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Osteoporotic Fractures in Patients With Atrial Fibrillation Treated With Conventional Versus Direct Anticoagulants

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ABSTRACT

BACKGROUND Elderly patients in long-term treatment with vitamin K antagonists (VKAs) are at high risk of osteoporotic fractures compared with the background population. It has been speculated that the choice of oral anticoagulant (OAC) may affect the risk of osteoporotic fractures.

OBJECTIVES The risk of osteoporotic fractures was evaluated among patients with atrial fibrillation treated with VKA or direct oral anticoagulants (DOACs).

METHODS Patients were identified using the Danish national registries. Patients were included only if they had no prior use of osteoporosis medication and they had undergone 180 days of OAC treatment. Outcomes were hip fracture, major osteoporotic fracture, any fracture, initiation of osteoporosis medication, and a combined endpoint.

RESULTS Overall, 37,350 patients were included. The standardized absolute 2-year risk of any fracture was low among DOAC-treated patients (3.1%; 95% CI: 2.9% to 3.3%) and among VKA-treated patients (3.8%; 95% CI: 3.4% to 4.2%). DOAC was associated with a significantly lower relative risk of any fracture (hazard ratio [HR]: 0.85; 95% CI: 0.74 to 0.97), major osteoporotic fractures (HR: 0.85; 95% CI: 0.72 to 0.99), and initiating osteoporotic medication (HR: 0.82; 95% CI: 0.71 to 0.95). A combined endpoint showed that patients treated with DOAC had a significantly lower relative risk of experiencing any fracture or initiating osteoporosis medication (HR: 0.84; 95% CI: 0.76 to 0.93).

CONCLUSIONS In a nationwide population, the absolute risk of osteoporotic fractures was low among patients with atrial fibrillation on OAC, but DOAC was associated with a significantly lower risk of osteoporotic fractures compared with VKA. (J Am Coll Cardiol 2019;74:2150–8) © 2019 by the American College of Cardiology Foundation.

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Osteoporotic fractures are associated with high mortality and reduced quality of life in an elderly population (1,2). Several studies report an increased risk of fractures among patients treated with oral anticoagulants (OACs) (3–5). Most patients with nonvalvular atrial fibrillation (AF) are treated with OAC for stroke prevention. The vitamin K antagonists (VKAs) were the only real option for thromboprophylaxis in AF patients for decades; however, in recent years, direct oral anticoagulants (DOACs) have emerged as alternatives. Warfarin is a VKA, and by regulating vitamin K, warfarin inhibits the γ-carboxylation of several proteins, including coagulation factors II, VII, IX, and X (6). Studies suggest a link between warfarin and undercarboxylated osteocalcin, which is associated with low bone mineral density (BMD) (7–9). These results correlate with findings that propose a connection between warfarin and an increased risk of osteoporotic fractures (3–5,10,11). Furthermore, patients who are treated with VKAs are subjected to several dietary restrictions that may contribute to a low BMD. DOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban, have proven noninferior, and in some cases superior, to VKAs with regard to risk of stroke/systemic embolism and major bleeding (12–14). DOACs have no impact on the synthesis of osteocalcin. However, only sparse research has been performed to clarify the difference between VKAs and DOACs regarding the risk of osteoporotic fractures. In recent years, the incidence of AF and AF-associated mortality has increased (15). Therefore, it is critically essential to clarify any factors that might affect the mortality and quality of life of these patients. This nationwide cohort study aimed to investigate the risk of osteoporotic fractures among patients with AF who are users of DOAC or VKA treatment.

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METHODS

DATA SOURCES. The key data source for this study was the Danish National Patient Register, which keeps records of all hospital admissions and contacts in Denmark since 1978 (16). The National Prescription Registry keeps records of all filled prescriptions (17). The Danish Civil Registration System keeps information regarding civil status, birth date, sex, and date of death (18).

The data from these registries were linked using the personal identification number, which all Danish citizens are registered by.

STUDY DESIGN AND POPULATION. The study period for this retrospective study was between January 1, 2013, and June 30, 2017. We identified all Danish patients with AF who were first-time users of either VKA, dabigatran, rivaroxaban, apixaban, or edoxaban. To ensure only patients with nonvalvular AF participated in the study, patients with mechanical valves and patients diagnosed with mitral stenosis were excluded from the study. In addition, we excluded patients with other indications for OAC, such as hip or knee arthroplasty within 5 weeks before initiation of anticoagulation, or patients with pulmonary embolism or deep vein thrombosis within 6 months from the initiation of OAC. Because the effect of VKA on bone metabolism is likely to accumulate and be most pronounced over time, we included only patients with at least 180 days of OAC treatment (i.e., the inclusion day and baseline were 180 days after the day of OAC initiation). Patients who died, shifted, or discontinued OAC treatment during the first 180 days were excluded, as were patients who had received osteoporotic medication before inclusion. Patients under the age of 30 years old, and patients >100 years old were excluded from the study.

