EPIDEMIOLOGICAL SCIENCE

Warfarin use and risk of knee and hip replacements

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ABSTRACT

Background Identification of modifiable risk factors and treatments for osteoarthritis (OA) are needed. Warfarin, a vitamin K antagonist, causes fetal and animal model skeletal abnormalities. Vitamin K insufficiency has been associated with OA, but whether warfarin is also detrimental to OA is not known.

Methods We conducted a nested case–control study using a UK general practitioner electronic medical records database. We identified cases of knee or hip replacement (KR or HR) from among adults with atrial fibrillation newly prescribed either warfarin or direct oral anticoagulants (DOACs). Cases were matched with four controls by age and sex. We assessed the relation of warfarin compared with DOAC use to risk of joint replacement using conditional logistic regression. We also evaluated different durations of warfarin use.

Results We identified 857 subjects with KR or HR (cases), of whom 64.6% were warfarin users, and 3428 matched controls, of whom 56.1% were warfarin users (mean age 75, 47% female). Warfarin users had a 1.59 times higher risk of joint replacement than DOAC users (adjusted OR 1.59, 95% CI 1.31 to 1.92). Longer duration of warfarin use was associated with higher risk of joint replacement in comparison with <1 year of warfarin use.

Conclusion Warfarin, a vitamin K antagonist, was associated with greater risk of KR and HR (an indicator for end-stage knee OA) than DOAC use, supporting the importance of adequate vitamin K functioning in limiting OA progression.

Key messages

What is already known about this subject?

► Vitamin K deficiency is associated with incidence and progression of osteoarthritis (OA). However, it is unclear whether vitamin K antagonism through warfarin is also detrimental to OA.

What does this study add?

► In this study, use of warfarin, a vitamin K antagonist, was associated with greater risk of knee and hip replacement (KR and HR; an indicator for end-stage knee OA) than direct oral anticoagulant (DOAC) use, suggesting that vitamin K antagonism may also be detrimental to OA.

How might this impact on clinical practice or future developments?

► These data raise the consideration of using DOACs over warfarin when appropriately indicated in people with OA.

INTRODUCTION

Warfarin is a commonly prescribed anticoagulant that is known to have adverse effects on the skeletal system in the context of human fetal embryopathy and in rat models characterised by abnormal skeletal mineralisation.[1–4] These effects could have implications for osteoarthritis (OA), the most common form of arthritis, for which no effective treatments exist. Thus, identifying modifiable risk factors remains a high priority.

Warfarin's anticoagulant effects occur through inhibition of the functioning of vitamin K.[5] Vitamin K, in turn, is an essential cofactor in the post-translational gamma carboxylation of Gla proteins, a step required for these proteins to be functional.[6] Gla proteins play an important role in blood coagulation, and also in the bone and cartilage, including matrix Gla protein (MGP), osteocalcin and Gas-6.[7–9] Thus, warfarin's inhibition of vitamin K leads to inadequate functioning of Gla proteins. Low vitamin K status has been associated with both incidence and progression of knee OA in observational studies.[10–13] Furthermore, in a randomised controlled trial of vitamin K supplementation versus placebo, those with insufficient vitamin K at baseline had trends towards less joint space narrowing on hand radiographs.[14]

Taken together, these data highlight the potentially detrimental effects of warfarin via vitamin K antagonism on joint tissues that could contribute to OA. We therefore sought to determine the relation of warfarin use to risk of knee and hip replacements (KR, HR), as a reflection of end-stage OA, in a large population-based cohort.

METHODS

Study design

We performed a nested case–control study using data from the IQVIA Medical Research Data (IMRD; incorporating The Health Improvement Network (THIN)). IMRD is a general practitioner (GP) electronic medical records database from the United Kingdom (UK) that is representative of the general UK population. This database has been validated for use in pharmacoepidemiological research.[15]

The nested case–control study was assembled from among a cohort of adults with atrial fibrillation, a common indication for long-term anticoagulation, to minimise confounding by indication. Because atrial fibrillation can be managed with warfarin or direct oral anticoagulants (DOACs), which do not antagonise vitamin K,[16] we used an active comparator approach to further minimise

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confounding by indication. Since DOACs were first introduced to the market in the UK in 2008, we identified eligible study participants from 2009 onwards to allow time for market uptake. Study entry criteria included adults aged between 40 and 89 with atrial fibrillation who had been enrolled with a GP for at least 1 year. Participants were further required to be incident warfarin or DOAC users, defined as those who were newly prescribed an anticoagulant after 2009, having ≥1 prescription after study entry and also within 1 year before the index date (defined below) to ensure a relevant time frame of use. From among this cohort, we identified cases as those patients with KR or HR between 2014 and 2018. The index date for cases was defined as the date of surgery. Each case was matched with four controls by age and sex; if more than four controls were eligible for matching, the four controls were selected randomly. The matched controls were assigned the same index date as that of their matching case's surgery date (figure 1).

