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Single-point Assessment of Warfarin Use and Risk of Osteoporosis in Elderly Men

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Abstract

Objectives—To determine if one-time assessment of warfarin use is associated with bone mineral density (BMD), rates of bone loss, and fracture risk among older men.

Design—Secondary analysis of data from a prospective cohort study.

Setting—Six U.S. clinical centers

Participants—Five thousand five hundred thirty-three community-dwelling, ambulatory men aged sixty-five and older with baseline warfarin use data.

Measurements—Warfarin use was assessed as current use of warfarin at baseline using an electronic medication coding dictionary. BMD was measured at the hip and spine at baseline, and hip BMD was repeated at a follow-up visit 3.4 years later. Self-reported non-spine fractures were centrally adjudicated.

Results—At baseline, the average age of the participants was 73.6 ± 5.9 years, and 321 men (5.8%) were taking warfarin. Compared to nonusers (n = 5,212), warfarin users had similar baseline BMD at the hip and spine (total hip 0.966±0.008 [users] vs. 0.959±0.002 [nonusers] g/cm^2, p=0.37; and total spine 1.079±0.010 vs. 1.074±0.003 g/cm^2, p=0.64). Among those with BMD at both visits, warfarin users (n = 150) also had similar annualized bone loss at the total hip (−0.509±0.082 vs. -0.421±0.019 %/yr, p=0.29) compared to nonusers (n = 2,683). During a mean follow-up of 5.1 years, the risk of non-spine fracture was similar among warfarin users and nonusers (adjusted HR 1.06 [95% CI, 0.68 to 1.65]).

Conclusion—In this cohort of elderly men, current warfarin use was not associated with lower BMD, accelerated bone loss, or higher non-spine fracture risk.

Keywords

warfarin; fractures; BMD; men

INTRODUCTION

As the population of older adults increases, the need for anti-coagulation with warfarin has also increased, which may pose additional risks in this population [1]. Warfarin, a coumarin derivative anticoagulant, is a vitamin K antagonist that produces its anticoagulant effect by interfering with the recycling of vitamin K thus blocking gamma-carboxyglutamate (Gla) formation [2-4]. In the coagulation cascade, vitamin K acts as an essential cofactor in the gamma-carboxylation conversion of glutamate to Gla residues on many clotting factors (factors II, VII, IX, and X) and anti-coagulation proteins (proteins C and S). Gla residues allow factors to interact properly with the substrates and modulators of the coagulation cascade. By inhibiting vitamin K, coagulation is also inhibited [2,3].

Vitamin K also plays an important role in bone metabolism. Osteocalcin, a Gla-containing protein [5-9], is synthesized and post-translationally modified in osteoblasts before it is secreted into serum [4]. Carboxylated osteocalcin plays a role in bone formation by facilitating calcium binding to the hydroxyapatite matrix of bone, and Gla residues are essential for this binding to occur [5-9]. Since warfarin can inhibit the actions of vitamin K in anti-coagulation factors, the carboxylation of osteocalcin may also be inhibited, but the clinical implications of uncarboxylated osteocalcin are not well understood [2,3,6,9,10,11]. It has been shown that

warfarin inhibits osteocalcin accumulation in the extracellular matrix of human osteoblasts in vitro. [12]

Findings in human studies of warfarin use and bone mass have been inconsistent [13]. A meta-analysis of cross-sectional studies [13] found that the effect of oral anticoagulants showed a negative association with BMD at the ultradistal radius but not spine or hip. In terms of fractures, some prior studies have found that oral anticoagulant use was associated with an increased risk of vertebral and rib fractures in women [14] but not hip [15] or other non-vertebral fractures [16] among men or women. In a recent study of older men and women, the association between warfarin use and osteoporotic fractures was found to be in men but not women [17]. Conversely, in a large study of older women no association was identified between warfarin use and BMD or fracture risk.[18]

The purpose of this study was to determine if current warfarin use is associated with BMD, rates of bone loss, and fracture risk among elderly men.

