remodeling. According to previous studies, using VKAs for an extended period can significantly alter the microarchitecture of the bone, which increases the risk of fractures, especially in the hip and vertebrae. However, DOACs do not interfere with vitamin K-dependent metabolism [8, 18, 19]. According to research, the effects of various DOACs on fracture risk may differ [7, 20]. Furthermore, a few studies indicate that DOACs might protect bone mineralization. However, the precise biological reasons behind this are still unclear [15, 21].

Fusaro et al. [22] found in an in-vivo study that rats receiving dabigatran had increased bone volume, lesser bone turnover, and reduced trabecular separation. Rivaroxaban may positively affect the healing of fractures, as demonstrated by large callus formation and increased bone mineral density in a femur fracture rat model. Edoxaban did not impact osteocalcin in rats even at a high dose of 54 mg/kg. In human studies, Nalevaiko et al. [23] evaluated the BMD and trabecular bone score (TBS) in three groups of participants. Out of the 150 cases, 50 patients were treated with DOACs, 50 were treated with warfarin, and the remaining 50 did not consume either DOACs or warfarin (control group). The mean TBS decreased progressively from the control group to the DOAC group and the warfarin group. No significant difference in BMD values was observed

between the DOAC and control groups. However, the DOAC group had higher BMD values in the hip compared to the warfarin group. In summary, this research demonstrated that individuals undergoing anticoagulant treatment exhibit reduced TBS and BMD values compared to the control group. Additionally, it sheds light on the possible detrimental impacts of anticoagulants on the skeletal system, emphasizing VKAs (such as warfarin) and DOACs. Although these results corroborate the protective effect of DOACs on bone health, their precise function in bone mineral metabolism remains unknown.

Recently, several meta-analyses compared the risk of fracture between DOACs and VKAs [9, 20, 24, 25]. All of these studies agreed on the higher risk of fracture following warfarin use compared to DOACs. However, their information must be more apparent when comparing DOAC versus DOAC. Therefore, they suggested conducting more studies in the future.

In 2022, Xie et al. [9] presented the results of their meta-analysis of six observational investigations evaluating fracture risks in patients with AF who have been treated with oral anticoagulation for at least 90 days. Patient inclusion was restricted to studies published from 2017 to 2020, focusing on individuals who had recently been diagnosed with AF and were using warfarin or a DOAC for the first time. A total of 9,424 fractures were documented in 351,208 patients, whose mean ages varied from 67 to 75 years, throughout a study period of 3 to 9 years. This meta-analysis found that AF patients treated with DOACs had a significantly lower risk of fractures compared to those treated with warfarin. The 2-year absolute standardized fracture risk was 0.68% lower for DOAC users. Apixaban and rivaroxaban were associated with significantly lower fracture risks than warfarin, but there was no significant difference between DOACs in head-to-head comparisons. When comparing DOACs to warfarin, fracture risk assessments at specific sites revealed that DOACs substantially reduced the risk of hip and vertebral fractures. However, individual analyses revealed that apixaban alone significantly reduced the incidence of hip fractures. The risk of fractures of the upper extremities was comparable across all oral anticoagulants. An intriguing discovery of this research was that DOAC use was associated with a reduced risk of fracture in specific high-risk populations, including females and patients with osteoporosis. Nevertheless, the adequacy of the sample sizes to attain statistical power for these results and the potential influence of menopause and hormone replacement therapy are aspects that remain obscure. This study was in line with the investigation by Tsai et al. [25] Also, a network meta-analysis demonstrated that the probability of osteoporotic fracture was highest with VKA and lowest with apixaban, followed by rivaroxaban, edoxaban, and dabigatran. However, fractures were statistically similar between apixaban and rivaroxaban. Due to the lack of understanding of some of the protective mechanisms of DOAC against fracture, they suggested future studies at cellular levels [20]. In another meta-analysis conducted by Wu et al. [24], they found that DOACs showed a decreased risk of overall fracture events compared with VKAs. Rivaroxaban and apixaban mainly showed reduced risks of fracture events. Although Lau et al. compared dabigatran and rivaroxaban regarding the osteoporotic fracture risk in AF patients, no significant difference was detected.

On the contrary, Huang et al. [15] concluded that rivaroxaban and apixaban exhibited the least fracture risk compared to warfarin. In line with this, an additional investigation concerning the risk of osteoporosis discovered that rivaroxaban and apixaban were linked to a reduced incidence of the disease compared to dabigatran. No statistically significant distinction in osteoporosis risk was observed between apixaban and rivaroxaban. Furthermore, there appeared to be a more pronounced correlation between the use of DOACs and a reduced occurrence of osteoporosis among patients whose treatment was prolonged beyond 180 days [16]. Therefore, further studies should confirm the association of DOAC with another DOAC in the risk of fracture.

The location of fracture occurrence is an important factor that needs careful attention. Elderly individuals are at a high risk of osteoporotic fractures, especially hip and vertebral fractures, which can lead to severe health issues, increased mortality rates, and economic burdens. As one age, the quality of bones tends to deteriorate, further increasing the risk of fractures. AF is linked to a higher incidence of

osteoporotic fractures. Diabetes mellitus, advanced age, and overlapping risk factors for stroke are some of the stroke risk factors that overlap with AF and osteoporotic fractures. Therefore, patients with AF who are being treated with anticoagulants should be considered prone to fractures [9, 20, 24, 25]. Based on our evaluation, the use of DOACs was associated with a reduced occurrence of overall fracture events.

Limitations

Our systematic review has several limitations. First, we inherit the methodological limitations of the primary studies analyzed, including potential confounding variables in predominantly observational studies. Second, heterogeneity existed across studies in their definitions of fracture outcomes, follow-up durations, and adjustment for confounding factors, which may have affected the comparability of the results. Third, most studies had relatively short follow-up periods (median < 2 years), which may have underestimated the long-term effects of anticoagulants on bone health. Finally, we could not fully account for the impact of concomitant medications that affect bone health, such as corticosteroids, anticonvulsants, and calcium/vitamin D supplementation.

Future directions

Future research should prioritize several critical areas to elucidate the relationship between anticoagulant use and fracture risk. Longitudinal prospective studies are essential to assess the cumulative effects of DOACs on bone health over extended periods. Furthermore, targeted randomized controlled trials comparing various DOACs with bone health endpoints would yield higher-quality evidence than the currently available observational data. The potential bone-protective mechanisms of specific DOACs, particularly apixaban and rivaroxaban, merit further exploration through basic scientific and translational research. Investigations into anticoagulant-related fracture risk across diverse patient subgroupsstratified by age, sex, prior fracture history, or concurrent osteoporosis treatmentswould facilitate the personalization of anticoagulation strategies. Lastly, cost-effectiveness analyses incorporating fracture risk reduction could further inform clinical decision-making in selecting the optimal anticoagulant therapy for patients with atrial fibrillation.

Conclusion

In conclusion, our systematic review found that DOACs are associated with a reduced risk of fractures in patients with AF compared to VKAs. According to all presently available DOACs, apixaban is associated with the lowest odds of fracture risk among most studies we reviewed. Among DOACs, dabigatran was associated with the most significant risk of fractures. In elderly patients with AF, the decision to prescribe anticoagulants should consider the risk of thrombotic and bleeding events, as well as osteoporotic fractures. This consideration and incorporation into contemporary cardiology practice is crucial. Our discoveries could prove valuable in personalizing the usage of anticoagulants in clinical practice. However, further comprehensive head-to-head prospective studies will be necessary to confirm these results.

Disclosure of conflict of interest

None.

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