ABBREVIATIONS AND ACRONYMS

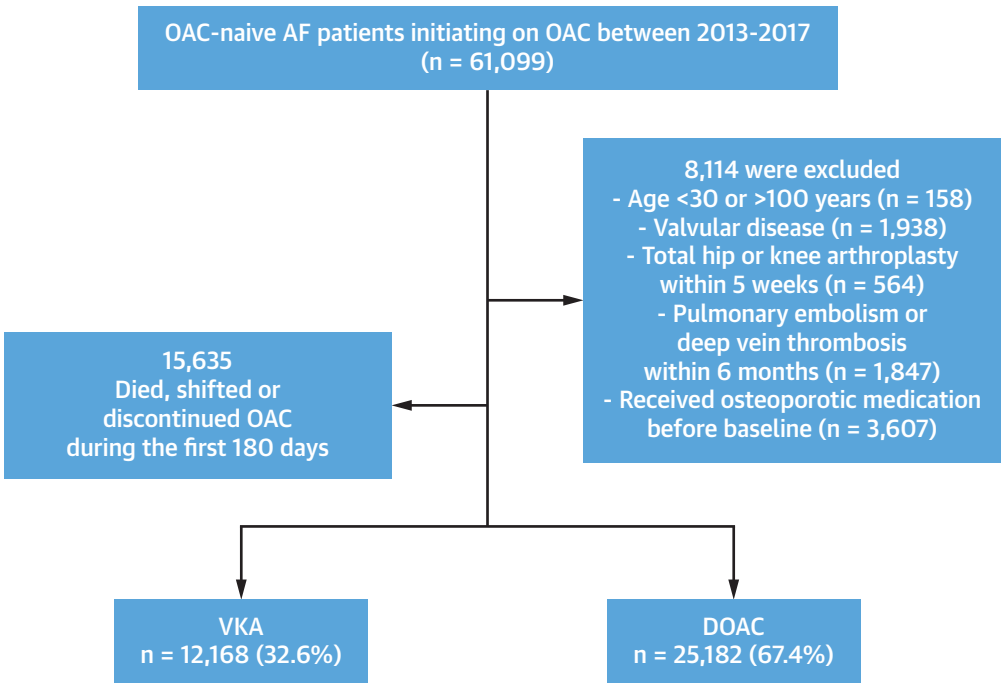
AF = atrial fibrillation
BMD = bone mineral density
CI = confidence interval
DOAC = direct oral anticoagulant
NNT = number needed to treat
OAC = oral anticoagulant
VKA = vitamin K antagonist

COMORBIDITY AND COMEDICATION. We identified concomitant medications from prescriptions filled 180 days before the inclusion day. Baseline comorbidities were identified using discharge diagnoses during the past 10 years before the inclusion day (Online Table 1).

OUTCOMES AND FOLLOW-UP. This study investigated 5 outcomes: 1) any fracture; 2) major osteoporotic fracture; 3) hip fracture; 4) initiation of osteoporosis medication; and 5) a combined endpoint of any fracture or initiation of osteoporosis medication, whichever came first. Major osteoporotic fracture was defined as a hospital admission with a diagnosis code for a fracture of the hip, forearm, vertebra, or proximal humerus. Any fracture was defined with the combined codes from hip fracture and major osteoporotic fracture, adding fractures of the femur, patella, tibia, fibula, ribs, pelvis, clavicle, and scapula (Online Table 1). The follow-up of patients started 180 days after they filled their first prescription for VKA or DOAC and lasted 2 years forth or until whichever of the following came first: outcome, emigration, death, or June 30, 2017.

STATISTICAL ANALYSES. The characteristics of the population were handled as count and percentage for categorical variables and medians and interquartile ranges for continuous variables. Cox regression analyses were used to calculate hazard ratios (HRs). We adjusted for age (in 5-year intervals), chronic obstructive pulmonary disease, previous syncope,

FIGURE 1 Selection of the Study Population



Graphic explanation of the exclusion and inclusion of patients in the study. AF = atrial fibrillation; DOAC = direct oral anticoagulant; OAC = oral anticoagulation, VKA = vitamin K antagonist.

hormone replacement therapy, heart failure diagnosis, stroke, diabetes, liver disease, inflammatory polyarthritis, antidepressant drugs, glucocorticoid medication, statin, sex, and alcohol abuse. The HR for the outcomes was calculated with 95% confidence intervals (CIs), and the VKA group was used as reference.

