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TITLE: Non-vitamin K Oral Anticoagulants and Risk of Fractures: A Systematic Review and Meta-Analysis

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What's New?

- The risk of fracture associated with the use of non-vitamin K antagonist oral anticoagulants (NOACs) and vitamin K antagonists (VKAs) in patients with atrial fibrillation (AF) remains unclear.

- We performed a meta-analysis assessing the risk of fracture with NOACs versus VKAs and between NOACs.

- Among 269,922 patients, NOAC use was associated with a lower risk of fracture compared to VKA use.

- No differences were observed in all head-to-head comparisons between NOACs.

- NOACs may be the preferred choice to VKAs in patients with AF who are at risk of fracture and require long term oral anticoagulant therapy.

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Abstract

Aims: Comparative fracture risk for non-vitamin K antagonist oral anticoagulants (NOACs) and vitamin K antagonists (VKAs) among patients with atrial fibrillation (AF) remains unclear. This study aimed to provide summary relative risk (RR) estimates for associations between NOACs versus VKAs and fracture risk.

Methods: PubMed, EMBASE, and Cochrane Library were searched from 2010 to 26th May 2020. Observational studies investigating the association between NOACs versus VKAs and fracture risk in patients with AF were included. The adjusted effect estimates were pooled using the DerSimonian–Laird random effects models. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiological (MOOSE) guidelines were followed.

Results: Five observational studies comprising 269,922 patients and 4,289 fractures were included. NOACs use was associated with a lower risk of any fractures compared to VKAs use, with moderate heterogeneity (pooled RR=0.83, 95% confidence interval [CI]: 0.75-0.92, p<0.001, I^2= 73.0%). When comparing individual NOAC to VKAs, a statistically significant lower risk of any fractures was found for rivaroxaban (pooled RR=0.79, 95% CI: 0.71-0.88, p <0.001, I^2= 55.2%) and apixaban (pooled RR=0.75, 95% CI: 0.60-0.92, p=0.007, I^2=54.5%), but not dabigatran (pooled RR=0.87, 95% CI: 0.74-1.01, p=0.061, I^2=74.6%). No differences were observed in all head-to-head comparisons between NOACs.

Conclusion: This large meta-analysis suggests that NOACs use was associated with a lower risk of fractures compared with VKAs. Fracture risks were similar between NOACs. These findings may help inform the optimal anticoagulant choice for patients with AF at high risk of fracture.

Keywords: atrial fibrillation, fractures, non-vitamin K antagonist oral anticoagulant, oral anticoagulant, osteoporotic fractures

INTRODUCTION

Atrial fibrillation (AF) is a common aged-related cardiac arrythmia associated with increased risk of cardioembolic stroke.[1,2] Disability and premature death due to stroke of AF can be mitigated through the use of vitamin K antagonists (VKAs), including warfarin, or non-vitamin K oral anticoagulants (NOACs). For decades, VKAs were the only anticoagulants available for stroke prevention in AF, until the approval of the NOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban since 2010. NOACs demonstrated at least non-inferiority compared to warfarin for the prevention of stroke or systemic embolism[3-6] and have been associated with lower risk of bleeding complications in both the landmark randomized controlled trials (RCTs),[3-6] and in post marketing observational studies.[7,8]

AF is a condition of ageing, and ageing is inherently linked to an increased risk of falls, therefore osteoporotic fracture is an important clinical concern in older people. Warfarin, through its effect on vitamin K, decreases osteocalcin content in bone.[9] Ultimately, links between warfarin use, low bone mineral density, and increased risk of osteoporotic fracture have been established.[10-12] NOACs are not known to impair bone quality, but uncertainty remains regarding the comparative risk of fracture with NOACs versus warfarin. Observational studies[13,14] and also a meta-analysis of adverse fracture events reported in RCTs[15] demonstrated lower fracture risk with NOAC treatment compared to warfarin. However, a meta-analysis of observational studies[16] has raised questions regarding fracture risk in patients using NOACs versus warfarin. This meta-analysis of four studies demonstrated no difference in fracture risk for NOACs versus warfarin. However, the meta-analysis has been criticised for inappropriate definition of the reference group and inconsistent use of adjusted and unadjusted data in the analyses.[17] Given the uncertainty of these findings, coupled with the availability of new data[14,18-20], the objective of this study was

to systematically investigate the osteoporotic fracture risk with NOACs versus VKAs in patients with AF, and to summarise the data using meta-analysis.

