REVIEWS

A Systematic Review and Meta-analysis of the Association Between Vitamin K Antagonist Use and Fracture

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BACKGROUND: Vitamin K antagonist (VKA) anticoagulant use is suspected to increase the risk of bone fracture through inhibition of vitamin K–dependent cofactors of bone formation, an effect not seen with non-vitamin K antagonist oral anticoagulants (NOACs). The purpose of our systematic review and meta-analysis is to investigate the association between VKA use and fracture.

METHODS: We searched PubMed, EMBASE, and Cochrane Library for studies analyzing fracture in adults using VKAs versus controls. Two authors independently reviewed articles. We assessed for risk of bias using the Newcastle-Ottawa Quality Assessment Scale and the Cochrane Risk of Bias Tool and calculated pooled effects using random effects models.

RESULTS: We included 23 articles (22 observational studies and 1 randomized controlled trial), studying 1,121,582 subjects. There was no increased odds of fracture in VKA users versus controls (pooled OR 1.01, 95% CI 0.89, 1.14) or in VKA users versus NOAC users (pooled OR 0.95, 95% CI 0.78, 1.15). Subjects using a VKA for 1 year or longer did not have increased odds of fracture (pooled OR 1.07, 95% CI 0.90, 1.27). Compared to controls, there was increased odds of fracture in women (pooled OR 1.11, 95% CI 1.02, 1.21) and older VKA users (≥ 65) (pooled OR 1.07, 95% CI 1.01, 1.14).

DISCUSSION: We found no increase in odds of fracture in VKA users versus controls or NOAC users. There was a small increase in odds of fracture among female and elderly VKA users, which may not be clinically important when accounting for other considerations in choosing an anticoagulant. Our findings suggest that, when anticoagulation is necessary, fracture risk should not be a major consideration in choice of an agent. Future studies directly comparing VKA to NOAC users and studies with longer duration of VKA use may be needed.

KEY WORDS: meta-analysis; osteoporosis; systematic reviews.

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BACKGROUND

Warfarin and other vitamin K antagonists (VKAs) inhibit the formation of vitamin K–dependent clotting factors. However, vitamin K is also a co-factor in bone formation.[1] Osteocalcin, the principal non-collagenous protein in bone, is incorporated into bone via vitamin K–dependent gamma-carboxylation. VKA use decreases bone osteocalcin levels, which decreases bone hardness.[2–4] Increased blood levels of undercarboxylated osteocalcin are associated with decreased bone mineral quality,[5] but an association between VKA use and decreased bone mineral density has not been found,[6, 7] suggesting that agents can affect bone structure without affecting bone density.

Whether vitamin K antagonism leads to an increase in bone fracture risk is controversial, as various studies have yielded differing results. One meta-analysis found an increased risk of fracture associated with VKA use in both cross-sectional and longitudinal studies. However, in sub-analysis of longitudinal studies which matched VKA users to controls, the association became insignificant. Analysis of risk ratios across study designs was not performed, which limited the power of the findings.

In recent years, several non-vitamin K antagonist oral anticoagulants (NOACs), including the direct thrombin inhibitor dabigatran as well as the direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, and betrixaban), have emerged as alternatives to VKAs for various indications. NOACs are not thought to interfere with bone metabolism or increase the risk of bone fracture. Therefore, it is important to clarify the risk of fracture due to VKA use to enable physicians and patients to make appropriate patient-centered clinical decisions when anticoagulation is necessary.

Given the uncertainty about VKA use and fracture risk as well as the availability of alternative anticoagulants, we conducted a systematic literature review and meta-analysis to investigate the association between VKA use and bone fracture. We analyzed the odds of overall fracture between VKA users and controls, including NOAC users. We calculated the odds of various fracture types (hip, vertebral, wrist, and rib) associated with VKA use as well as the association between VKA use and fracture by gender, age, and duration of VKA use.

