Background: Vitamin K allows for γ-carboxylation of glutamyl residues, a conversion that activates clotting factors and bone proteins. Vitamin K antagonists such as warfarin inhibit this process. Our goal was to quantify the association between warfarin and osteoporotic fractures in patients with atrial fibrillation.

Methods: This was a retrospective cohort study of Medicare beneficiaries with atrial fibrillation who were hospitalized between March 1998 and April 1999 in all 50 US states. The study outcome was osteoporotic fractures, identified by an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for a fracture of the hip, spine, or wrist.

Results: Compared with 7587 patients who were not prescribed warfarin, the adjusted odds ratio (OR) of fracture was 1.25 (95% confidence interval [CI], 1.06-1.48) in 4461 patients prescribed long-term warfarin therapy (>1 year). The association between osteoporotic fracture and long-term warfarin use was significant in men (OR, 1.63; 95% CI, 1.26-2.10) but nonsignificant in women (OR, 1.05; 95% CI, 0.88-1.26). In 1833 patients prescribed warfarin for less than a year, the risk of osteoporotic fracture was not increased significantly (OR, 1.03). Odds ratios (95% CIs) of independent predictors of osteoporotic fractures were as follows: increasing age, 1.63 (1.47-1.80) per decade; high fall risk, 1.78 (1.42-2.21); hyperthyroidism, 1.77 (1.16-2.70); neuropsychiatric disease, 1.51 (1.28-1.78); and alcoholism, 1.50 (1.01-2.24). Factors with a reduced OR (95% CI) included African American race, 0.30 (0.18-0.51); male sex, 0.54 (0.46-0.62); and use of β-adrenergic antagonists, 0.84 (0.70-1.00).

Conclusions: Long-term use of warfarin was associated with osteoporotic fractures, at least in men with atrial fibrillation. β-Adrenergic antagonists may protect against osteoporotic fractures.

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W ARFARIN AND OTHER vitamin K antagonists are prescribed to millions of people worldwide to decrease their risk of clotting. These drugs work by interfering with the γ-carboxylation of glutamic acid (Glu) residues on clotting factors II, VII, IX, and X. Because γ-carboxylation of specific Glu residues is also required for activation of osteocalcin and other bone matrix proteins, vitamin K antagonists might increase the risk of osteoporotic fractures. Evidence for this hypothesis comes from experimental studies of rats, which found that therapeutic use of warfarin decreases the rate of bone formation and increases the rate of bone resorption in the rat femur, resulting in decreased femoral bone strength.

In utero, vitamin K antagonists interfere with bone formation, but their effect on bone health in older adults is unclear. During the first trimester, exposure to warfarin causes embryopathy that includes nasal hypoplasia and epiphyses stippling.2,3 Children who receive long-term warfarin therapy have reduced bone density.4 Adults who take vitamin K antagonists may lose bone mineral density at an accelerated rate in the femur5,6 and distal radius,7 but this observation is inconsistent.1,8 Prior studies addressing the question of whether exposure to warfarin in the elderly population is associated with osteoporotic fracture reached conflicting results.5,11

We hypothesized that patients with long-term use of warfarin would have an increased risk of osteoporotic fracture. Quantifying the risk of osteoporotic fracture from warfarin and other clinical factors is important because patients at high risk of fracture could choose to take anticoagulants in which the mechanism of
action is independent of vitamin K.\textsuperscript{12,13} or they could alter their diet, behavior, or pharmacotherapy to decrease their risk of fracture.\textsuperscript{14} The secondary aim of this study was to quantify how other medications and clinical factors (eg, hyperthyroidism) affect the risk of osteoporotic fracture.