METHODS

Participants

The Osteoporotic Fractures in Men (MrOS) Study is a multi-center prospective longitudinal, observational study of risk factors for vertebral and all non-vertebral fractures in 5,995 community-dwelling men aged 65 and older. The design, measures, and recruitment methods employed by the study have been previously described [19,20]. Briefly, enrollment for this study was between March 2000 and April 2002, and participants were recruited from the communities of Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; and San Diego, CA. Approval of the conduct of MrOS was obtained from the institutional review boards of the participating institutions, and written informed consent was obtained from all study participants.

To qualify for MrOS enrollment, participants must have been able to walk without the assistance of another, have had at least one original hip (must not have had bilateral hip replacements), planned to live in the area surrounding the study site for the duration of the study, not have a severe medical condition that would preclude participation in follow-up, and able to provide informed consent and self-reported data. The participants had to complete the self-administered questionnaire, attend the clinic visit, and complete at least the anthropomorphic, BMD, and vertebral X-ray procedures. There were no other exclusion criteria.

Of the 5,995 men enrolled in the study, we excluded from this analysis 118 men who were taking osteoporosis medications at baseline (bisphosphonates, calcitonin, fluoride, or raloxifene). Baseline medication use data were not available for an additional 344 men. Of the 5,533 men who remained, 1 man did not have a technically adequate hip BMD measurement, and 9 men did not have technically adequate spine BMD measurements. Thus, the cross-sectional analyses included 5,532 men for the baseline hip BMD outcome and 5,524 men for the spine BMD outcome. A subset of the 5,533 men (N=2,866) were invited to participate in an ancillary sleep visit beginning in December 2003. Hip BMD was repeated at the sleep visit, though scans were unavailable for 7 of the 2,866 men. Change in hip BMD from baseline to the sleep visit could not be calculated for an additional 26 men since the same hip was not scanned at both visits. There remained 2,833 men who formed the cohort for the longitudinal analyses. The mean interval between the baseline and sleep examinations was 3.4 ± 0.5 years.

Warfarin Use

Participants were asked to bring with them to the baseline clinic visit current prescription medications used daily or almost daily for at least the past month. If a participant forgot to bring in one or more medications, each clinic site was responsible for obtaining the information via telephone or return visit. All prescription medications recorded by the clinics were stored in an electronic medications inventory database (Version 6.15, San Francisco Coordinating Center, California Pacific Medical Center Research Institute, San Francisco, CA). Each medication was matched to its ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA). Participants were considered users of warfarin if they were taking an ingredient that was categorized by IDIS as "Anticoagulants — coumarin derivative." The only medication that was classified as "anti-coagulants-coumarin derivative" among our men was warfarin. Current warfarin use was categorized as a binary "yes/no" variable. No information on current dose, duration, or compliance was collected. Indication for warfarin and achievement of treatment outcomes were not collected.

Measurement of Bone Density

At the baseline examination, participants underwent BMD (g/cm^2) measurement of the hip and lumbar spine (L1-L4) with dual energy x-ray absorptiometry (DXA) (QDR 4500W, Hologic, Inc., Waltham, MA). DXA of the hip was repeated during the sleep visit 3.4 years later. The change in hip bone density was determined by subtracting BMD at baseline from BMD at the sleep visit and was expressed as an annualized percentage of the baseline value (%/yr). All hip BMD measurements were made on the right hip unless the participant reported a right hip replacement or metal objects in the right leg, in which case the left hip was measured. Lumbar spine BMD was measured in the anterior-posterior projection and calculated as the mean of the BMD from the first through fourth lumbar vertebrae. A central quality control lab, certification of DXA operators, and standardized procedures for scanning were used to insure reproducibility of DXA measurements. At baseline, a set of spine, hip and linearity phantoms were circulated and measured at the six clinical sites. The variability across clinics was within acceptable limits, and cross-calibration correction factors were not required. Inter-clinic coefficients of variation (CV) were 0.9% (hip) and 0.6% (spine). To adjust for inter-clinic differences, statistical models included indicator variables for the individual scanners. Each clinic scanned a spine and hip phantom throughout the study to monitor longitudinal changes, and correction factors were applied to participant data as appropriate. The precision of DXA scans of the spine and hip is 1-2% [21].