We excluded participants with KR or HR prior to 2014, those with warfarin or DOAC use prior to study entry (criteria defined above) and those who used both warfarin and DOAC within 1 year prior to the index date. We also excluded those with high-risk cancer (oesophageal, gastric, pancreatic and metastatic cancer), body mass index (BMI) >40 kg/m^2, joint infection and oxygen therapy, as these are severe comorbidities that would limit surgical candidacy.

Analytic approach

For our primary analysis, we assessed the relation of warfarin use compared with DOAC use, both within 1 year prior to the index date, to risk of KR and HR. Because the biological effects of warfarin may become evident only after a period of use, in a secondary analysis, we assessed the relation of duration of warfarin use to risk of KR and HR, defined as ≥4 years, 2–<4 years, and 1–<2 years, compared with warfarin use of <1 year prior to the index date. Duration of use was calculated based on the sum of each prescription duration between study entry and the index date.

We considered the following potential confounders for adjustment in our models: BMI, renal disease, severe liver disease, prior gastrointestinal bleeding, prior intracranial haemorrhage, mitral stenosis, presence of prosthetic heart valve, prior falls, cancer, chronic obstructive pulmonary disease, dementia or cognitive impairment, diabetes, heart failure, hypertension, hyperlipidaemia, ischaemic heart disease, stroke, venous thromboembolism, medication use (antihypertensive drugs, oral hypoglycaemic drugs, insulin, lipid-lowering drugs, non-steroidal anti-inflammatory drugs and paracetamol), GP visits and hospitalisations. Confounders were assessed by Read codes for medical conditions and with prescription records for medication. Of these, severe liver disease, prior intracranial haemorrhage, mitral stenosis and presence of prosthetic heart valve had a prevalence of <1% and were subsequently not included in multivariable adjusted models. We assessed the relation of warfarin compared with DOAC use, and duration of warfarin use, to risk of KR or HR using conditional logistic regression in separate models, adjusting for these potential confounders.

We performed two additional sensitivity analyses. Because there may be variation across GP practices in both choice of anticoagulant and referral for surgery, we matched cases and controls according to GP practice, and adjusted for age and sex in addition to the other potential confounders listed above. Each GP practice typically serves the same geographical area but could include multiple GPs. In a second set of sensitivity analyses, we repeated the primary analysis stratified by type of joint replacement, with the recognition that 97% of knee replacements are performed for knee OA, whereas hip replacements can be performed for other indications, such as hip fracture.[17]

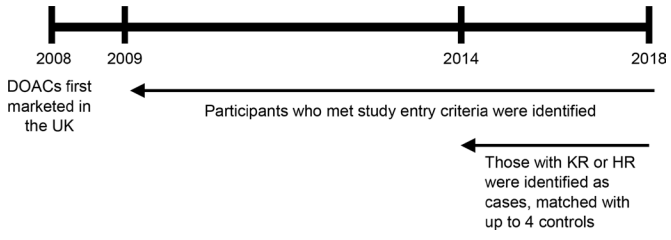

Figure 1 Study design and timeline. DOACs, direct oral anticoagulants; HR, hip replacement; KR, knee replacement.