### METHODS

#### NRAF II DATA SET

The National Registry of Atrial Fibrillation (NRAF) II data set includes Medicare Part A claims records, Part B records, and chart-abstracted data from 3386 hospitals in all 50 states during the years 1995 through 1999. Participants were selected as a stratified random sample from Medicare beneficiaries who were hospitalized with atrial fibrillation (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 427.31, in any diagnostic position) between April 1, 1998, and March 31, 1999. The structured abstraction of data from medical charts was performed by the Clinical Data Abstraction Centers (CDACs) as part of the National Stroke Project. Through review of electrocardiogram reports and physician documentation, CDAC researchers confirmed the presence of atrial fibrillation during the index admission and documented the presence of comorbid conditions. To allow for full characterization of risk factors prior to index hospitalization, we excluded subjects without Part A and Part B claims data for years 1995 and 1996 (n = 422) and Medicare patients who were younger than 68 years at baseline admission during the study period (n = 1936).

#### STATISTICAL ANALYSIS

We analyzed the effect of warfarin exposure on the adjusted odds ratio (OR) of osteoporotic fracture by stepwise logistic regression, retaining variables independently associated with warfarin use at the \( P < .10 \) level. We considered 2-tailed \( P \) values less than .05 to be statistically significant. We tested for the effect of key prebaseline clinical risk factors (Table 1) and medications (Table 2). In the logistic regression model, we tested for an interaction between sex and the use of warfarin.

#### DEFINITION OF COMORBID CONDITIONS

The CDACs used structured abstraction of data from patient medical records to confirm the presence of nonacute atrial fibrillation during the index admission and identify the presence or absence of all demographic and clinical variables (Table 1). Patients who had schizophrenia, dementia, or Parkinson disease were classified as having “neuropsychiatric impairment.” Patients were classified as at “high risk for falls” if the medical record from the index hospitalization contained any of the following terms: “frequent falls,” “history of falls,” “multiple falls,” or “tendency for falls”; a single fall was insufficient documentation for this designation.

#### ASSESSMENT OF OSTEOPOROTIC FRACTURES

We identified fractures likely to be related to osteoporosis\textsuperscript{15,16} at the time of the index hospitalization and in the follow-up period using ICD-9-CM diagnostic codes in any diagnostic position of Medicare Part A (inpatient) and Part B (outpatient) claims. We identified vertebral fractures from ICD-9-CM codes 805.2, 805.3, 805.4, 805.5, 805.6, 805.7; wrist fracture from codes 813.4, 813.5, 814.0, and 814.1; and hip fractures from codes 820.0 through 820.9. In a secondary analysis, we also included closed rib fractures (code 807.0).

#### COHORT FORMATION

We identified subjects who were receiving warfarin therapy preceding hospitalization by noting warfarin monitoring each 90 days or fewer between international normalized ratio (INR) tests. We assessed the INR monitoring by searching Part A and Part B claims for Healthcare Common Procedure Coding System (HCPCS) code 85610 (prothrombin time). We stratified warfarin exposure prior to the index hospitalization into those who had at least 1 year of use and those who had 90 to 364 days of warfarin therapy. We classified patients as not taking warfarin if they met 2 conditions: (1) they were not taking warfarin when admitted for index hospitalization (according to medical record review) and (2) they did not have 2 or more outpatient prothrombin times measured within 90 days of each other during the 3 years prior to the index hospitalization. We excluded subjects (n = 2294) whose warfarin exposure was trivial (1-89 days of therapy) or ambiguous (ie, patients with no claims for prothrombin time monitoring prior to index hospitalization but who were taking warfarin as recorded on the medical record [n = 742]). We also excluded subjects who were terminally ill (according to medical record review) (n = 653) and subjects who had a Medicare Part A claim for fractures in the 3 years (1995-1998) prior to the index hospitalization (n = 2842). In the primary analysis, we excluded subjects who died within 30 days of baseline hospitalization (n = 683). We did not exclude subjects who carried a diagnosis of osteoporosis (eg, ICD-9-CM code 733.0) because osteoporosis is on the causal pathway leading from warfarin use to osteoporotic fracture and adjusting for exposures on a causal pathway typically leads to an underestimate of association.\textsuperscript{17}

