Long-Term Care Updates

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Oral Anticoagulant-Associated Fracture Risk

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Introduction

As patients age the concern for the risk of falls and osteoporotic fractures increases. Fractures can not only negatively impact patients' overall health but can also impose a significant financial burden. Some studies have suggested an association between warfarin and increased fracture risk.[1] Prior to the approval of non-vitamin K antagonist oral anticoagulants (NOACs), warfarin was the traditional oral anticoagulant (OAC) selected for preventing thrombotic events in patients with atrial fibrillation (AF) or venous thromboembolism (VTE).[2] Since then, there have been many studies comparing the safety and efficacy of NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) to warfarin for thromboprophylaxis and bleeding risk, but few have compared NOACs and warfarin relative to fracture risk.[1]

In this newsletter, we will discuss the evidence evaluating and comparing the association between specific OACs and fracture risk.

Clinical Evidence

The first study investigating this relationship was a systematic review and meta-analysis comparing fracture risk in patients taking NOACs or warfarin. Researchers searched various electronic databases, ClinicalTrials.gov, and references of relevant studies for randomized control trials (RCTs) that reported fracture risk in association with the use of NOACs and warfarin. The primary outcome of study was a composite of any fracture events reported. A total of 12 RCTs met inclusion criteria, among which 5 were AF studies and 7 were VTE studies. A total of 89,549 patients were enrolled with 44,816 (50%) taking NOACs and 44,733 (50%) taking warfarin. Researchers found a total of 1,139 (1.3%) patients developed a fracture, of which 515 (1.1%) were on NOACs and 624 (1.4%) were on warfarin. Results were consistent amongst studies (I^2=15.0%; p=0.30), with NOACs significantly reducing fracture risk by 18% (RR 0.82; 95% CI 0.73-0.93; p=0.001) compared to warfarin, which translated to a number needed to treat (NNT) of 333. Subgroup analysis of each NOAC found that only rivaroxaban (RR 0.78; 95%CI 0.61-0.99, p=0.04) and apixaban (RR 0.70; 95%CI 0.55-0.90; p=0.01) had a statistically significant lower fracture risk compared to warfarin. AF patients had a statistically significant lower fracture risk with NOACS compared to warfarin (RR 0.82; 95%CI 0.73-0.93; p<0.01), while VTE patients did not (RR 0.82; 95%CI 0.61-1.11; p=0.20). Additionally, in patients on long-term anticoagulant therapy (>1 year), NOACs significantly reduced fracture risk compared to warfarin (RR 0.82; 95%CI 0.73-0.93; p<0.01), while the same result was not found in patients on short-term anticoagulant therapy (RR 0.87; 95%CI 0.64-1.19; p=0.38). Researchers concluded that NOACs had a lower risk of fracture compared to warfarin, with a very low absolute risk reduction, and NOACs may be a preferable alternative to warfarin in patients with high fracture risk.[2]

More recently, one retrospective cohort study involving real-world evidence also examined the relationship between OACs and fracture risk. Researchers focused on nonvalvular AF patients alone, and the same NOACs were studied except for edoxaban which was not on the market during the study window. International Business Machines (IBM) Corporation's MarketScan Commercial Claims and Encounters and MarketScan Medicare Supplemental and Coordination of Benefits databases were searched from January 1, 2010 through September 30, 2015. Patients with <3 months of continuous enrollment before the first OAC prescription or any fracture in the 90-day run-in period were excluded. The primary study outcomes were incidence of hip fractures, fractures requiring hospitalization, and all clinical fractures (inpatient and outpatient claims). Patients were matched based on age, sex, CHA_2DS_2-VASc, and high-dimensional propensity scores in order to reduce confounding. A total of 167,275 patients were matched and analyzed, among which 84,650 were on NOACs and 82,625 were on warfarin. Researchers identified 817 hip fractures, 2,013 hospitalized fractures, and 7,294 clinical fractures during an average 16.9-month follow-up. NOACs as a group resulted in a statistically significant lower risk of fractures requiring hospitalization ($p=0.007$) and all clinical fractures ($p=0.009$). Subgroup analysis of each NOAC found that while dabigatran did not significantly lower any fracture risk outcomes, rivaroxaban resulted in a statistically significant lower risk of fractures requiring hospitalization ($p=0.003$) and all clinical fractures ($p<0.001$). Apixaban alone resulted in statistically significant lower fracture risk compared to warfarin for all three primary fracture outcomes.[3] Adjusted hazard ratios and 95% CIs for the primary outcomes amongst the OACs are outlined below in Table 1.