Table 1 Characteristics of participants

Participants	Cases (KR/HR) (n=857)	Controls (n=3428)
General demographics		
Age (years), mean±SD	75.4±7.2	75.4±7.2
Female	403 (47.0%)	1612 (47.0%)
BMI 25–<30	313 (36.5%)	1297 (37.8%)
BMI ≥30	365 (42.6%)	1088 (31.7%)
Comorbidities		
Cancer	154 (18.0%)	648 (18.9%)
COPD	214 (25.0%)	825 (24.1%)
Dementia/cognitive impairment	6 (0.7%)	106 (3.1%)
Diabetes	170 (19.8%)	782 (22.8%)
Heart failure	113 (13.2%)	600 (17.5%)
Hyperlipidaemia	153 (17.9%)	702 (20.5%)
Hypertension	590 (68.8%)	2303 (67.2%)
IHD	191 (22.3%)	959 (28.0%)
Mitral stenosis	8 (0.9%)	17 (0.5%)
Prior falls	153 (17.9%)	576 (16.8%)
Prior GI bleeding	26 (3.0%)	98 (2.9%)
Prior intracranial haemorrhage	4 (0.5%)	37 (1.1%)
Prosthetic valve	3 (0.4%)	6 (0.2%)
Renal disease (CKD 1–3)	203 (23.7%)	895 (26.1%)
Renal disease (CKD 4–5 and renal transplant)	10 (1.2%)	54 (1.6%)
Severe liver disease	5 (0.6%)	17 (0.5%)
Stroke	135 (15.8%)	702 (20.5%)
Venous thromboembolism	36 (4.2%)	154 (4.5%)
Medication use		
Antihypertensive drugs	775 (90.4%)	3076 (89.7%)
Insulin	13 (1.5%)	110 (3.2%)
Lipid-lowering drugs	492 (57.4%)	2090 (61.0%)
NSAIDs	337 (39.3%)	1275 (37.2%)
Oral hypoglycaemic drugs	87 (10.2%)	463 (13.5%)
Paracetamol	581 (67.8%)	1340 (39.1%)
GP visits (assessed within 1 year before first warfarin/DOAC prescription)		
0–5	330 (38.5%)	1606 (46.8%)
>5	527 (61.5%)	1822 (53.2%)
Hospitalisations (assessed within 1 year before first warfarin/DOAC prescription)		
0–2	820 (95.7%)	3189 (93.0%)
≥3	37 (4.3%)	239 (7.0%)

Results are shown as N (%) unless stated otherwise.
BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; GI, gastrointestinal; GP, general practitioner; HR, hip replacement; IHD, ischaemic heart disease; KR, knee replacement; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 2 Warfarin use and risk of knee and hip replacements

A. Warfarin versus DOAC use within 1 year of index date, regardless of duration	Cases (KR/HR)	Controls
Participants (n)	857	3428
Warfarin use	554 (64.6%)	1923 (56.1%)
DOAC use	303 (35.4%)	1505 (43.9%)
Odds ratio (95% CI), matched by age and gender	1.57 (1.32 to 1.86)	
Adjusted* odds ratio (95% CI)	1.59 (1.31 to 1.92)	
B. Warfarin versus DOAC use, matched by practice	**Cases (KR/HR)**	**Controls**
Participants (n)	857	3422
Warfarin use	554 (64.6%)	2077 (60.7%)
DOAC use	303 (35.4%)	1345 (39.3%)
Odds ratio (95% CI), matched by practice	1.25 (1.05 to 1.50)	
Adjusted† odds ratio (95% CI)	1.36 (1.11 to 1.66)	
C. Warfarin versus DOAC use, stratified by anatomic location of joint replacement	**Cases (KR only)**	**Controls**
Participants (n)	497	1988
Warfarin use	324 (65.2%)	1139 (57.3%)
DOAC use	173 (34.8%)	849 (42.7%)
Odds ratio (95% CI), matched by age and gender	1.52 (1.21 to 1.92)	
Adjusted* odds ratio (95% CI)	1.58 (1.22 to 2.04)	
	Cases (HR only)	**Controls**
Participants (n)	485	1940
Warfarin use	304 (62.7%)	1129 (58.2%)
DOAC use	181 (37.3%)	811 (41.8%)
Odds ratio (95% CI), matched by age and gender	1.27 (1.01 to 1.60)	
Adjusted* odds ratio (95% CI)	1.33 (1.03 to 1.72)	

*Adjusted for the same variables as in table 1 excluding age and sex, which were matching variables.
†Adjusted for age and gender in addition to variables in table 1.
DOAC, direct oral anticoagulant; HR, hip replacement ; KR, Knee replacement.

Patient and public involvement

Patients and the public were not involved in this study.

RESULTS

We identified 857 cases with KR or HR and matched them to 3428 controls. The mean age of both groups was 75 years and 47% were female. Other baseline characteristics are listed in table 1. Notable differences in comorbidities included a higher prevalence of diabetes, heart failure, stroke and ischaemic heart disease among controls, probably because individuals with these comorbidities were less likely to be surgical candidates. As expected, obesity (BMI ≥30) was more commonly seen among cases (42.6% vs 31.7%).

Of the 857 cases, 64.6% were warfarin users and the remaining 35.4% were DOAC users. Among the 3428 controls, 56.1% were warfarin users and 43.9% were DOAC users. Warfarin use was associated with 59% higher risk of having a KR or HR than DOAC use (adjusted OR 1.59, 95% CI 1.31 to 1.92; table 2A).