Ascertainment of Fractures

After the baseline examination, participants were contacted about fractures every 4 months by postcard or telephone. We were able to complete 99% of these contacts in surviving men. Reports of fracture were followed up by study staff to determine date, description of how the fracture occurred, and any trauma that resulted in the fracture. Fractures were adjudicated centrally by physician review of medical records and x-ray reports. Unconfirmed fractures were not considered in the analyses, nor were pathologic fractures. Excessive trauma was determined by the physician adjudicators; generally, moderate or severe trauma other than a fall (such as a motor vehicle accident) or a fall from more than standing height were considered excessive trauma and were excluded from this analysis (46 for the non-spine fracture outcome, 3 for the hip fracture outcome, 5 for the wrist fracture outcome, and 16 for the rib fracture outcome). Men whose fracture had not yet been adjudicated for excessive trauma status were also excluded from the analysis (33 for the non-spine fracture outcome, 1 for the hip fracture outcome, 3 for the wrist fracture outcome, and 13 for the rib fracture outcome). In addition, fractures that occurred near prostheses or other hardware were excluded from the analyses (5

for the non-spine fracture outcome and 2 for the hip fracture outcome). Hence, 5,449 men were included in the non-spine fracture analyses, 5,527 men were included in the hip fracture analyses, 5,525 men were included in the wrist fracture analyses, and 5,504 men were include in the rib fracture analyses. All confirmed fractures occurring after the baseline examination and before February 7, 2007 were included in these analyses. Average follow-up was 5.1 ± 1.2 years for any non-spine fracture and 5.2 ± 1.1 years for hip, wrist, and rib fractures.

Covariate Measurements

At baseline, participants completed a questionnaire and were interviewed about age, race, self-reported health, falls during the previous year, and smoking status. A selected medical history was obtained, including a history of physician diagnosis of diabetes, hyperthyroidism, hypertension, chronic obstructive pulmonary disease, cardiovascular disease (stroke, myocardial infarction, angina, congestive heart failure), osteoporosis, and cancer. Participants were asked to bring with them to the clinic current prescription medications used daily or almost daily for at least the past month for verification of use. Some medications that may influence risk of fracture were considered potential covariates for analysis: diuretics (loop, thiazide, or potassium-sparing), beta-blockers, oral glucocorticoids, and thyroid agonists. Participants were considered users of these medications if they were taking an ingredient that was categorized as such by IDIS. Daily dietary vitamin K intake (μg) was assessed with the Block 98 semi-quantitative food frequency questionnaire (FFQ) (Block Dietary Data Systems, Berkeley, CA). The Block 98 FFQ was specifically modified for MrOS to capture the most important sources of calcium and vitamin D, and other nutrients associated with osteoporosis, in older men in the US. The nutrient composition was calculated using the USDA Database for Standard Reference, Version 12 and the 1994-1996 Continuing Survey of Food Intake in Individuals (CSFII) database.

Statistical Analysis

Chi-square tests of homogeneity and t-tests were used to compare the baseline characteristics of men who were taking warfarin at baseline with men who were not.

To examine the adjusted association between warfarin use and baseline BMD, the average BMD and its 95% confidence interval (CI) were calculated for warfarin users and non-users using the least squared means procedure. In addition, the relationship between warfarin use and baseline BMD was analyzed using linear regression models, with results presented as beta coefficients (difference in mean BMD between warfarin users and non-users) and 95% CI's. Least squared means models and linear regression models were used to analyze the association between baseline warfarin use and subsequent rate of change in total hip BMD among the men included in the longitudinal analyses. Adjusted Cox proportional hazards models were used to analyze the association between baseline warfarin use and subsequent risk of non-spine fracture, hip fracture, wrist fracture, and rib fracture, with results presented as hazard ratios and 95% CI.

Baseline characteristics related to warfarin usage at $p \leq 0.05$ were considered potential confounders of the association between warfarin use and BMD, rate of hip bone loss, and fracture risk and were included in multivariate models. Models were adjusted for age, race (categorized as whites, blacks, and others), clinic site, hypertension, cardiovascular disease, at least two falls in the past year, self-reported health status (categorized as excellent/good and fair/poor/very poor), diuretic medication use, and beta-blocker medication use.