The Aalen-Johansen estimator was used for estimating cumulative incidences. Death from all causes was considered competing risk for the events under investigation. Standardized absolute risk according to treatment was computed using the G-formula, and a multiple covariate-adjusted Cox regression model for each outcome was combined with a multiple covariate-adjusted Cox regression model for all-cause death; 95% CIs were computed using percentile bootstrap based on 2,000 replications. The level of significance was set at 5%. Age-standardized incidence rates were calculated using person-years in age groups and direct standardization, and number needed to treat (NNT) was calculated from the standardized absolute risk difference. We conducted a sensitivity analysis in which patients were followed from the day they filled their first prescription of VKA or DOAC (i.e., the follow-up period began at day 1 instead of day 180). Furthermore, we tested the effect of initiation of osteoporotic medication after baseline in time-dependent Cox models, and we tested interaction of initiation of osteoporotic medication after baseline with effect of VKA versus DOAC. Finally, we performed subgroup analyses of VKA versus DOAC for all adjustment variables and tested interactions in the fully adjusted models.

SAS version 9.4 for Windows (SAS Institute, Cary, NC) and RStudio version 3.3.0 for Windows (R Foundation for Statistical Computing, Vienna, Austria) were used for the programming and statistical analysis of the data.

ETHICS. Studies conducted on data from the national registries do not require ethical approval in Denmark, and patients were anonymized in this study to ensure that no personal identification was possible. The study was approved by the Danish Data Protection Agency (ref no: 2007-58-0015/GEH-2014-013, I-Suite no: 02731).

RESULTS

INCLUSION AND FOLLOW-UP. As shown in Figure 1, 61,099 patients with AF initiating OAC were initially

identified, and a total of 23,749 patients were excluded from the study population. Among these, 158 patients were age >100 years or <30 years, 1,938 had a valvular disease, 564 received total hip or knee arthroplasty within 5 weeks before the baseline, 1,847 had a pulmonary embolism or deep vein thrombosis within 6 months before the study start, and 3,607 patients received osteoporosis medication before the baseline. Furthermore, 15,635 persons died, shifted, or discontinued OAC treatment during the first 180 days, leaving 37,350 OAC-treated patients who were included in the final study population. The included patients were categorized into 2 groups: VKA containing 12,168 (32.6%) treated patients and DOAC containing 25,182 (67.4%) patients.

STUDY POPULATION CHARACTERISTICS. In Table 1, the characteristics of the 2 exposure groups are shown. The median age was significantly higher in the DOAC group than in the VKA group, and 44.1% of the patients in the DOAC group were women, whereas 38.2% of the patients receiving VKAs were women. The fraction of patients who had experienced a previous stroke was highest in the DOAC group, and a diagnosis for alcohol abuse was likewise more common in the DOAC group than in the VKA group. The DOAC group comprised more patients who received hormone replacement therapy compared with the VKA group, and the fraction of patients who had experienced a prior fracture was higher in the DOAC group (4.1%) than in the VKA group (2.9%).

RISK OF OSTEOPOROTIC FRACTURES. The 2-year absolute standardized risk of major osteoporotic fractures was 2.29% (95% CI: 2.02% to 2.49%) for DOAC-treated patients and 2.82% (95% CI: 2.46% to 3.19%) for VKA-treated patients (Table 2). DOAC was associated with a 0.53% (95% CI: 0.94% to 0.13%) standardized absolute risk reduction of experiencing a major osteoporotic fracture compared with VKA (Table 2). The adjusted relative risk of major osteoporotic fracture was significantly lower among patients treated with DOAC compared with patients treated with VKA (HR: 0.85; 95% CI: 0.72 to 0.99) (Figure 2).

The absolute standardized 2-year risk of any fracture was 3.09% (95% CI: 2.85% to 3.33%) for DOAC-treated patients with AF and 3.77% (95% CI: 3.37% to 4.19%) for VKA-treated patients. The analysis showed that DOAC treatment was associated with a 0.68% (95% CI: 1.17% to 0.21%) absolute risk reduction of any fractures compared with VKA. Patients with AF in DOAC treatment had a significantly lower relative risk of any fracture than patients in VKA treatment (HR: 0.85; 95% CI: 0.74 to 0.97) (Figure 2).