METHODS

We followed guidelines for meta-analysis established by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and Meta-Analysis and Systemic Reviews of Observational Studies (MOOSE).[8, 9]

SEARCH STRATEGY

We searched PubMed, EMBASE (Elsevier), and Cochrane Library (Wiley) from inception to December 31, 2017, with the help of an expert librarian using subject headings and keywords such as "vitamin K antagonist," "warfarin," "Coumadin," and all other brand names of warfarin, "fracture," "broken bone," and "skeleton fracture" (online appendix A). We used SCOPUS to review references from selected articles to identify additional relevant studies. We reviewed publications in all languages using Google Translate (https://translate.google.com) for non-English articles.

STUDY SELECTION

We included observational studies (case control, cross-sectional, and prospective and retrospective cohort) and clinical trials analyzing bone fracture in adult patients using VKAs versus controls. A control group was defined as a group not taking VKAs and without an increased risk of fracture. As NOACs are not suspected to increase fracture risk, patients using NOACs were considered an appropriate control. We excluded case reports, systematic reviews, meta-analyses, and review articles. We also excluded studies reporting only the outcomes of bone mineral density scores or osteoporosis but not bone fracture, studies not comparing VKA users to an appropriate control group, and studies reporting duplicate data.

DATA EXTRACTION

Two authors (WF and KW) independently reviewed studies for inclusion and extracted data with a standardized approach (online appendix B). Differences were resolved by consensus. Abstracted variables included study design, location, dates, sample size, demographics (age, gender), method of ascertainment of VKA exposure, duration of use, measure of compliance (prothrombin time or international normalized ratio (INR)), method of ascertainment of fracture, type of fracture, and crude and adjusted measures of effect, both overall and stratified by fracture type, age, gender, and duration of VKA exposure. Risk of bias was assessed using the Newcastle-Ottawa Quality Scale for case control studies and cohort studies (online appendix C).[10] A modified version of the Newcastle-Ottawa Quality Scale was used for cross-sectional studies (online appendix C). The Cochrane Risk of Bias Tool was used for clinical trials (online appendix C).[11]

STATISTICAL ANALYSIS

Our primary outcome was overall odds of fracture in VKA users versus controls. When overall fracture risk was not available, odds of hip fracture or vertebral fracture was used. We preferred adjusted ORs over crude data to control for variables that may have contributed to fracture risk. ORs were used to create pooled ORs using generic inverse weighting in a random effects model.[12] We stratified overall odds of fracture by methodologic subtype. We calculated overall odds of fracture in VKA users versus all controls and NOAC users. Additional subgroup analysis of VKA users versus controls included assessment of[1] four types of fracture (hip, vertebral, wrist, and rib),[2] gender,[3] age ≥ 65 years, and[4] duration of VKA use ≥ 1 year.

Statistical analyses were performed using Review Manager.[12] Heterogeneity of studies was analyzed using the Cochrane Q statistic chi-square test[13] and the I^2 test,[14] with higher I^2 percentages suggesting more heterogeneity. We used Comprehensive Meta-Analysis software V3 to assess publication bias using the modified Egger test.[15]

RESULTS

The systematic literature review yielded 1897 studies. Two hundred eighty-six duplicate articles were excluded, and 1551 articles were excluded after title and abstract review. Sixty full-text articles were reviewed, of which 37 were excluded (Fig. 1). Twenty-three studies, with a total of 1,121,582 subjects, were included in our final analyses.[16–38]

The characteristics of included studies are outlined in Table 1. Twenty-two of the 23 studies were observational: 8 prospective cohort studies,[22, 23, 27, 33, 35–38] 7 retrospective cohort studies,[16, 18, 21, 24, 25, 28, 30] 3 case control studies,[19, 31, 32] and 4 cross-sectional studies.[17, 20, 26, 29] One study was a randomized controlled trial.[34] Four studies directly compared the risk of fracture in VKA users versus NOAC users.[24, 25, 28, 34] One study included only females,[22] and one study included only males.[38] Eleven studies included only patients ≥ 65 years old.[17, 19, 21, 22, 27, 30, 31, 33, 35, 36, 38] Five studies specified a duration of VKA use for ≥ 1 year for at least part of their study population.[20–22, 27, 32] Many of the studies focused on a particular study population, i.e., dialysis patients[20, 39] or patients hospitalized with atrial fibrillation.[21]

There was no difference in odds of fracture between VKA users and controls (pooled OR 1.01, 95% CI 0.89, 1.14, I^2 = 74%) (Fig. 2) or between VKA users and NOAC users (pooled OR 0.95, 95% CI 0.78, 1.15, I^2 = 56%) (Fig. 3). In most subgroup analyses, we found no difference in odds of fracture with VKA use, including individual fracture type (hip, vertebral, wrist, and rib), male VKA users, and those using VKAs for ≥ 1 year (Table 2). We did find increased odds of fracture in female VKA users (pooled OR 1.11, 95% CI 1.02, 1.21, I^2 = 0%) and VKA users aged ≥ 65 years (pooled OR 1.07, 95% CI 1.01, 1.14, I^2 = 0%).