METHOD

This study was undertaken in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[21] and the Meta-analysis of Observational Studies in Epidemiological (MOOSE) guideline (Supplementary Table S1).[22]

Search strategy

We searched PubMed, EMBASE, and the Cochrane Library for relevant studies without language restrictions, from 2010 to 9th February 2020 and the search was updated up to 26th May 2020. We searched from 2010 onwards because the first NOAC (dabigatran) was approved for patients with non-valvular AF in 2010. Keywords, Emtree terms and truncated search terms related to anticoagulants and bone fracture outcomes were combined. Full details of search strategies are provided in Supplementary Table S2. The reference lists of the included studies, prior systematic reviews, and introduction and discussion sections of retrieved studies were also reviewed to identify additional relevant studies.

Study selection

Three investigators (PM, LF, and KW) screened titles and abstracts independently. Disagreement regarding study inclusions were resolved by discussion among investigators and if a consensus could not be reached, a third party (WL) was consulted.

Inclusion criteria

Studies were included if they (i) were observational studies; (ii) were conducted in patients with AF; (iii) evaluated the association between NOAC use and risk of any fractures compared with warfarin or VKAs; (iv) reported the outcomes as hazard ratio (HR), relative risk (RR), incidence rate ratio (IRR), or odds ratio (OR) with 95% confidence intervals (CI).

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Studies were excluded if they were cross-sectional studies, case series or case reports, letters, editorials, systematic review and meta-analyses, or review articles. We restricted only articles published in full-text based on quality of study and it had been peer reviewed. The primary outcome of interest was the incidence of any fractures among patients with AF treated with NOACs compared to those treated with warfarin or other VKAs. The secondary outcomes included i) hip fractures; ii) vertebral fractures; iii) hip or vertebral fractures; iv) hip or pelvic fractures; v) humerus/forearm/wrist fractures; vi) a composite of hip, vertebral, humerus, forearm, or wrist fractures, and vii) hospital admission due to any fractures. If necessary, the authors were contacted when primary outcome data was missing. If the authors did not respond, the study was excluded.

Data extraction and quality assessment

Information was extracted independently by two investigators (PM and LF) using a pre-designed data extraction form. Data extraction variables included study design, country of study, source of data, study period, duration of follow-up, study population, study sample characteristics (age and gender), NOAC use, site of fractures, and method used to ascertain fractures. For outcome data, the HR, RR, IRR or OR with 95% CI were extracted and included in the meta-analysis. Disagreements were resolved by discussion between the two investigators (PM and LF). Any discrepancies were resolved by a third reviewer (WL). Further, two investigators (PM and LF) independently appraised the risk of bias for the included observational studies using the Newcastle–Ottawa Scale (NOS).[23] Criteria included: selection of the exposed/unexposed cohort, comparability of the study group and the outcome assessment. Studies with a total score of 8 or more were defined as high quality.

Data synthesis

For primary analysis, the risk of any fractures for NOAC users as a group were compared with warfarin or other VKAs users. For studies that only reported results of individual NOACs comparing to a common VKA group, we pooled the results using the 'exact adjustment' method that corrects the standard errors between correlated multi-arm comparisons,[24, 25] before adding the data into the overall meta-analysis for NOAC users. The overall pooled estimates with 95% CI were pooled using DerSimonian–Laird random effects models.[26] Heterogeneity was assessed by using the Cochran Q test, with a cut-off of $P < 0.10$ for statistical significance.[27] The I^2 index was used to estimate the degree of inconsistency. The heterogeneity was indicated as low ($I^2 < 25\%$), moderate ($I^2 \geq 25\%$ but $<75\%$) or high ($I^2 \geq 75\%$).[27] Subgroup analyses were performed based on the individual NOACs and participant characteristics including age and sex. Furthermore, baseline study-level characteristics were included in a random effects univariate meta-regression to explore heterogeneity.