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### Table 1. Demographics and Morbidity\textsuperscript{*}

<table>
<thead>
<tr>
<th>Factor</th>
<th>Warfarin Therapy ≤ 1 y (n = 4652)</th>
<th>Warfarin Therapy &gt; 1 y (n = 1905)</th>
<th>No Warfarin (n = 8007)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y\textsuperscript{†}</td>
<td>79.4 (6.3)</td>
<td>78.9 (6.4)</td>
<td>80.8 (7.2)</td>
</tr>
<tr>
<td>Male\textsuperscript{‡}</td>
<td>46.4</td>
<td>47.2</td>
<td>43.1</td>
</tr>
<tr>
<td>Race\textsuperscript{‡}</td>
<td>White</td>
<td>85.2</td>
<td>81.8</td>
</tr>
<tr>
<td>African American</td>
<td>2.8</td>
<td>4.7</td>
<td>4.8</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.5</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>10.4</td>
<td>11.0</td>
<td>10.2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>History of stroke/</td>
<td>36.4</td>
<td>33.4</td>
<td>24.5</td>
</tr>
<tr>
<td>TIA\textsuperscript{‡}</td>
<td>5.3</td>
<td>4.8</td>
<td>6.3</td>
</tr>
<tr>
<td>High fall risk\textsuperscript{‡}</td>
<td>13.3</td>
<td>12.5</td>
<td>16.1</td>
</tr>
<tr>
<td>Neuropsychiatric impairment\textsuperscript{‡}</td>
<td>1.9</td>
<td>2.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>8.7</td>
<td>8.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Heart failure\textsuperscript{‡}</td>
<td>48.6</td>
<td>48.4</td>
<td>43.5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>32.0</td>
<td>30.0</td>
<td>24.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>68.6</td>
<td>71.6</td>
<td>69.6</td>
</tr>
<tr>
<td>Cancer</td>
<td>3.0</td>
<td>2.6</td>
<td>2.7</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>0.9</td>
<td>1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>1.6</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Seizure disorder\textsuperscript{‡}</td>
<td>4.8</td>
<td>4.5</td>
<td>3.6</td>
</tr>
<tr>
<td>Discharged with warfarin\textsuperscript{‡}</td>
<td>77.4</td>
<td>64.6</td>
<td>24.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Outcomes of Osteoporotic Fractures—NRAF II Data Set (n = 8007)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Osteoporotic fracture</td>
</tr>
<tr>
<td>Hip fracture</td>
</tr>
<tr>
<td>Wrist fracture</td>
</tr>
<tr>
<td>Rib fracture</td>
</tr>
</tbody>
</table>

**Abbreviation:** TIA, transient ischemic attack.

\*Data are given as percentages unless otherwise indicated.

\†\textsuperscript{P}<.001 (Wilcoxon test).

\‡\textsuperscript{P}<.05 (χ² test).
In a secondary analysis, we considered only incident fractures after the index hospitalization. To prevent mistaking an old fracture for a new one, for these time-to-event analyses we excluded patients with an ICD-9-CM code for fracture during the index hospitalization. We plotted Kaplan-Meier curves and used Cox proportional hazards model that censored patients after their first fracture, the date of death, or the end of follow-up (December 31, 1999). We performed Cox analyses stratified by a prebaseline diagnosis of osteoporosis based on a prebaseline Part B claim (ICD-9-CM code 733.x) or as inferred by an admission medication of raloxifene hydrochloride, calcitriol, fluoride, teriparatide, or any bisphosphonate.

We identified 4652 subjects who had cumulative long-term (≥365 days) warfarin use before baseline, 1905 subjects who had short-term warfarin use (90-364 days), and 8007 subjects with no warfarin therapy in the 3 years preceding the index hospitalization. These 14,564 subjects were mostly white (83%), and more than half were female (Table 1). Hypertension and heart failure were the most common comorbid conditions (Table 1). Subjects without prebaseline exposure to warfarin were significantly more likely to be female, nonwhite, have a high risk of falls, and have neuropsychiatric disorders. Loop diuretics and β-adrenergic antagonists were the most common medications on admission and were prescribed more often to subjects receiving warfarin therapy (Table 2).