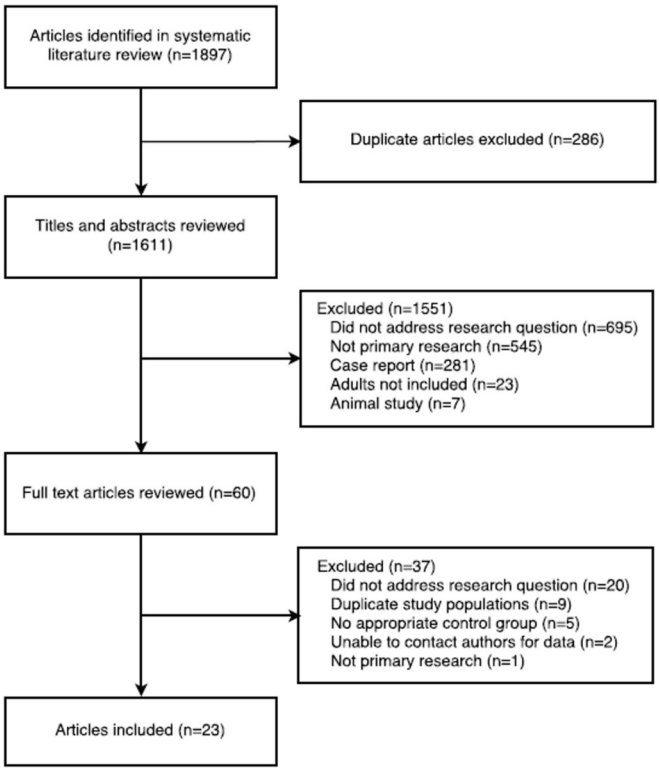

Fig. 1 Study selection diagram.

There was no publication bias by the Egger test (two-tailed *p* value 0.19).

DISCUSSION

We found that VKA use did not increase the odds of fracture, neither for overall fracture nor for specific types of fracture (hip, vertebral, wrist, or rib). While there were statistically significant increased odds of fracture in female VKA users and VKA users aged 65 years and older versus controls, the clinical significance of these findings is unclear. The odds were small (OR 1.11, 95% CI 1.02, 1.21 and OR 1.07, 95% CI 1.01, 1.14, for female VKA users and VKA users aged 65 and older, respectively), and thus likely less important than the other factors that must be considered when choosing an anticoagulant. Such factors include cost, dosing regimen (twice daily dosing required for dabigatran and apixaban), and required laboratory monitoring for VKAs. In addition, the risk of bleeding must be weighed. A meta-analysis from 2015 showed a lower risk of fatal bleeding in NOAC users versus warfarin users (RR 0.53, 95% CI 0.43, 0.64).[40] However, reversal agents are currently only available for VKAs and dabigatran. Thus, while the risk of fracture in female VKA users and those aged 65 years and older is statistically significant, the clinical significance seems minimal when accounting for all factors that must be considered in anticoagulant choice.