Sensitivity analyses were performed by (i) removing individual studies using a leave-one-out approach and (ii) including a post-hoc analysis from ENGAGE AF-TIMI 48 trial which compared the risk of fracture between edoxaban users and warfarin users.[28] Statistical significance was defined as a two-tailed P<0.05. All analyses were performed using STATA software version 14.0 (StataCorp, College Station, TX, USA).

RESULTS

Search strategy and study characteristics

There were 4,523 articles identified through database searching. Five hundred and ninety-six duplicate articles were removed and 3,917 articles were excluded after title and abstract screening. The remaining ten articles were eligible for full-text assessment, of which five articles[14,18-20,29] met the eligibility criteria and were included in the systematic review and meta-analysis (Figure 1). All included studies were retrospective observational studies with a

study duration ranging from 4.5 years[18] up to 9 years.[20] A total of 269,922 participants were involved, of which 137,184 (50.8%) were NOAC users. All of the five studies[14,18-20,29] used a new user design. Baseline characteristics of each study are summarized in Table 1.

According to the risk of bias by NOS, five studies[14,18-20,29] had summary scores ranging from 8 to 9 which represented as high quality (Supplementary Table S3).

Primary outcomes: risk of any fractures

Among 269,922 participants, 4,289 (1.59%) developed fractures, of which 2,035 were NOAC users (1.48%) and 2,254 were VKA users (1.70%) (Supplementary Table S4). NOAC use was associated with a significantly lower risk of any fracture compared with VKA use (pooled RR=0.83, 95% CI: 0.75-0.92, p<0.001, I^2= 73.0%) (Figure 2). There were four studies[14,19,20,29] investigating the risk of fractures among individual NOACs and VKA users [dabigatran (n=3 studies[14,19,20]), rivaroxaban (n=4 studies[14,19,20,29]), apixaban (n=3 studies[14,19,20])]. The results from meta-analyses showed that rivaroxaban and apixaban were associated with a lower risk of fractures when compared with VKAs, pooled RR=0.79, 95% CI: 0.71-0.88, p <0.001, I^2= 55.2% and pooled RR=0.75, 95% CI: 0.60-0.92, p=0.007, I^2= 54.5%, respectively. However, there were no statistically significant difference in fracture risk between dabigatran users and VKA users (pooled RR=0.87, 95% CI: 0.74-1.01, p=0.061, I^2=74.6%) (Figure 3). None of the included studies compared the risk of fracture between edoxaban and VKAs. Two studies[14,20] conducted head-to-head comparisons of the risk of fracture between each NOACs. The results showed that there was no significant difference between individual NOACs with regards to fractures (pooled RR= 1.01, 95% CI: 0.97-1.23, p=0.128, I^2=0.0% for dabigatran vs rivaroxaban; pooled RR=1.00, 95% CI: 0.88-1.15, p=0.941, I^2=0.0% for apixaban vs rivaroxaban, and pooled RR=1.03, 95% CI: 0.85-1.25, p=0.769, I^2=0.0% for apixaban vs dabigatran).

Secondary outcomes: risk of fractures at different sites

Hip fractures

There were three studies[14,18,19] comparing risk of hip fractures among NOAC users and VKA users. The results showed that NOAC use was associated with 11% lower risk of hip fractures with no significant heterogeneity among included studies (pooled RR=0.89, 95% CI: 0.80-0.99, p=0.036, I^2=0.0%). For individual NOACs, apixaban was associated with a lower risk of hip fracture compared to VKAs (pooled RR=0.62, 95% CI: 0.45-0.86, p=0.004, I^2=0.0%), but no significant difference in hip fracture risk was found for dabigatran and rivaroxaban.

Vertebral fractures

There was only one study investigating risk of vertebral fracture and the result showed a lower risk of vertebral fracture in NOAC users when compared to VKA users (HR=0.75, 95% CI: 0.65-0.86, p<0.001).[19]

Hip and vertebral fractures

One study compared a composite of hip and vertebral fractures between each NOAC and VKAs.[20] The results demonstrated that NOAC use was associated with a lower risk of hip and vertebral fractures compared to VKAs (Table 2).

Hip or pelvic fractures

One study reported results for a composite of hip and pelvic fractures between rivaroxaban and VKAs.[29] The results suggested an association of a lower fracture risk with rivaroxaban compared to VKAs (RR=0.83, 95% CI: 0.70-0.99).