A total of 1005 subjects (6.9%) had an osteoporotic fracture: 387 occurred at the index hospitalization and 618 occurred during the follow-up interval (median follow-up time to fracture, 6.3 months). Most fractures 656 (65.3%) were of the hip, 198 (19.7%) were vertebral, 105 (10.4%) were of the wrist, and 46 (4.6%) had more than 1 of these osteoporotic fractures. The 30-day mortality was 39.0% after hip fracture, 37.4% after vertebral fracture, and 26.1% after multiple osteoporotic fractures.

We fitted a logistic model on 13,881 subjects who survived for over 30 days after baseline hospitalization. Compared with 7587 subjects without previous warfarin exposure, 4461 subjects who received long-term warfarin therapy had higher odds (OR, 1.25; 95% CI, 1.06-1.48) of osteoporotic fractures (Table 3). However, there was no significant increase in fractures for 1833 subjects who were receiving short-term warfarin therapy (OR, 1.03; 95% CI, 0.82-1.29). Adjusted ORs (95% CIs) of independent predictors of osteoporotic fractures were as follows: increasing age, 1.63 (1.47-1.80) per decade; high fall risk, 1.78 (1.42-2.21); hyperthyroidism, 1.77 (1.16-2.70); neuropsychiatric disease, 1.51 (1.28-1.78); and alcoholism, 1.50 (1.01-2.24). Factors independently associated with a reduced OR (95% CI) of fractures included African American race, 0.30 (0.18-0.51); male sex, 0.54 (0.46-0.62); and use of β-adrenergic antagonists, 0.84 (0.70-1.00).

There was a significant warfarin use by sex interaction (P = .01). Stratified analysis revealed that warfarin therapy significantly increased the risk of fractures in men but not in women. In men, long-term use of warfarin was significantly associated with fractures (OR, 1.63; 95% CI, 1.26-2.10) compared with men without prior warfarin exposure. In women, the association between incident fracture and long-term warfarin use was not significant (OR, 1.05; 95% CI, 0.88-1.26).

Excluding fractures diagnosed during or prior to the index hospitalization, the incident rate of osteoporotic fractures in 6389 men was 2.6 (95% CI, 2.1-3.2) per 100 patient-years without warfarin and 3.6 (95% CI, 3.0-4.3) per 100 patient-years of long-term warfarin use. In 7775 women, the incident rate of osteoporotic fractures was 5.8 (95% CI, 5.1-6.6) per 100 patient-years without warfarin and 5.4 (95% CI, 4.70-6.30) per 100 patient-years of long-term warfarin use. In men, fractures (Figure 1) correlated with long-term warfarin use (P = .01, log-rank test), but in women (Figure 2), there was no significant association (P = .60, log-rank test). After adjusting for confounding variables (Table 1) and stratified by osteoporosis diagnosis (prevalence, 16.7%), warfarin use was significantly correlated with incident fracture in women.
the entire cohort: the hazard ratio (95% CI) for incident osteoporotic fracture was 1.32 (1.08-1.61) with long-term warfarin use and 1.10 (0.83-1.42) for short-term warfarin use (compared with no warfarin use).

When rib fractures were reclassified as an osteoporotic fracture, the association between osteoporotic fracture and long-term warfarin use was nonsignificantly stronger. When we repeated the analyses for each fracture site, we found warfarin to be associated with vertebral and rib fractures (Table 4).

In this retrospective cohort study of 14,564 patients with atrial fibrillation, long-term use of warfarin was associated with a 25% increased risk (OR, 1.25) of osteoporotic fracture. In contrast, use of warfarin for less than 1 year had no significant association with osteoporotic fracture. Among those with long-term use, warfarin was most strongly associated with vertebral fractures.