If exposure to VKAs did inhibit bone formation that resulted in clinically significant bone fracture, we would expect that longer duration of exposure would increase risk. Patients using VKAs for 1 year or longer did not have increased odds of fracture compared to controls. However, the critical duration of VKA exposure that would result in increased risk of fracture is not known. It is possible that the included studies did not evaluate a period of VKA use sufficiently long enough to increase fracture risk. Lai et al. reported the longest duration of VKA use, with a mean duration of use of 3.6 years.[23] Twelve studies did not specify duration of VKA use.[16–18, 25, 26, 28–30, 35–38]

To our knowledge, only one prior meta-analysis studied the risk between VKA use and fracture. Veronese et al. found an increased risk of fracture in VKA users compared to controls in both cross-sectional studies (3 studies, pooled RR 1.24, 95% CI 1.12, 1.39) and longitudinal studies (7 studies, pooled RR 1.09, 95% CI 1.01, 1.18).[7] However, in analysis of only longitudinal studies comparing VKA users to matched controls, the association became non-significant (2 studies, RR 1.03, 95% CI 0.90, 1.18). No analysis across study types was reported. Veronese et al. concluded that there was no increased risk of prospectively assessed fracture in VKA users compared to matched medical controls. While we appreciate the rigor of these methods to evaluate risk using high quality data, we would argue that the use of only matched data risks excluding data from studies that are still high in quality. We analyzed data from all studies, then performed sub-analysis of data based on study methodology. We did not find increased odds of fracture overall or in any methodologic design. Using these methods, we included more studies in our analysis than Veronese et al.

We also analyzed four recent studies that directly compared the risk of fracture in VKA users versus NOAC users,

Table 1 Characteristics of Included Studies

First author, year of publication	Study design	Study population characteristics	Study size	Percent female	Ages studied (years)	Method to ascertain fracture	Method to ascertain VKA use	Duration of VKA use	Risk of bias score
Bhattacharya, 2016	Retrospective cohort, 2003–2013	Patients admitted after ground level fall	5088	61.8	Mean 73.3 ± 17.6	Administrative or claims data	Administrative or claims data	Not specified	5/9
Boltz, 2015	Cross-sectional, 2007–2010	Trauma patients with diagnosis of fall and inpatient stay > 24 h	118,467	Oral anticoagulant users: 58.8 Oral anticoagulant nonusers: 61.6	≥ 65 Anticoagulant users: mean 78.5 Anticoagulant nonusers: mean 79.1	Administrative or claims data	Administrative or claims data	Not specified	3/7
Chiang, 2013	Retrospective cohort, 2000–2009	No special population	43,790	55.1	≥ 18 Mean 70 ± 17.4	Administrative or claims data	Administrative or claims data	Not specified	9/9
Drozdinsky, 2017	Case control, 2005–2016	Patients seen in emergency department	328	Patients with fracture: 68 Patients without fracture: 40	> 65 Patients with fracture: mean 82.0 ± 8.2 Patients without fracture: mean 80.0 ± 8.6	Medical record review	Medical record review	Patients with fracture: mean 13.5 ± 34.7 months Patients without fracture: mean 11.4 ± 34.77 months	6/9
Fusaro, 2015	Cross-sectional, 2008–2009	Patients on hemodialysis for > 1 year	387	Warfarin users: 41.3 Warfarin non-users: 37.0	≥ 18 Warfarin users: mean 69.8 ± 10.7 Warfarin nonusers: mean 63.4 ± 14.3	Radiology report	Not specified	> 1 year Mean 50 months	4/7
Gage, 2006	Retrospective cohort, 1998–1999	Patients hospitalized with atrial fibrillation	14,564	Warfarin users ≥ 1 year: 53.6 Warfarin non-users: 56.9	≥ 68 Warfarin users ≥ 1 year: mean 79.4 ± 6.3 Warfarin nonusers: mean 80.8 ± 7.2	Administrative or claims data	Administrative or claims data	90–364 days, ≥ 1 year	9/9
Jamal, 1998	Prospective cohort, 1992–1994	Caucasian ambulatory women	6201	100	≥ 65 Warfarin users: 76 Warfarin nonusers: 77	Patient report, confirmed by radiology report	Structured medication review	Any, > 2 years	8/9
Lai, 2015	Prospective cohort, 2005–2009	Patients with new diagnosis of atrial fibrillation	34,625	42.2	≥ 18 Mean 74.1 ± 11.0	Administrative or claims data	Administrative or claims data	Mean 3.6 years	9/9
Lau, 2017	Retrospective cohort, 2010–2016	Patients with new diagnosis of atrial fibrillation	8152	Warfarin users: 49.0 Dabigatran users: 50.7	Warfarin users: Mean 73.3 ± 11.0 Dabigatran users: mean 74.2 ± 10.1	Administrative or claims data, confirmed by physician	Administrative or claims data	Median 267 days	9/9
Lucenteforte, 2017	Retrospective cohort, 2015	No special population	16,850	48.91	67.22% ≥ 75	Administrative or claims data	Administrative or claims data	Not specified	8/9
Lyons, 2011	Cross-sectional, 1989–not specified	Patients with heart failure	623	31	≥ 50 Median 69, IQR 59–78	Radiology report	Medical record review	Not specified	5/7
Misra, 2014	Prospective cohort, 2000–2010	Patients with incident atrial fibrillation	20,346	48	≥ 65 Mean 77.0 ± 6.3	Administrative or claims data	Administrative or claims data	≥ 1 year, ≥ 3 years	9/9