Humerus/forearm/wrist fractures

Huang et al., (2020)[19] found a trend of lower fracture risk in patients using NOACs compared to those using VKAs on the risk of humerus/forearm/wrist fractures, but this did not reach statistical significance (HR=0.88, 95% CI: 0.73-1.06), p=0.190) (Table 2).

A composite of hip, vertebrae, or humerus, forearm, or wrist fractures

Compared with VKAs, NOACs were associated with a lower risk of a composite of hip, vertebrae, or humerus, forearm, or wrist fractures (HR=0.84, 95% CI: 0.77-0.93, p<0.001). Similar trends were observed for each NOAC, namely dabigatran (HR=0.88, 95% CI, 0.78-0.99), rivaroxaban (HR=0.81, 95% CI: 0.72-0.90), and apixaban (HR=0.67, 95% CI: 0.52-0.87).[19]

Hospital admission due to fractures

Patients treated with NOACs had a lower risk of hospital admission due to any fracture compared with patients treated with VKAs (pooled RR=0.87, 95% CI 0.80-0.94, p=0.001, I^2=0.0%).

Subgroup analysis based on participant characteristics

There were three studies[14,19,20] which provided information about the risk of any fracture between NOACs and VKAs across gender. Our meta-analysis demonstrated that the use of NOAC was associated with a lower risk of any fracture compared to VKAs among females (pooled RR=0.82, 95% CI: 0.72-0.95, p=0.006, I^2=67.3%) while no statistically significant association was observed among males (pooled RR=0.82, 95% CI: 0.65-1.02, p=0.077, I^2=80.8%). In addition, the risk of any fracture tended to be lower among NOAC users compared with VKA users in patients less than 75 years of age (pooled RR=0.94, 95% CI: 0.87-1.01, p=0.100, I^2=0.0%) and ≥ 75 years (pooled RR=0.89, 95%CI: 0.77-1.02, p=0.096, I^2=68.9%) but the results did not reach the statistical significance (Supplementary Table S5). Lutsey et al[14] investigated the risk of any fractures in patients with and without history of osteoporosis, the finding demonstrated that NOAC use was associated with lower risk of any fractures among patients with history of osteoporosis (HR=0.90, 95% CI: 0.83-0.98). For different NOAC doses, Lutsey et al[14] reported that the risk of any fracture for

rivaroxaban was lower for standard doses (HR=0.86, 95% CI, 0.76-0.98 for rivaroxaban 20 mg) and for reduced doses (HR=0.78, 95% CI, 0.72-0.86) when compared with warfarin.

Sensitivity analysis and meta-regression

After removing an individual study during the leave-one-out analysis, the risk of any fracture among NOAC users compared to VKA users appeared to be robust (Supplementary Table S6). In addition, when adding the post-hoc result from ENGAGE AF-TIMI-48 trial, the result was consistent with the primary analysis (Supplementary Figure S1). In the meta-regression, the heterogeneity of the included studies was not explained by any of the baseline study-level characteristics and risk of any fractures (Supplementary Table S7).

DISCUSSION

This systematic review and meta-analysis of real-world data demonstrated that in patients with AF, NOAC use was significantly associated with a 17% lower risk of fractures compared with VKA use. The results were based on a moderate degree of heterogeneity. For each NOAC, rivaroxaban and apixaban use was associated with a lower risk of any fractures compared to VKAs. Furthermore, the lower risk of any fractures associated with NOAC use was observed in female participants only. Given that NOACs were not anticipated to alter fracture risk, our findings support the hypothesis that patients treated with VKAs were at an increased risk of fracture. The results from this study were in line with a previous meta-analysis of the adverse reports in RCTs[23] demonstrating that NOACs were associated with a lower risk of fracture compared to warfarin.