The correlation between warfarin use and fracture differed in men and women (P = .01): long-term warfarin use was significantly associated with osteoporotic fractures in men (OR, 1.63) but not women (OR, 1.05). The interaction arose primarily from hip fractures, which were associated with warfarin use in men but not in women. Why warfarin would not increase the risk of fracture in women is unclear, but perhaps other factors (eg, pre-existing osteoporosis) overshadow warfarin’s effect in women.

There are 2 mechanisms by which warfarin use could predispose to osteoporotic fractures: (1) directly, by inhibition of γ-carboxylation in osteocalcin and other bone matrix proteins; and (2) indirectly, because patients taking warfarin may limit their dietary intake of foods rich in vitamin K. In the Nurses’ Health Study, the 20% of nurses who consumed the lowest quintile of dietary vitamin K (<109 µg/d) had a relative risk of subsequent fracture that was significantly increased (age-adjusted relative risk, 1.43) compared with nurses with the highest quintile of dietary vitamin K consumption. Low levels of dietary vitamin K intake are common in patients who take warfarin because many patients taking warfarin have been instructed to moderate their intake of green vegetables that are rich in vitamin K. Unfortunately, green leafy vegetables are also an important dietary source of folic acid so that limiting their intake also may predispose to hyperhomocysteinemia, an independent risk factor for osteoporotic fractures in the elderly. We hypothesize that both mechanisms predispose to osteoporosis in patients taking vitamin K antagonists and therefore predispose to osteoporotic fracture.

The association between warfarin use and subsequent fracture supports the role of vitamin K in normal bone formation. It also suggests that patients who are more likely to have lower vitamin K epoxide reductase activity based on their genotype may be predisposed to osteoporotic fracture—a testable hypothesis. Finally, the putative role of vitamin K argues for adequate intake of vitamin K1 (found especially in green vegetables) and vitamin K2 (present in fermented dairy and soy products, fish, meat, liver, and eggs). A balanced diet will also provide micronutrients essential for bone integrity.

The OR of 1.25 (hazard ratio, 1.32) for osteoporotic fracture in long-term warfarin users lies between the ORs in prior studies. Caraballo et al compared the incidence of fracture in 572 women in Olmsted County, Minnesota, who had a venous thromboembolism with age-adjusted fracture rates. They found an increased incidence of osteoporotic fractures of 1.5 in patients who took warfarin for 3 to 12 months and an increased incident of fractures (primarily vertebral and rib fractures) of 1.6 in patients with long-term warfarin use. In contrast, Pilon

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Table 4. Warfarin Effect on the Odds of Fractures in the Adjusted Logistic Model

<table>
<thead>
<tr>
<th>Fracture</th>
<th>&lt;1 y of Warfarin Therapy</th>
<th>≥1 y of Warfarin Therapy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral</td>
<td>0.8 (0.5-1.3)</td>
<td>1.7 (1.3-2.2)</td>
<td>.001</td>
</tr>
<tr>
<td>Rib</td>
<td>1.6 (1.1-2.3)</td>
<td>1.3 (1.0-1.8)</td>
<td>.02</td>
</tr>
<tr>
<td>Hip</td>
<td>1.1 (0.9-1.3)</td>
<td>1.0 (0.8-1.3)</td>
<td>.42</td>
</tr>
<tr>
<td>Wrist</td>
<td>1.1 (0.7-1.6)</td>
<td>1.4 (0.9-2.4)</td>
<td>.36</td>
</tr>
</tbody>
</table>
et al found no significant association between prior use of a vitamin K antagonist and fracture of the hip or wrist (vertebral fractures were not studied). However, 98% of their participants who had taken a vitamin K antagonist had 90 or fewer days of use. In the subset of participants with longer exposure in the study by Pilon et al, the adjusted OR of a fracture was 1.2 (95% CI, 0.9-1.6), similar to our findings. In a retrospective cohort study by Mamdani et al, the adjusted risk ratio for hip fractures was not increased (0.94; 95% CI, 0.81-1.09) in 52 701 elderly Ontario residents who were prescribed warfarin (mean duration of 1.2 years) rather than a proton pump inhibitor, but no subgroup analysis of long-term warfarin use was provided and the 2 cohorts had different underlying disease. An alternative explanation for the negative findings of Mamdani et al is that warfarin may decrease bone mineral density in the distal (or ultradistal) radius or the vertebrae with less effect at the hip.