(continued on next page)

Table 1. (continued)

First author, year of publication	Study design	Study population characteristics	Study size	Percent female	Ages studied (years)	Method to ascertain fracture	Method to ascertain VKA use	Duration of VKA use	Risk of bias score
Norby, 2017	Retrospective cohort, 2010–2014	Patients with nonvalvular atrial fibrillation	227,799	Warfarin users: 40.1 Rivaroxaban users: 38.7	Warfarin users: mean 71.1 ± 12.5 Rivaroxaban users: mean 69.3 ± 12.2	Administrative or claims data	Administrative or claims data	Not specified	8/9
Ogura-Tomomatsu, 2012	Cross-sectional, not specified	Patients with moderate to very severe COPD	85	8	> 40	Radiology report	Patient report	Not specified	0/7
Pieracci, 2007	Retrospective cohort, 2004	Patients hospitalized after fall	47,717	70.8	≥ 65 Mean 81.7	Administrative or claims data	Administrative or claims data	Not specified	5/9
Pilon, 2004	Case-control, 1992–1994	No special population but excluded stroke patients	16,728	Patients with fracture: 76.4 Patients without fracture: 63.7	≥ 70 Mean 83.2 ± 6.7	Administrative or claims data	Administrative or claims data	0–3 months, > 3 months	9/9
Rejnmark, 2007	Case-control, 2000	No special population	498,617	51.8	Mean 43.44 ± 27.39	Administrative or claims data	Administrative or claims data	< 100, 100–499, ≥ 500 defined daily dosages	9/9
Sato, 2010	Prospective cohort, not specified	Patients hemiplegic due to stroke	177	Warfarin users: 54.8 Warfarin non-users: 60.2	≥ 70 Warfarin users: mean 76.0 ± 4.2 Warfarin nonusers: mean 75.1 ± 4.8	Patient report, confirmed by radiology report	Medical record review	Mean 1.4 ± 0.2 months	6/9
Steffel, 2016	Clinical trial, 2008–2010	Patients with atrial fibrillation and moderate to high risk of stroke	20,205	37.6	≥ 21 Median 72, IQR 64–77	Study case report, not confirmed	As assigned in clinical trial	Study median follow-up 2.8 years	*
van Diepen, 2008	Prospective cohort, 1998–2001	Patients seen in emergency department for cardiovascular diagnosis	16,294	Patients with fracture: 74.2 Patients without fracture: 52.7	≥ 65 Patients with fracture: median 79.4, IQR 72.8–85.2 Patients without fracture: median 74.1, IQR 69.2–80.0	Administrative or claims data	Administrative or claims data	Not specified	6/9
Wallace, 2017	Prospective cohort, 1991–2009	No special population	4462	59.4	≥ 65 Mean 74 ± 5	Administrative or claims data	Structured medication review	Not specified	6/9
Wang, 2013	Prospective cohort, 2000–2006	Patients with systemic lupus erythematosus	14,544	90.0	≥ 18 Mean 38.1 ± 13.5	Administrative or claims data	Administrative or claims data	Not specified	7/9
Woo, 2008	Prospective cohort, 2000–2002	Ambulatory men with at least one native hip	5533	0	≥ 65 Mean 73.6 ± 5.9	Patient report, confirmed by chart and radiology report review	Structured medication review	Not specified	8/9

The study had a low risk of bias in all 7 domains of the Cochrane Risk of Bias Tool