TABLE 1 Baseline Characteristics of the Study Population

	DOAC (n = 25,182)	VKA (n = 12,168)	p Value
Age, yrs	73 (67–81)	72 (65–79)	<0.001
Male	14,081 (55.9)	7,515 (61.8)	<0.001
Comorbidities			
Hormone replacement therapy	1,754 (7.0)	738 (6.1)	0.001
Prior fracture	1,038 (4.1)	347 (2.9)	<0.001
Syncope	1,765 (7.0)	804 (6.6)	0.157
Inflammatory polyarthritis	433 (1.7)	199 (1.6)	0.584
Alcohol abuse	813 (3.2)	292 (2.4)	<0.001
COPD	2,468 (9.8)	1,114 (9.2)	0.049
Prior stroke	4,420 (17.6)	1,503 (12.4)	<0.001
Prior bleeding	3,100 (12.3)	1,547 (12.7)	0.276
Heart failure diagnosis	4,367 (17.3)	2,235 (18.4)	0.015
Vascular disease	5,487 (21.8)	3,229 (26.5)	<0.001
Deep vein thrombosis	206 (0.8)	108 (0.9)	0.529
Diabetes mellitus	3,480 (13.8)	1,713 (14.1)	0.509
Liver disease	302 (1.2)	171 (1.4)	0.105
Concomitant medication			
Aspirin	2,365 (9.4)	1,947 (16.0)	<0.001
Statin	10,796 (42.9)	5,326 (43.8)	0.103
Beta-blocker	18,920 (75.1)	8,960 (73.6)	0.002
RASis	12,815 (50.9)	6,150 (50.5)	0.537
NSAIDs	2,199 (8.7)	927 (7.6)	<0.001
Antidepressants	3,383 (13.4)	1,304 (10.7)	<0.001
Glucocorticoids	1,522 (6.0)	763 (6.3)	0.405

Values are median (interquartile range) or n (%).

COPD = chronic obstructive pulmonary disease; DOAC = direct oral anticoagulant; NSAIDs = nonsteroidal anti-inflammatory drugs; RASis = renin-angiotensin system inhibitors; VKA = vitamin K antagonist.

DOAC-treated patients were found to have a 2.44% (95% CI: 2.22% to 2.66%) absolute standardized 2-year risk of starting osteoporosis medication, whereas VKA-treated patients had a 2-year absolute standardized risk of 3.14% (95% CI: 2.79% to 3.51%) (Figure 3). DOAC was associated with a 0.71% (95% CI: 1.12% to 0.30%) absolute risk reduction of initiating osteoporosis medication than VKA-treated patients with AF (Table 2). The adjusted relative risk of initiating osteoporosis medication was significantly lower among DOAC-treated patients (HR: 0.82; 95% CI: 0.71 to 0.95) (Figure 2). When considering the outcomes as a combined endpoint of any fractures and initiation of osteoporotic medication, DOAC-treated patients had an absolute standardized 2-year risk of 5.21% (95% CI: 4.90% to 5.52%), and VKA-treated patients had an absolute standardized 2-year risk of 6.43% (95% CI: 5.89% to 6.94%) (Figure 3).

DOAC treatment was associated with a 1.22% (95% CI: 1.82% to 0.64%) absolute risk reduction of the combined endpoint (Table 2) and was found to have a significantly lower adjusted relative risk than

TABLE 2 Age-Standardized Incidence Rates and Standardized Absolute Risks of Any Fracture, Major Osteoporotic Fracture, Hip Fracture, Initiation of Osteoporotic Medication, and the Combined Endpoint During the First 2 Years After Inclusion Among Anticoagulated Atrial Fibrillation Patients

	No. of Events	Age-Standardized Incidence Rate per 1,000 Patients per Patient-Year (95% CI)	Standardized Absolute 2-Year Risk (95% CI)	Standardized Absolute 2-Year Risk Difference (95% CI)
Hip fracture				
VKA	134	7.26 (6.0 to 8.78)	1.65% (1.38% to 1.92%)	Reference
DOAC	280	7.39 (6.52 to 8.37)	1.40% (1.24% to 1.56%)	−0.25% (−0.58% to 0.06%)
Major osteoporotic fracture				
VKA	242	12.88 (11.23 to 14.78)	2.82% (2.46% to 3.19%)	Reference
DOAC	453	12.22 (11.09 to 13.46)	2.29% (2.02% to 2.49%)	−0.53% (−0.94% to −0.13%)
Any fracture				
VKA	329	17.83 (15.87 to 20.04)	3.77% (3.37% to 4.19%)	Reference
DOAC	606	16.85 (15.51 to 18.30)	3.09% (2.85% to 3.33%)	−0.68% (−1.17% to −0.21%)
Initiation of osteoporotic medication				
VKA	302	14.41 (12.75 to 16.29)	3.14% (2.79% to 3.51%)	Reference
DOAC	479	12.82 (11.64 to 14.11)	2.44% (2.22% to 2.66%)	−0.71% (−1.12% to −0.30%)
Combined endpoint				
VKA	592	32.69 (30.07 to 35.56)	6.43% (5.89% to 6.94%)	Reference
DOAC	1,027	29.99 (28.18 to 31.92)	5.21% (4.90% to 5.52%)	−1.22% (−1.82% to −0.64%)

Abbreviations as in Table 1.

