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Association of Anticoagulant Therapy With Risk of Fracture Among Patients With Atrial Fibrillation

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Key Points

Question Are oral anticoagulants differentially associated with risk of fracture among patients with atrial fibrillation?

Findings In this comparative effectiveness cohort study of 167 275 patients with atrial fibrillation, direct oral anticoagulants (ie, dabigatran, rivaroxaban, and apixaban) were associated with modestly lower fracture risk compared with warfarin. This protective association was more pronounced among patients with atrial fibrillation who also had a diagnosis of osteoporosis; among the direct oral anticoagulants, fracture risk was lowest among apixaban users.

Meaning These findings add to speculation that warfarin may be harmful to bone health and suggest that direct oral anticoagulants may be preferred among patients with atrial fibrillation and high fracture risk.

Abstract

Importance Warfarin is prescribed to patients with atrial fibrillation (AF) for the prevention of cardioembolic complications. Whether warfarin adversely affects bone health is controversial. The availability of alternate direct oral anticoagulant (DOAC) options now make it possible to evaluate the comparative safety of warfarin in association with fracture risk.

Objective To test the hypothesis that, among patients with nonvalvular AF, use of DOACs vs warfarin is associated with lower risk of incident fracture.

Design, Setting, and Participants This comparative effectiveness cohort study used the MarketScan administrative claims databases to identify patients with nonvalvular AF and who were prescribed oral anticoagulants from January 1, 2010, through September 30, 2015. To reduce confounding, patients were matched on age, sex, CHA₂DS₂-VASc (congestive heart failure, hypertension, age [>65 years = 1 point; >75 years = 2 points], diabetes, and previous stroke/transient ischemic attack [2 points], vascular disease) score, and high-dimensional propensity scores. The final analysis included 167 275 patients with AF. Data were analyzed from February 27, 2019 to September 18, 2019.

Exposures Warfarin and DOACs (dabigatran etexilate, rivaroxaban, and apixaban).

Main Outcomes and Measures Incident hip fracture, fracture requiring hospitalization, and all clinical fractures (identified using inpatient or outpatient claims) defined by *International Classification of Diseases, Ninth Revision, Clinical Modification* codes.

Results In the study population of 167 275 patients with AF (38.0% women and 62.0% men; mean [SD] age, 68.9 [12.5] years), a total of 817 hip fractures, 2013 hospitalized fractures, and 7294 total fractures occurred during a mean (SD) follow-up of 16.9 (13.7) months. In multivariable-adjusted, propensity score-matched Cox proportional hazards regression models, relative to new users of warfarin, new users of DOACs tended to be at lower risk of fractures requiring hospitalization (hazard ratio [HR], 0.87; 95% CI, 0.79-0.96) and all clinical fractures (HR, 0.93; 95% CI, 0.88-0.98), whereas the association with hip fractures (HR, 0.91; 95% CI, 0.78-1.07) was not statistically significant. When comparing individual DOACs with warfarin, the strongest findings were for apixaban (HR for hip fracture, 0.67 [95% CI, 0.45-0.98]; HR for fractures requiring hospitalization, 0.60 [95% CI, 0.47-0.78]; and HR for all clinical fractures, 0.86 [95% CI, 0.75-0.98]). In subgroup analyses, DOACs appeared more beneficial among patients with AF who also had a diagnosis of osteoporosis than among those without a diagnosis of osteoporosis.

Conclusions and Relevance In this real-world population of 167 275 patients with AF, use of DOACs—particularly apixaban—compared with warfarin use was associated with lower fracture risk. These associations were more pronounced among patients with a diagnosis of osteoporosis. Given the potential adverse effects of warfarin on bone health, these findings suggest that caution should be used when prescribing warfarin to patients with AF at high risk of fracture.

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