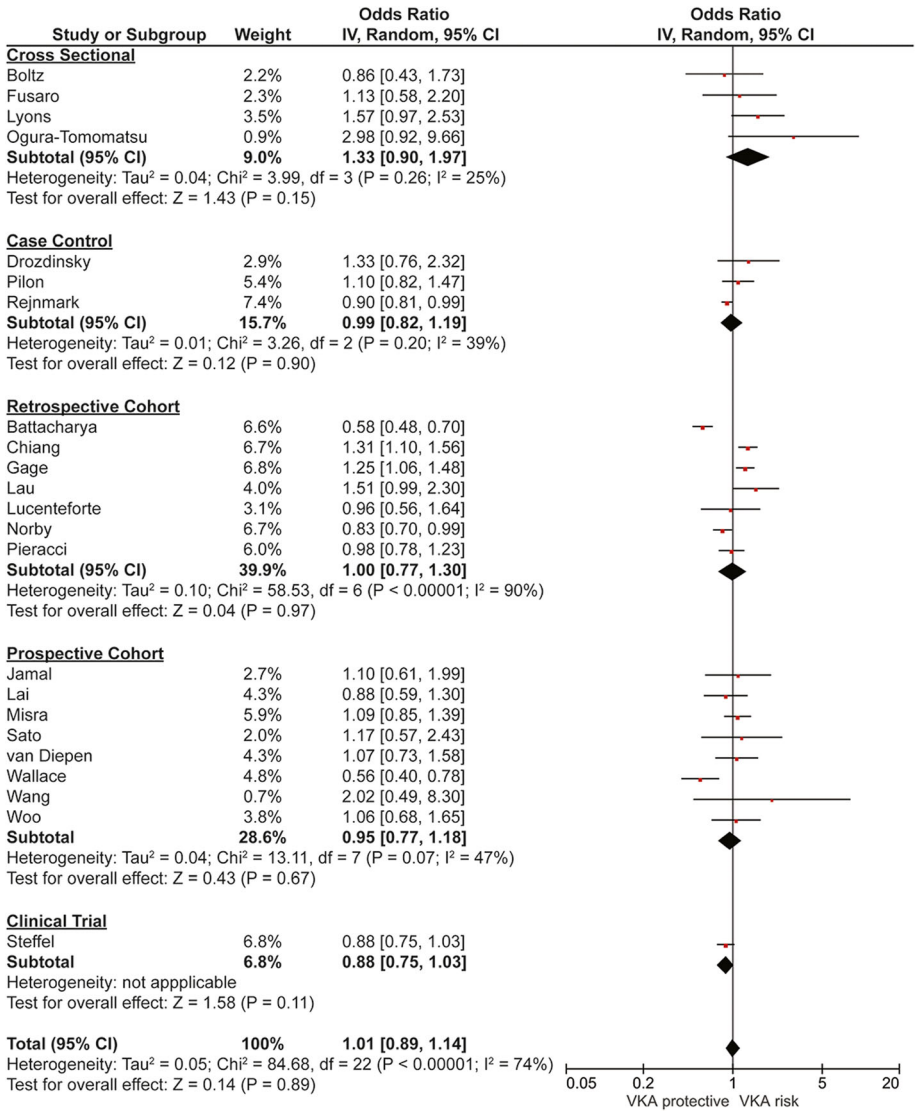

Fig. 2 Pooled odds of fracture in VKA users versus controls, stratified by study design.

including the direct thrombin inhibitor dabigatran[24, 25] and direct factor Xa inhibitors.[25, 28, 34] While the mechanisms of action of the direct thrombin inhibitors differ from the direct factor Xa inhibitors, neither are thought to affect bone structure to increase fracture risk. We found no difference in odds of fracture between VKA users and NOAC users.

It has been suspected that VKA use may increase risk of bone fracture by inhibition of vitamin K–dependent gamma-carboxylation of osteocalcin, one of the major proteins in bone that contributes to bone hardness. However, two meta-analyses have shown no association between VKA use and lower bone mineral density.[6, 7] Sugiyama et al. argue that even if bone *quantity* is decreased by vitamin K inhibition, an increase in bone *quality* may compensate.[41] Thus, reduced bone mineral density may not necessarily increase risk of bone fracture. This might be especially true in weight-bearing sites.