Several additional analyses were performed. First, to determine if excluding the 118 men who were taking osteoporosis medications at baseline affected our findings, we repeated our analyses to include these men. To determine if vitamin K intake confounded the association

between warfarin use and the outcomes, we added dietary vitamin K intake to the models. We also tested whether dietary vitamin K intake modified the effect of warfarin use on the outcomes by testing the significance of the interaction between dietary vitamin K intake and warfarin use in the models. Finally, because exclusion of fractures resulting from excessive trauma has been reported to underestimate the contribution of osteoporosis to fractures in women, we repeated our analyses to include all fractures regardless of trauma level [22].

All significance levels reported were two-sided, and all analyses were conducted using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Characteristics of the study population

At baseline, the average age of the participants was 73.6 ± 5.9 years, and 321 men (5.8%) were taking warfarin. Characteristics of the 5,533 men according to warfarin use are shown in Table 1. Compared to non-users, warfarin users were older, a higher percentage were Caucasian, they were more likely to have suffered at least 2 falls in the year before baseline, and they were more likely to report poorer health. In addition, a higher percentage of warfarin users reported a history of hypertension and cardiovascular disease, and they were more likely to use diuretic and beta-blocker medications. There were no significant differences between warfarin users and non-users with regard to single assessment of oral glucocorticoid use, thyroid agonist use, smoking status or history of diabetes, hyperthyroidism, COPD, osteoporosis or cancer.

Baseline warfarin use and baseline BMD

At baseline, warfarin users and non-users had similar age-site-adjusted BMD of the total hip (0.966 ± 0.008 (users) vs. 0.959 ± 0.002 (nonusers) g/cm^2, p=0.37) and the total spine (1.079 ± 0.010 vs. 1.074 ± 0.003 g/cm^2, p=0.64). These associations were attenuated after multivariate adjustment (Table 2). Results were similar when femoral neck BMD was substituted for total hip BMD in the analyses (data not shown).

Baseline warfarin use and subsequent hip bone loss

Among the 2,833 men who had BMD measurements at both visits, warfarin users (n=150) had similar age-site-adjusted bone loss at the total hip (−0.509 ± 0.082 vs. −0.421 ± 0.019 %/yr, p=0.29) compared to nonusers (n=2,683). The association weakened slightly after multivariate adjustment (data not shown). Results were similar when bone loss at the femoral neck was substituted for bone loss at the total hip in the analyses (data not shown).

Baseline warfarin use and subsequent risk of fracture

During an average follow-up of 5.1 years, 306 (5.6%) men experienced at least one non-spine fracture, including 68 (1.2%) men who suffered a hip fracture, 38 (0.7%) who suffered a wrist fracture, and 64 (1.2%) who suffered a rib fracture. A higher percentage of warfarin users experienced fractures during follow-up than non-users, but these differences were not significant (Table 3). Compared to non-users, warfarin users did not have an increased multivariate-adjusted risk of non-spine fractures, hip fractures, wrist fractures, or rib fractures.

Additional Analyses

We repeated our analyses including the 118 men who were taking osteoporosis medications at baseline, but the results did not change (data not shown).

Results were similar after further adjustment for dietary vitamin K intake. There was no evidence of an interaction between dietary vitamin K intake and warfarin use for the BMD

outcomes or for the prediction of bone loss or subsequent risk of fracture (all interaction p-values>0.10).

Including traumatic fractures and fractures occurring near prostheses did not alter our results (data not shown).

DISCUSSION

In this cohort of community-dwelling older men, we found no association between a single assessment of current warfarin use and bone mass (total hip or total spine), rates of hip bone loss, or risk of non-spine fractures. These results were not altered by including men who took osteoporosis medications at baseline or by including excessive traumatic fractures, nor did the results differ by level of dietary vitamin K intake. Since warfarins inhibit carboxylaton of osteocalcin, we had hypothesized that current warfarin users would have lower bone mass, accelerated bone loss and increased fracture risk.