Table 1. Adjusted HRs for Incident Fracture[3]

Primary Outcomes	NOAC Users (No. of Events)	Matched Warfarin Users (No. of Events)	HR (95% CI)	p Value
Any NOAC				
Hip fractures	293	312	0.91 (0.78-1.07)	0.27
Inpatient fractures	697	791	0.87 (0.79-0.96)	0.007
All clinical fractures	2,685	2,829	0.93 (0.88-0.98)	0.009
Dabigatran				
Hip fractures	182	186	0.98 (0.80-1.20)	0.86
Inpatient fractures	447	510	0.88 (0.78-1.00)	0.06
All clinical fractures	1,764	1,803	0.96 (0.90-1.03)	0.23
Rivaroxaban				
Hip fractures	128	170	0.89 (0.71-1.12)	0.33
Inpatient fractures	307	445	0.80 (0.69-0.93)	0.003
All clinical fractures	1,124	1,493	0.82 (0.76-0.89)	<0.001
Apixaban				
Hip fractures	41	70	0.67 (0.45-0.98)	0.04
Inpatient fractures	92	174	0.60 (0.47-0.78)	<0.001
All clinical fractures	396	521	0.86 (0.75-0.98)	0.02

Additionally, subgroup analysis of patients diagnosed with osteoporosis compared to those without osteoporosis showed that NOACs had a significantly reduced risk of hip fracture (HR 1.06; 95% CI 0.86-1.30; p=0.03 for interaction) compared to warfarin. Researchers concluded that NOACs, specifically apixaban, was associated with lower fracture risk compared to warfarin, which suggests caution may be necessary when prescribing warfarin to patients with AF and high fracture risk.[3]

Similar to the previous study, Taiwan's National Health Insurance Research Database was searched for real-world data. Adult patients (≥20 years old) with newly diagnosed AF between 2012 and 2016 who were being continuously treated with NOACs or warfarin for ≥90 days were included in this retrospective cohort study. Patients taking a NOAC and warfarin for ≥90 days, taking more than one NOAC for ≥90 days, or who developed any new fracture before the first 90 days of anticoagulant therapy were excluded. The primary study outcome was the development of any new hip, vertebrae, humerus, forearm, or wrist fracture on or after the 91st day after starting OAC therapy. Patients were followed from that 91st day until December 31, 2017, they developed the primary outcome, or death. After propensity score matching, a total of 19,414 patients were included, with 9,707 patients in each NOAC and warfarin cohort. Researchers identified 737 patients taking NOACs and 1,009 patients taking warfarin who achieved the primary outcome. Compared to warfarin, NOACs were associated with a 16% lower fracture risk (HR 0.84; 95% CI 0.78-0.93; p<0.001). Subgroup analyses of each NOAC also showed that dabigatran (HR 0.88; 95% CI 0.78–0.99; p=0.027), rivaroxaban (HR 0.81; 95% CI 0.72–0.90; p< 0.001) , and apixaban (HR 0.67; 95% CI 0.52–0.87; p=0.003) significantly lowered fracture risk compared to warfarin. Researchers concluded that if OAC treatment is needed, NOACS would be preferred over warfarin to lower fracture risk.[1]

Lastly, real-world evidence from Hong Kong Hospital Authority's electronic health record database led to similar conclusions as the previous studies. Researchers searched between 2010 and 2017 for newly diagnosed AF patients who were prescribed warfarin or a NOAC. The primary study outcome was osteoporotic hip or vertebral fracture incident, which was compared using propensity score-weighted cumulative incidence differences. A total of 23,515 patients were included, of which 13,974 were on NOACs and 9,541 were on warfarin. Researchers identified 401 total fractures, which translated to a significantly lower fracture risk associated with each NOAC compared to warfarin after a 24-month follow up.[4] The results amongst OACs are outlined below in Table 2.

Table 2. Fracture Risk[4]

NOACs vs. Warfarin	Cumulative Incident Difference (95% CI)
Apixaban	-0.88% (-1.66% to -0.21%)
Dabigatran	-0.81% (-1.34% to -0.23%)
Rivaroxaban	-1.13% (-1.67% to -0.53%)

There were no statistically significant differences in fracture risk observed between each NOAC. Researchers concluded that NOACs might result in a reduced risk for osteoporotic fracture compared to warfarin, selection of a specific NOAC does not seem to impact fracture risk, and such results may better inform the risk-benefit assessment when selecting an anticoagulant.[4]

Although the first study was a systematic review and meta-analysis of RCTs, none of the studies included were specifically designed to assess the fracture risk of OACs. Therefore, the fact that the primary outcome of this meta-analysis (fracture incidence) was observational in nature, along with the observational design of the three cohort studies means none of them can prove increased fracture risk is a consequence of OAC therapy alone. The clinical evidence outlined can only help understand the incidence of fracture and suggest an association between OAC therapy and fracture risk in patients with AF

or VTE. Patient specific factors such as comorbid conditions, medications, or family history could have also impacted fracture risk. Thus, it can also only be assumed that NOACs have a reduced risk of fracture compared to warfarin. Additionally, medication adherence can only be assumed, and the retrospective nature of the cohort studies increases the potential for missing data. The results from these cohort studies are also limited to the data available in their respective databases. However, the fact that real-world populations were evaluated increases the generalizability of the cohort studies' results, because they more accurately reflect real-world clinical practice when compared to RCTs. While the results across all four studies differed relative to statistical significance for each NOAC, all studies came to the same general conclusion: NOACs may be associated with a reduced fracture risk compared to warfarin, which has the potential to positively impact patients with AF or VTE who have high fracture risk.

Conclusion

Considering older patients are at an increased risk for falls and ultimately fractures, optimizing their therapy with medications that reduce fracture risk should be one of many goals for healthcare professionals. While more RCTs and observational studies are needed to prove and understand the pharmacological mechanism behind warfarin's potential increased risk for fracture, clinical research has consistently shown a significant association between lower fracture risk and NOACs as a class when compared to warfarin. Therefore, when working with AF patients with high fracture risk, a NOAC may be preferable to warfarin.

References

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