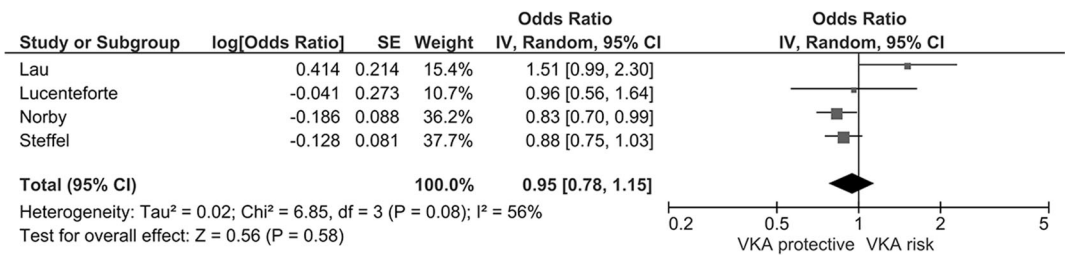

Fig. 3 Pooled odds of fracture in VKA users versus NOAC users.

Table 2 Sub-analysis of Odds of Fracture in VKA Users Versus Controls

Subgroup	Pooled OR (95% CI)	Heterogeneity (I^2) (%)
Hip fracture[16, 18, 21, 27, 32, 33, 36–38]	0.91 (0.69, 1.20)	85
Vertebral fracture[16, 17, 20, 21, 26, 27, 29, 30, 32, 33, 39]	1.18 (0.96, 1.46)	47
Wrist fracture[21, 27, 32, 38]	1.06 (0.87, 1.30)	0
Rib fracture[16, 17, 21, 30, 33, 38]	1.14 (0.86, 1.50)	55
VKA users ≥ 65 years old[19, 21, 22, 25, 27, 31–33, 35, 38]	1.07 (1.01, 1.14)	0
Female VKA users[20, 22, 25, 32, 33]	1.11 (1.02, 1.21)	0
Male VKA users[20, 21, 25, 32, 33, 38]	1.26 (0.93, 1.72)	67
VKA use ≥ 1 year[20–22, 27, 32, 33]	1.07 (0.90, 1.27)	59

Our meta-analysis did not show increased odds of fracture at weight-bearing sites (hip or spine) or non-weight-bearing sites (wrist or rib).

The quality of our meta-analysis is inherently limited by the quality of the studies included. As 22 of the 23 studies were observational, the strength of the evidence is 2B based on GRADE criteria.[42] There were several sources of potential bias. Selection bias may have played a significant role, as many of the studies examined patients in limited study populations. The patients in these populations may have other risk factors for fracture. For example, dialysis patients are at increased risk of fracture independent of VKA use.[42, 43] In addition, patients of special populations may not represent the general population of VKA users. As most of the included studies are observational, there is risk of misclassification of exposure or outcome. Many studies used administrative or claims data to define VKA use, and most did not confirm patient adherence or maintenance of therapeutic levels. Several studies relied on patient report for ascertainment of fracture. While some studies confirmed patient report with radiologic imaging, some fractures, particularly vertebral and rib fractures, are subclinical and may be missed by patient report.

As NOACs are now widely available, and their mechanism of action is not thought to increase risk of fracture, it is important to clarify the risks of the various anticoagulants so that patients and physicians can make an informed choice of anticoagulant. Four studies directly comparing VKA users to NOAC users revealed no difference in odds of fracture. VKA users did not have increased odds of overall fracture nor specific type of fracture compared to controls, and there was no difference in the odds of fracture in those taking VKAs for 1 year or longer versus controls. While we found increased odds of fracture associated with VKA use in females and patients aged 65 and older, the magnitude was small and likely clinically insignificant when accounting for other factors that must be considered when choosing an anticoagulant. Thus, the results of this meta-analysis suggest that risk of bone fracture should not be a major consideration in anticoagulant choice. Future studies of patients truly representative of VKA users (and not special populations), studies that examine VKA use for longer durations and document compliance, and additional studies that compare VKA use with NOAC use would strengthen this conclusion.

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Compliance with Ethical Standards:

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

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