Our results were consistent with some but not all previous observational studies. In a meta-analysis of the effect of anti-coagulants on bone mineral density, Caraballo et al [13] did not find statistically significant differences for bone mass measured at the distal radius, lumbar spine, femoral neck or femoral trochanter, but did find a difference for bone mass measured at the ultradistal radius, based on 2 studies, one of men and one of women. We did not examine bone mass at the wrist, but there is no obvious reason why warfarin would preferentially affect the ultradistal radius.

In studies that looked at changes in bone mineral density, Piro et al [23] reported no change at the distal radius after 4 years in the 17 men and women studied, but another study by Resch et al [24] reported a significant decrease in BMD at the distal radius in 35 men and 43 women. Both studies are limited by the small sample size. Jamal and colleagues [18] looked at changes in BMD at the hip and found no differences between older women who had taken warfarin (n=149) and those who had not (n=6052). The findings of Jamal et al were limited to women, but were consistent with our findings.

Several studies have examined the association between warfarin use and fractures; two studies included only women [14,18] and three studies included both men and women [15-17]. Most studies have reported no increased risk of hip fracture [14-18] or wrist fracture [14,16,17] associated with warfarin or other anti-coagulant use, which is consistent with the results of the present study. Two studies did report an association with vertebral fractures and rib fractures [14,17]. In the study by Caraballo et al [14], this association was only studied in women. For vertebral fractures, the increased risk in fracture with warfarin use was seen regardless of duration of warfarin use. For rib fractures, the assocation was only observed in women that had exposure to long-term use (at least 12 months) of warfarin. In the study by Gage et al [17], this association was seen in both men and women, but these results were not stratified by gender. Increased risk in vertebral fractures was only observed in the elderly that had exposure to long term use (at least 12 months) of warfarin and increased risk in rib fracture was observed regardless of duration of warfarin use. Contrary to these two studies, we found no evidence that warfarin use was associated with an increased risk of rib fracture. Our study did not stratify by duration of warfarin use nor did we examine the association with vertebral fractures.

It should be noted that while we did not find significant differences in incident fracture risk between warfarin users and nonusers, the point estimates for each group differed by a fair amount. For example, compared to nonusers, warfarin users experienced 27% more non-spine fractures, had a 16% higher age-adjusted incidence of non-spine fractures, and had a 6% multivariate-adjusted increased risk of non-spine fractures. These differences were even more pronounced for the hip and wrist fracture outcomes (adjusted HR 1.15 [95% CI, 0.51 to 2.61]

for hip fractures and HR 1.55 [95% CI, 0.46 to 5.26] for wrist fractures); we may have lacked the power to detect significant associations due to the small number of these particular fractures (68 hip fractures and 38 wrist fractures).

Our study had several limitations. Regarding warfarin use, we knew only whether or not the subjects were taking warfarin at baseline; we did not have specific information such as duration, dosage, magnitude of warfarin effects on blood clotting, compliance, indication for use, achievement of therapeutic outcomes, or prior use of warfarin. Without knowledge of prior use of warfarin, some persons classified as non-users may have had a history of warfarin use, thus potentially biasing the results toward the null. Our results apply to primarily Caucasian older men and may not apply to other populations. We did not study BMD changes at other skeletal sites. Despite these limitations, our study had many strengths, including the large size, community-based sampling, high rates of follow-up, and careful confirmation of fracture outcomes. Medication use was validated in the clinic and accurately recorded on the electronic Medication Inventory Form, which minimized the potential for misclassification based on self-report. Lastly, this study was able to simultaneously examine both fractures and BMD outcomes (cross-sectional BMD as well as change in BMD) in men, whereas other studies only looked at one or the other.

In summary, in this large cohort of elderly community-dwelling men, we found no association between current warfarin use and bone mass, bone loss or fracture risk. Although warfarin use was based upon a single assessment, our findings suggest that current warfarin use in older men does not appear to have clinically important effects on the skeleton.