VKA treatment (HR: 0.84; 95% CI: 0.76 to 0.93) (Figure 2).

Taken together, this is equivalent to 6.8 fewer osteoporotic fractures and 7.1 fewer osteoporosis treatment initiations for each 1,000 persons treated with DOAC as opposed to VKA for 2 years, corresponding to an NNT of 147 and 141, respectively. The combined endpoint was associated with an NNT of 82.

Additional analyses. Subgroup analysis was conducted to show the risk of any fracture (Online Figure 1) and the combined endpoint (Online Figure 2) in different subgroups of the study population. Patients with risk factors for osteoporotic fractures (e.g., patients diagnosed with cancer and patients in treatment with hormone replacement therapy) were generally more likely to experience a fracture if they were treated with VKA instead of DOAC.

Furthermore, we conducted a sensitivity analysis in which we included patients on the day they filled their first OAC prescription to investigate the risk of an osteoporotic event during the first 180 days of treatment. The results obtained in the sensitivity analysis were similar to the results presented in the primary investigation (Online Figure 3).

We also examined the number of fractures among patients who discontinued OAC treatment during the first 180 days. Among the 8,262 patients who discontinued OAC treatment during the first 180 days, 105 (1.3%) experienced any fracture during the same period, and 61 of these patients had initiated VKA, whereas 44 had initiated DOAC.

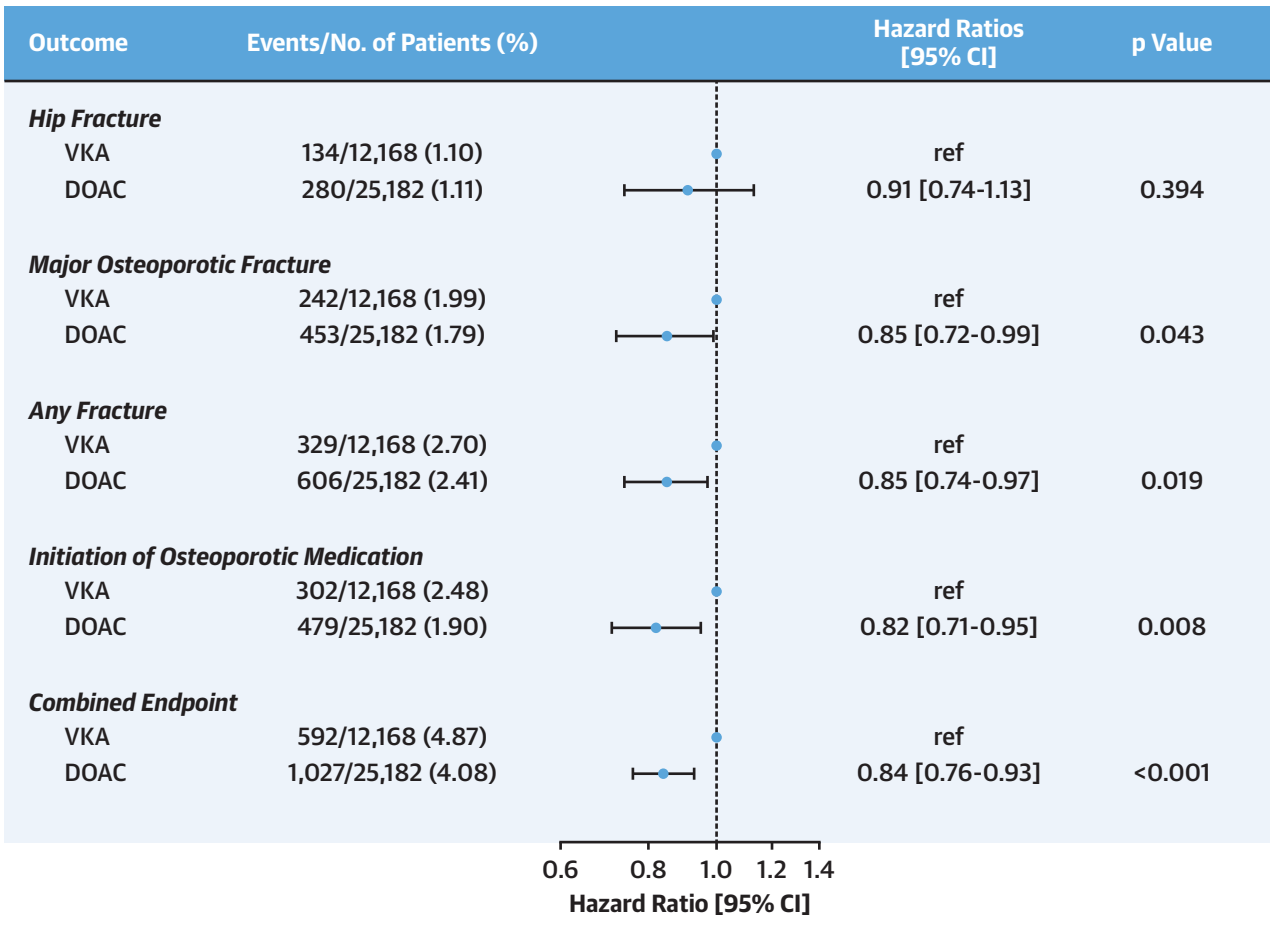
Analyses investigating the unadjusted risk of osteoporotic fractures and the risk of osteoporotic fractures adjusted only for age and sex were performed. The difference between VKA and DOAC regarding the risk of osteoporotic fractures was not present before adjustments and was nonsignificant after adjustment for only age and sex (Online Table 2), reflecting the higher burden of comorbidities associated to fractures in the DOAC group (**Table 1**). Online Figure 4 shows the unadjusted absolute risk of the 4 outcomes.