Clinical trials support the role of vitamin K in maintaining bone health. In randomized, controlled trials of osteoporotic women, participants randomized to receive vitamin K2 (menatetrenone, 45 mg/d) had slower loss of bone mineral density and a reduced risk of subsequent osteoporotic fractures than control women. In other randomized, controlled trials of patients with a recent stroke or patients beginning prednisolone therapy, control participants lost bone mineral density, which was prevented in participants randomized to receive vitamin K2, 45 mg/d. In a randomized trial of vitamin K1 (1 mg/d), vitamin K2 reduced bone loss at the femoral neck but not of the lumbar spine.

The observational nature of the present study has several limitations. Although we adjusted for many clinical variables (Table 1 and Table 2), we were unable to capture others that are associated with osteoporotic fracture (smoking status, bone mineral density, vitamin D status, and body habitus). If these unmeasured variables correlated with warfarin use, they would confound the observed association between warfarin and fracture. A second limitation is that we were unable to verify the diagnosis in patients having an ICD-9-CM code for an osteoporotic fracture. Likewise, we were unable to assess duration of warfarin use in 742 patients and had to exclude them. A minor limitation is that we could not verify the duration of warfarin therapy, which we inferred from the billing code for prothrombin time monitoring. A final limitation is that we had to exclude patients in whom warfarin exposure was ambiguous.

Despite these limitations, the observed association between warfarin use and osteoporotic fracture may be real. If confirmed, ideally in a randomized trial, the association would be clinically significant because of the high mortality and morbidity of these fractures and because of the development of new anticoagulants that do not inhibit the action of vitamin K. In contrast to newer agents, low-molecular-weight heparin and especially unfractionated heparin are not good alternatives to warfarin for patients with atrial fibrillation and osteoporosis because they also can cause osteoporosis and fracture.

When combined with other studies, the present study also supports the protective effect of β-adrenergic antagonists on bone density and risk of fracture. We found that patients prescribed β-adrenergic antagonists had a 16% reduction in subsequent osteoporotic fracture (OR, 0.84; 95% CI, 0.70-1.00), similar to the OR of 0.77 (95% CI, 0.72-0.83) for β-adrenergic antagonists in a recent case-control study.

In this observational cohort study, we can neither determine whether the association between β-adrenergic antagonism and osteoporotic fracture is real nor elucidate a biological explanation. However, studies in wild-type and ovarioectomized mice show that β-adrenergic antagonism increases bone mass. The association between hyperthyroidism and osteoporotic fractures observed here (OR, 1.77) and previously (OR, 1.7) suggests that part of the possible benefit of β-adrenergic antagonists could be mediated via the known inhibition of thyroxine.

In our study and others, falls were an important contributor to osteoporotic fracture. An increased risk of falls also likely contributed to the increased odds of osteoporotic fracture in patients with neuropsychiatric impairment (OR, 1.51) and alcoholism (OR, 1.50). When prescribing warfarin to elderly patients at high risk of falling, health care providers can instruct them to wear stable shoes, exercise regularly, have adequate intake of calcium and vitamin D, use walking aids, and discontinue unnecessary medications.

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Correspondence: Brian F. Gage, MD, MSc, Division of General Medical Sciences, Washington University School of Medicine, Campus Box 8005, 660 S Euclid, St Louis, MO 63110 (bgage@im.wustl.edu).

Author Contributions: The authors assume full responsibility for the accuracy and completeness of the ideas presented. Dr Gage and Ms Birman-Deych had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the analyses.

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