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Table 1

Baseline Characteristics of the Participants by Current Warfarin Use

Variable	Warfarin Nonusers (n=5212)	Warfarin Users (n=321)	*P*-value
Age, mean ± SD, years	73.5 ± 5.8	76.0 ± 6.2	<0.001
Race			0.05
White, %	88.9	92.8	
African American, %	4.3	3.7	
Other, %	6.8	3.4	
Good/Excellent Health (Self-Reported), %	86.6	72.0	<0.001
Current Smoker, %	3.5	2.5	0.34
History of Cardiovascular Disease*, %	25.2	60.4	<0.001
History of Hypertension, %	43.5	49.8	0.03
History of Diabetes, %	10.7	14.0	0.06
History of Hyperthyroidism, %	1.6	2.8	0.10
History of COPD, %	10.5	12.8	0.20
History of Osteoporosis, %	2.1	2.2	0.88
History of Cancer, %	28.9	28.7	0.93
2+ Falls in the Past Year, %	8.9	12.5	0.03
Diuretic Use†, %	17.8	40.8	<0.001
Beta-Blocker Use‡, %	18.0	32.4	<0.001
Oral Corticosteroid Use	1.8	2.8	0.19
Thyroid Agonist Use	6.7	8.1	0.35

*History of one or more selected medical conditions including stroke, myocardial infarction, angina, and congestive heart failure.

†Participants were considered users of diuretic medication(s) if they were taking thiazide, loop, or potassium-sparing diuretics.

‡Participants were considered users of beta-blocker medication(s) if they were taking beta- adrenergic blockers for non-ophthalmic reasons.

Table 2

Association between Baseline Warfarin Use and Baseline Bone Mineral Density (BMD)

	Age and Clinical Site-Adjusted				Multivariate Adjusted*			
Skeletal Site	**Warfarin Nonusers (mean ± SE)**	**Warfarin Users (mean ± SE)**	**Mean Difference† (95% CI)**	***P*-value**	**Warfarin Nonusers (mean ± SE)**	**Warfarin Users (mean ± SE)**	**Mean Difference† (95% CI)**	***P*-value**
Total Hip BMD (g/cm^2)	0.959 ± 0.002	0.966 ± 0.008	0.007 (−0.008 to 0.023)	0.37	0.959 ± 0.002	0.963 ± 0.008	0.004 (−0.012 to 0.019)	0.64
Total Spine BMD (g/cm2)	1.074 ± 0.003	1.079 ± 0.010	0.005 (−0.016 to 0.026)	0.64	1.074 ± 0.003	1.073 ± 0.011	0.001 (−0.023 to 0.020)	0.90

*Adjusted for age, race, site, hypertension, cardiovascular disease, 2 or more falls in the past year, self-reported health, and use of diuretics and beta-blockers.

†Negative differences indicate lower BMD in Warfarin users group.

Table 3

Current Warfarin Use and Subsequent Risk of Fractures

Type of Fracture	Warfarin Nonusers		Warfarin Users		
	% with fracture (n/N)*	Age-adj. Rate (95% CI)†	% with fracture (n/N)*	Age-adj. Rate (95% CI)†	HR (95% CI)‡
Any Non-spine	5.5 (284/5133)	10.9 (9.6, 12.2)	7.0 (22/316)	12.6 (7.1, 18.1)	1.06 (0.68, 1.65)
Hip	1.2 (61/5206)	2.3 (1.7, 2.9)	2.2 (7/321)	3.5 (0.8, 6.2)	1.15 (0.51, 2.61)
Wrist	0.7 (35/5205)	1.3 (0.9, 1.7)	0.9 (3/320)	2.3 (0.0, 4.9)	1.55 (0.46, 5.26)
Rib	1.2 (60/5185)	2.2 (1.7, 2.8)	1.3 (4/319)	1.8 (0.0, 3.6)	1.06 (0.38, 2.99)

*Chi-square *p*-value > 0.05.

†per 1000 person-years.

‡Hazard ratios adjusted for age, race, site, hypertension, cardiovascular disease, 2 or more falls in the past year, self-reported health, and use of diuretics and beta-blockers.