Furthermore, we conducted a sensitivity analysis in which we examined the risk of osteoporotic fractures with osteoporotic medication as a time-varying covariate (Online Table 3). Time-dependent osteoporotic medication was associated with a higher risk of fractures but had no statistically significant interaction with VKA versus DOAC. Moreover, adjustment for time-dependent osteoporotic medication had no influence on the estimates of VKA versus DOAC.

DISCUSSION

This nationwide cohort study included 37,350 OAC users with AF who were analyzed according to the risk of osteoporotic fractures. The main results showed that patients with AF treated with DOAC had a 15% lower relative risk of any fracture, a 15% lower relative risk of major osteoporotic fractures, and an 18% lower

FIGURE 2 Adjusted Relative 2-Year Risks



Adjusted hazard ratio of any fracture, major osteoporotic fracture, hip fracture, initiation of osteoporotic medication, and a combined endpoint among OAC-treated patients with atrial fibrillation. Hazard ratios were calculated using adjusted Cox regressions. ref = reference; other abbreviations as in Figure 1.

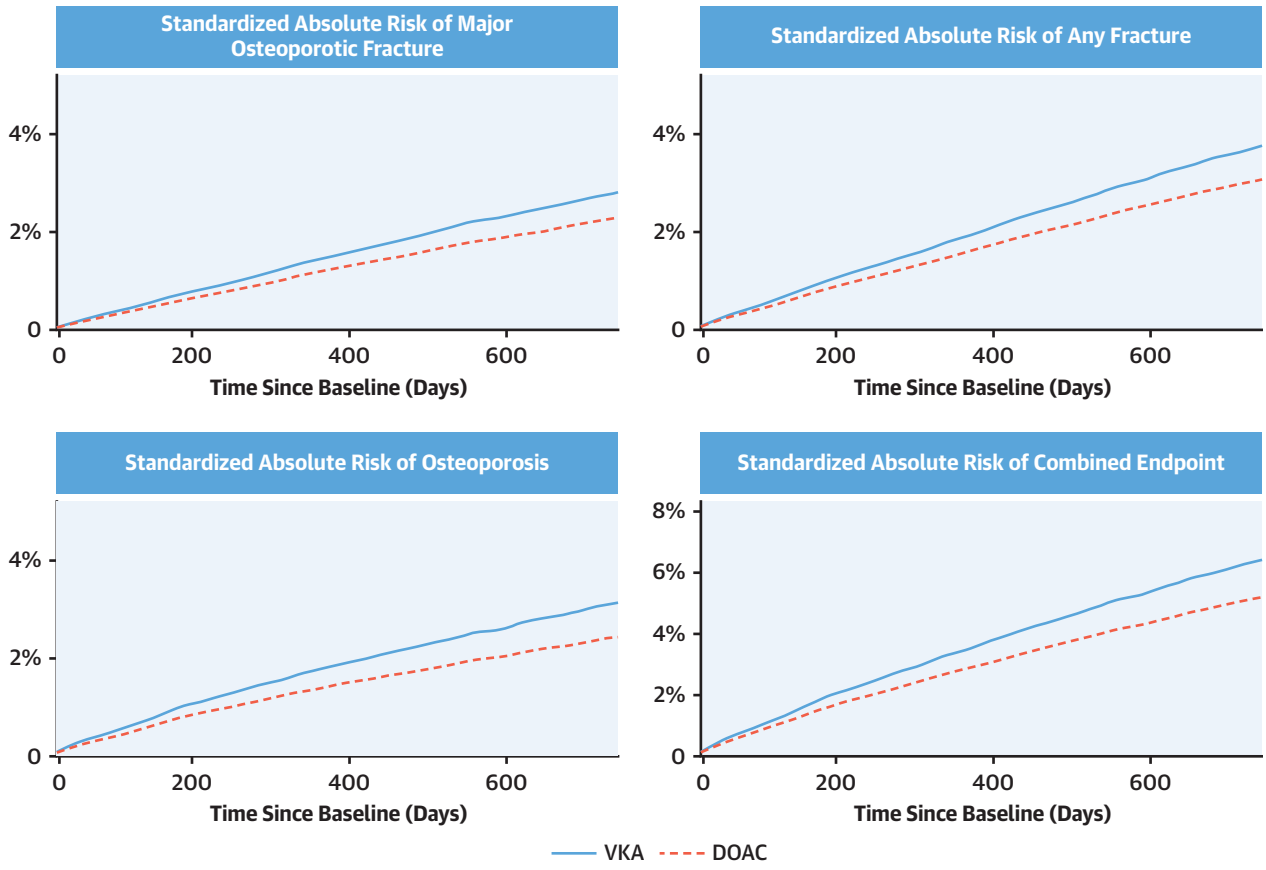
relative risk of initiating osteoporosis medication than patients treated with VKA (Central Illustration). When a combined endpoint was analyzed, the results showed that patients with AF treated with DOAC had a 16% lower relative risk of experiencing any fracture or initiating osteoporosis medication.