A plausible mechanism by which NOAC use may result in a lower risk of fracture than VKA use is that the VKAs can interfere with the process that contributes to bone formation. VKAs such as warfarin can affect the carboxylation of vitamin K-dependent bone protein including osteocalcin, which plays an important role in bone mineralization.[9] An experimental rat model has suggested that warfarin usage decreased osteocalcin content and

impaired bone material hardness.[30] In addition, dietary restrictions of vitamin K-rich foods is common in VKA users, while there is no such need in NOAC users. The limited intake of vitamin K-containing vegetables could lead to a low consumption of folic acid, contributing to hyperhomocysteinemia. This condition is associated with an increase in osteoclast activity, thus reducing bone strength.[31] These may constitute reasons why we observed an increased risk of fracture in VKA users compared to NOAC users.

Our study also found a 21% and 25% lower risk of any fractures associated with rivaroxaban and apixaban, respectively, compared with VKAs. The results were supported by a previous animal study illustrating that rivaroxaban does not impair fracture healing in a rodent fracture model.[32] This may suggest a possible benefit of rivaroxaban on bone compared to VKAs, given that VKAs may have negative impacts on bone. In contrast, we did not find an association between dabigatran use and risk of fracture, although a previous study in rats demonstrated a superior bone safety profile of dabigatran when compared with warfarin.[33] However, the resulting RR was marginal (95% upper CI=1.01) and the possibility of the lack of statistical power cannot be ruled out. Nonetheless, this finding is in line with a previous retrospective cohort study showing a lower risk of osteoporosis in patients treated with rivaroxaban and apixaban, but not in those treated with dabigatran.[34]

This study has several strengths. First, the meta-analysis included observational studies which reflect real-world practices of anticoagulant use. In addition, the studies included in this meta-analysis had a long follow-up ranging from 4.5 to 9 years, which is reasonably long to observe the development of fracture. Second, a comprehensive search strategy without language restriction was performed to ensure that the included studies were representative of real-world patients with AF. Third, our study expanded on a previous systematic review[16] that examined the association between VKA use and fracture by including the most recent published studies[14,18,19] and is the first to meta-analyze risk of

fracture for individual NOACs, and fractures that occur at different skeletal sites. Fourth, the analyses were performed using rigorous statistical approaches, including exact adjustment method, meta-regression, and leave-one-out meta-analysis. Finally, our study adheres to the standard methodology of systematic review and meta-analysis as required by the Cochrane and PRISMA checklists.[21,35]

Our study has limitations that warrant mention. First, observational studies are prone to bias due to unmeasured confounders. Although the included studies used sophisticated analysis methods such as propensity score modelling[14,19,20,29] and machine-learning techniques,[20] unmeasured confounders could remain. Therefore, the causality of NOAC use vs VKA use with fracture risk cannot be fully established through this meta-analysis, thus the finding should be interpreted with some caution, and ultimately confirmed in RCTs. However, there have been no head-to-head trials conducted to provide the necessary evidence on the comparative fracture risks of NOACs. Second, the included studies were observational studies relying on routinely collected electronic health records that were not collected for the purpose of studying fracture, which might lead to misclassification bias in fracture outcomes. For example, information on bone mass density was not available for defining the fracture outcome in all the included studies. Finally, a moderate to high degree of heterogeneity might limit the findings. However, subgroup analyses undertaken found that an individual NOAC and gender might be potential factors contributing to heterogeneity.

CONCLUSION

This systematic review and meta-analysis of real-world evidence demonstrated that NOAC use was associated with a lower risk of fracture compared with VKA use in patients with AF. Among each NOAC, the association of a lower fracture risk compared to VKAs was demonstrated in rivaroxaban and apixaban only. No differences were found between individual NOACs. Further studies including RCTs are needed to confirm the comparative

risk of fractures for different NOACs and warfarin to inform the optimal anticoagulant choice for patients with AF who are also at high risk of fractures.

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Figure Titles and Legends

Figure 1. PRISMA flow chart

Figure 2. Risk of any fractures among NOAC users and VKA users

Abbreviations: NOACs=Non-vitamin K antagonist oral anticoagulants; VKAs=vitamin K antagonists; RR=relative risk; CI=confidence interval

Figure 3. Risk of any fractures among each NOACs vs VKAs; (A) Dabigatran and VKAs, (B) Apixaban and VKAs, (C) Rivaroxaban and VKAs

Abbreviations: NOACs=Non-vitamin K antagonist oral anticoagulants; VKAs=vitamin K antagonists; RR=relative risk; CI=confidence interval