Warfarin Therapy and Risk of Hip Fracture Among Elderly Patients


Study Objective. To ascertain the relationship between warfarin therapy and subsequent hip fracture in a large elderly population.

Design. Retrospective, population-based cohort study.


Patients. Elderly patients receiving warfarin (52,701 patients), thyroid replacement therapy (40,555), an oral corticosteroid (43,915), or a proton pump inhibitor (60,383). The proton pump inhibitor group served as controls.

Measurements and Main Results. The association between warfarin therapy and subsequent hospitalization for hip fracture in elderly patients was examined by researching administrative data from January 1, 1994–March 31, 1999, for the elderly population of Ontario. Relative to patients receiving proton pump inhibitors, patients receiving warfarin (adjusted risk ratio [aRR] 0.94, 95% confidence interval [CI] 0.81–1.09) or thyroid replacement therapy (aRR 1.02, 95% CI 0.89–1.18) incurred similar risks of hip fracture. As expected, patients receiving oral corticosteroids incurred an increased risk (aRR 1.44, 95% CI 1.21–1.70) relative to patients receiving proton pump inhibitors.

Conclusion. Warfarin was not associated with increased risk of hip fracture.

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Warfarin therapy is commonly administered to elderly patients for treatment and prevention of thromboembolic disorders. Of particular concern with this population is warfarin’s effect on bone integrity. One hypothesis suggests that vitamin K, the synthesis of which is inhibited by warfarin, is necessary for the γ-carboxylation of osteocalcin, which binds to hydroxyapatite and may be important for bone mineralization. Evidence from transgenic mice models suggests that γ-carboxylated bone morphogenic protein rather than osteocalcin may be the critical factor; however, studies of oral anticoagulant therapy and bone mineral density have produced conflicting results. Separate from the possible detrimental effects of warfarin is the observation that low levels of vitamin K are also indicative of poor nutritional status, and malnutrition is a risk factor for osteoporosis.

The findings of these studies may be clouded by referral bias. Two recent epidemiologic...
studies failed to report an association between warfarin therapy and risk of hip fracture. However, their analyses were limited to female patients and small samples (fewer than 600 patients receiving warfarin). Consequently, we designed a retrospective, population-based cohort study to ascertain the relationship between warfarin therapy and subsequent hip fracture in a large elderly population.

**Methods**

**Identification of Patients and Events**

We created a retrospective open cohort by linking population-based health care administrative databases from January 1, 1994–March 31, 1999 covering over 1.4 million Ontarians aged 65 years or older. Patients were included if they had been newly prescribed warfarin, a thyroid replacement drug, an oral corticosteroid, or a proton pump inhibitor. Those receiving a proton pump inhibitor represented a control group as these agents are not associated with bone metabolism. Those receiving thyroid replacement therapy served as a neutral comparison group since risk of hip fracture may be negligible in patients with a hypothyroid disorder who receive drug therapy. Patients receiving oral corticosteroid therapy were a positive comparison group since this treatment increases the risk of hip fracture.

The Ontario Drug Benefits Database was used to identify the drugs that each patient was prescribed during the observation period. This database is maintained by the Ontario Ministry of Health and contains encrypted patient identifiers, prescription dates, and drug information for all Ontarians aged 65 years or older. Patients who received drugs from any of the four groups (warfarin, thyroid replacement drugs, oral corticosteroids, or proton pump inhibitors) during the year before cohort entry were excluded; thus, only relatively recent recipients of the drugs were included.

We used the Discharge Abstract Database of the Canadian Institute for Health Information to identify hospitalized patients; with this information we characterized subsequent events and comorbid illnesses. The discharge abstracts contain each patient’s health care number, age and sex, date of admission, and up to 16 diagnoses as coded by the International Classification of Diseases, 9th revision (ICD-9). Patients were excluded from analysis if hospitalization data within 5 years of the start of the study revealed a history of hip fracture (ICD-9 codes 820.0–820.9), pathologic fracture (ICD-9 198.5, 733.1), or conditions that predispose to fracture, such as epilepsy (ICD-9 345 or 780.3); trauma (ICD-9 E800–848); malignancies of the breast (ICD-9 170), bone (ICD-9 174), colon (ICD-9 153), rectum (ICD-9 154), or lung (ICD-9 162); and multiple myeloma (ICD-9 203.0) or metastatic cancer (ICD-9 199). The remaining patients were followed for up to 5 years to document subsequent hospital admissions involving hip fracture (the primary outcome measure) after drug exposure.