Some prior studies have been examining this subject; however, this study identified the largest population of OAC users and was conducted on nationwide data. This study was the first to consider a predominantly white population in terms of risk of osteoporotic fractures among patients with AF treated with DOACs and the first to include not only dabigatran but also rivaroxaban, apixaban, and edoxaban. A recent study by Lau et al. (19) found a significantly lower risk of osteoporotic fractures among Chinese patients treated with dabigatran compared with patients treated with warfarin (0.7 vs. 1.1 per 100 person-years). These results correlated with the findings of this study.

VKA users might have a greater risk of osteoporotic fractures because of VKA's interference with γ-carboxylation. VKA is an inhibitor of γ-carboxylation, and by regulating this reaction, VKA not only inhibits proteins in the coagulation cascade but also inhibits the γ-carboxylation of other proteins in the body, including osteocalcin. Osteocalcin is secreted by osteoblasts, and several studies show a link between warfarin and undercarboxylated osteocalcin, which is associated with low BMD (7–9).

There are no dietary restrictions with any of the DOACs, whereas the dietary restrictions associated with VKA treatment regarding several vegetables could contribute to a low intake of folic acid and an increased risk of hyperhomocysteinemia. Hyperhomocysteinemia is associated with a decrease

FIGURE 3 Standardized Absolute Risks



Standardized absolute 2-year risk of any fracture, major osteoporotic fracture, hip fracture, initiation of osteoporotic medication, and a combined endpoint among patients with atrial fibrillation according to treatment with VKA versus DOAC. G-formulas based on adjusted Cox regressions were used to calculate standardized absolute 2-year risks. Abbreviations as in Figure 1.

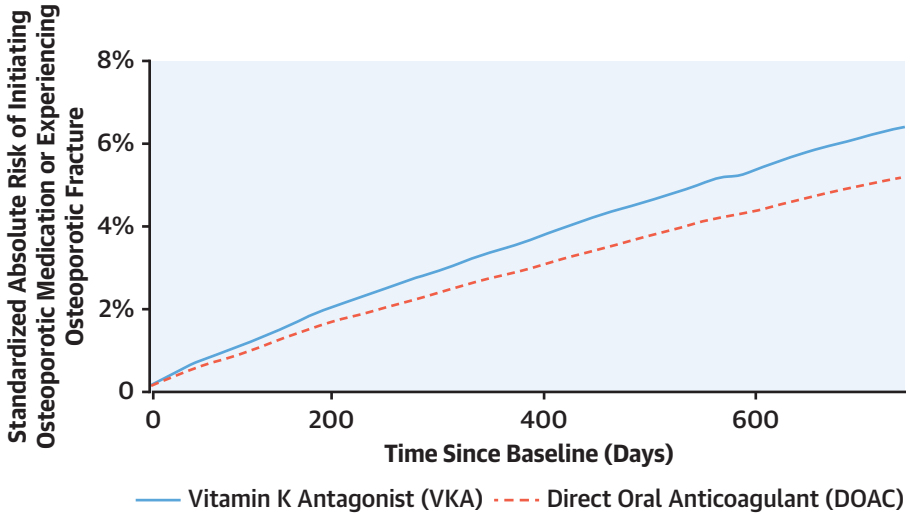
in osteoblast activity and an increase in osteoclast activity, thus reducing bone strength. Hyperhomocysteinemia is also found to increase the amount of matrix metalloproteinases, which is associated with degradation of extracellular bone matrix (20). These reasons are why VKA treatment and dietary restrictions could contribute to an increased risk of fractures.

The effects of VKA treatment on bone strength was investigated in a retrospective cohort study of elderly U.S. patients in which the risk of osteoporotic fractures was examined among patients in warfarin treatment and patients not in warfarin treatment (3). The study found an increased risk of osteoporotic fractures among male patients in long-term warfarin treatment compared with patients not treated with warfarin, thus supporting the theory of VKA as a bone strength reducing anticoagulant, and the results correlate with the findings of our study.

In our study, we included patients who had undergone 180 days of OAC treatment. This selection criterion was established in order to make certain that patients in our study had a significant exposure time to the studied OACs, independent of whether they discontinued the initial drug treatment after inclusion because the effects on bone metabolism are more likely to be measurable only after a period with treatment. In our sensitivity analysis, we examined the risk of osteoporotic fractures among patients without 180 days of initial treatment, and we found the same main results (Online Figure 3).

The results of our study not only support what other studies have suggested, but also more importantly they show that the risk reductions apply to nationwide data from a Western society and persist when all DOACs are analyzed and compared with VKA. Furthermore, the results show that patients at risk of osteoporosis or at risk of osteoporotic fractures

CENTRAL ILLUSTRATION **Standardized Absolute 2-Year Risk of Osteoporotic Fractures Among Atrial Fibrillation Patients**



	Standardized Absolute 2-Year Risk (95% CI)
Any Fracture	
VKA	3.77% (3.37% to 4.19%)
DOAC	3.09% (2.85% to 3.33%)
Initiation of Osteoporotic Medication	
VKA	3.14% (2.79% to 3.51%)
DOAC	2.44% (2.22% to 2.66%)

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Standardized, absolute 2-year risk of any fracture and initiation of osteoporotic medication among patients with atrial fibrillation according to treatment with VKA versus DOAC. G-formulas based on adjusted Cox regressions were used to calculate standardized absolute 2-year risks. CI = confidence interval; DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.

had a larger risk reduction from treatment with DOAC as opposed to treatment with VKA. The results of this study will aid to a more enlightened and safe use of OACs, which will benefit a fragile group of patients.

STUDY STRENGTHS AND LIMITATIONS. This study was performed on a nationwide population, and because of the welfare benefits of the Danish society, no selection bias regarding social status and no loss to follow-up occurred. The AF diagnosis is well validated (21), and the HRs were adjusted for variables known to have an impact on fractures and osteoporosis (i.e., chronic obstructive pulmonary disease, previous syncope, hormone replacement therapy, heart failure diagnosis, stroke, glucose-lowering medication, liver disease, osteoporosis medication, inflammatory polyarthritis, antidepressant drugs, glucocorticoid medication, statin medication, age, sex, and alcohol abuse).

The risk of residual confounding is always a potential limitation, and confounders might have persevered in this study because of unmeasured variables, (e.g., international normalized ratio, body mass index, hemoglobin, and renal function).

CONCLUSIONS

Among patients with nonvalvular AF, treatment with DOAC was associated with a significantly lower risk of

any fracture, major osteoporotic fractures, and initiation on osteoporosis medication compared with treatment with VKA. Because of a more favorable skeletal health profile, DOAC treatment could be preferred to VKA in patients with AF with strong risk factors for osteoporotic fractures.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with AF, the risk of osteoporotic fractures is lower in those treated with target-specific anticoagulants than with VKAs.

TRANSLATIONAL OUTLOOK: Studies with larger numbers of patients will be needed to compare rates of osteoporotic fractures with 1 target-specific oral anticoagulant versus another and to assess the effect of treatment adherence on this outcome.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.