Sex and age of the patients at study entry were retrieved from the Registered Persons Database, which is maintained by the Ontario Ministry of Health. It contains demographics and health care numbers for all individuals eligible for the Ontario provincial health insurance program.

**Duration of Exposure**

We defined duration of exposure as the period of continuous enrollment in any of the study drug groups. Exposure began from the time the first study drug was prescribed during the 5-year observation period. Patients who were given drugs from more than one study drug group on the starting date were excluded. Patients were allowed to change drugs within the same study drug class. We assumed that a drug was discontinued if it was not renewed within 180 days. Observation took place from the date the patients started taking their study drug to 30 days after the last recorded prescription date. Observation stopped if patients were hospitalized for hip fracture. Patients were censored if they died, temporarily or permanently discontinued their study drug, received a drug from another study group, experienced a hip fracture, or reached the end of the observation period.

**Comorbidity Assessment and Exposure to Other Drugs**

Comorbidity measures were obtained from hospital discharge data. All hospital admissions during the 5 years preceding study entry through the end of the observation period were analyzed for diagnoses of arthritis, back problems, chronic mental health disorders, cerebrovascular disease, dementia, depression, peripheral neuropathy, Parkinson’s disease, urinary incontinence, chronic obstructive pulmonary disease, cardiac disorders, hypertension, glaucoma or cataracts, diabetes, chronic renal disease, or osteoporosis.
Because numerous other drugs may affect the risk of hip fracture in elderly patients, we examined receipt of antidepressants, sedatives, antipsychotics, anticonvulsants, insulin or oral hypoglycemic drugs, bisphosphonates, systemic (injectable or rectal) or inhaled corticosteroids, cardiac drugs, antiparkinsonian drugs, injectable anticoagulants, oral estrogen, and statin therapy. Patients were classified as exposed if prescriptions for any of these drugs were dispensed within 100 days preceding study entry through the end of the observation period.

Statistical Considerations

Time-to-event analyses were conducted using Cox proportional hazard models, with patients taking a proton pump inhibitor as the reference. The outcome variable was the incidence of hip fracture. Patient age was an independent continuous variable in the model. Independent binary variables for each condition listed above were placed in the model to adjust for comorbid illness and drug exposure. All analyses were performed using SAS for UNIX, Version 6.12 (SAS Institute, Cary, NC).

Results

Patient demographics and information regarding comorbid illnesses are presented in Table 1. During approximately 223,300 patient-years of follow-up, the crude incidence of hip fracture/10,000 patient-years among those receiving warfarin (52,701 patients), thyroid replacement therapy (40,555), an oral corticosteroid (43,915), and a proton pump inhibitor (60,383) was 61.9, 65.8, 92.2, and 57.5, respectively. After adjusting for potential confounders, the effect of warfarin (adjusted risk ratio 0.94, 95% confidence interval [CI] 0.81–1.09) and thyroid replacement (adjusted risk ratio 1.02, 95% CI 0.89–1.18) on the risk of hip fracture was similar to that of proton pump inhibitors. The risk of hip fracture was greater for patients taking an oral corticosteroid (adjusted risk ratio 1.44, 95% CI 1.21–1.70) than for those taking a proton pump inhibitor.
Discussion

Our study results suggest that warfarin, as commonly prescribed, is not associated with an increased risk of hip fracture in elderly patients. These results support previous findings in studies that had much smaller samples and involved only women.6,7 To the best of our knowledge, ours is the largest study to date that explores this association.

However, several limitations must be acknowledged. We examined warfarin administration for up to 5 years after the start of therapy, and our findings are limited to this time period. Although we controlled for numerous confounding variables through restriction and modeling, we were unable to control for other pertinent factors, such as calcium and vitamin D supplements, body mass index, diet, smoking, and exercise status, because available data were limited.

The impact of these factors on the results of our analysis is largely unknown. Although patients taking warfarin may have experienced more illness than the other groups, their risk of hip fracture was similar to that of the patient groups treated with thyroid replacement therapy and proton pump inhibitors in the multivariate analysis. As expected, the risk of hip fracture was greater in patients receiving an oral corticosteroid than in those receiving a proton pump inhibitor. These findings suggest that the effects of any unknown confounding influence may be minimal. Only patients whose fractures required hospitalization were assessed.

Conclusion

Given the favorable outcomes associated with warfarin for prevention of thromboembolism in patients with conditions such as atrial fibrillation, our findings suggest that fears of adverse effects on bone integrity should not prevent warfarin administration in routine practice.

References