Longer durations of warfarin were associated with higher risk of KR or HR compared with <1 year of warfarin use (figure 2 and online supplemental table 1). Participants with warfarin use for ≥4 years had 86% higher risk of KR or HR compared with new warfarin users (<1 year) (95% CI 1.35 to 2.57).

When analyses were repeated with matching by GP practice, the magnitude of the association was slightly diminished but remained statistically significant (adjusted OR 1.36, 95% CI 1.11 to 1.66) (table 2B). When we stratified analyses by type of joint replacement (knee or hip), the results were similar to the primary analysis for KRs, and slightly diminished for HRs. Warfarin use was associated with 58% higher risk of KR (95% CI 1.22 to 2.04) and 33% higher risk of HR (95% CI 1.03 to 1.72) compared with DOAC users (table 2C).

DISCUSSION

In this population-based case–control study of older adults with atrial fibrillation, warfarin use was associated with a higher risk of knee and hip replacements, an indicator of end-stage OA, compared with DOAC use. Furthermore, longer duration of warfarin use was associated with greater risk of joint replacement compared with shorter duration of its use.

The mechanism for this observed association of warfarin on risk of end-stage OA as assessed by joint replacement is probably related to warfarin's role as a vitamin K antagonist. Warfarin's antagonism of vitamin K would be expected to recapitulate effects of insufficient vitamin K. Because vitamin K confers functionality to Gla proteins through gamma-carboxylation, insufficient vitamin K or inhibition of vitamin K's functioning through warfarin leads to undercarboxylation of vitamin K-dependent proteins, limiting their functionality. An important vitamin K-dependent protein that has been specifically linked to abnormalities in soft tissue mineralisation and OA is MGP. Genetic deficiencies of MGP in humans, known as Keutel syndrome, and in transgenic mice result in cartilage calcification, highlighting the role of MGP as an inhibitor of mineralisation.[18–21] Of specific

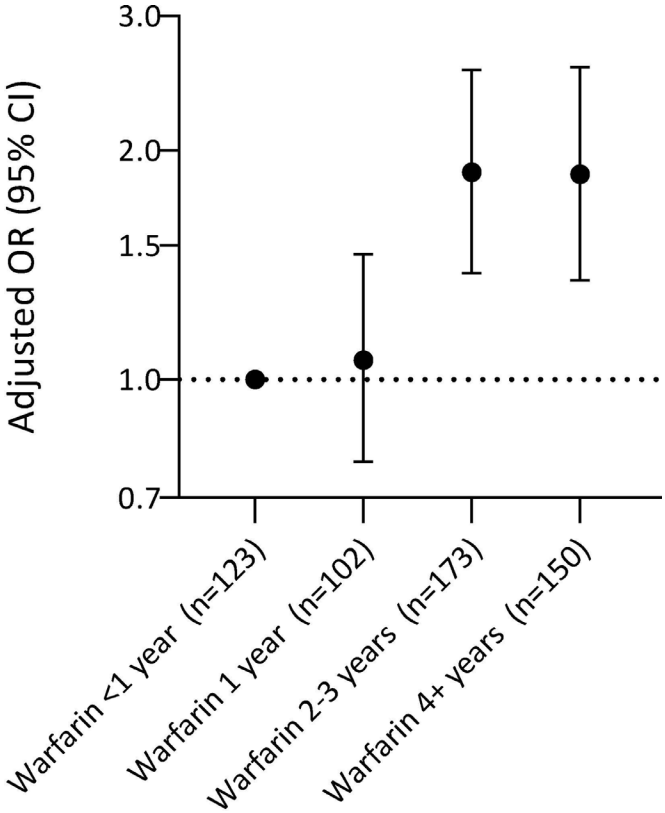

Figure 2 The relation of duration of warfarin use to risk of knee or hip replacement. Analyses adjusted for potential confounders in table 1, with the exception of age and sex, which were matching variables.

relevance to OA, MGP is primarily uncarboxylated in human OA cartilage, whereas it is primarily carboxylated (and therefore functional) in healthy cartilage.[22] Furthermore, a genome-wide association study identified coding variants of *MGP* as associated with hand OA, and complementary functional studies demonstrated that *MGP* RNA expression of the hand OA allele was higher than that of the reference allele in human OA cartilage.[23] These findings complemented a smaller study that also identified *MGP* single nucleotide polymorphism in hand OA.[24] Thus, the detrimental effects of warfarin through inhibition of vitamin K's activities may be further exacerbated in those with genetic polymorphisms of *MGP*.

Our results add to the existing literature, extending insights into the importance of vitamin K and its dependent proteins in OA. Low levels of plasma phylloquinone, the major form of circulating vitamin K, were associated with prevalence of both radiographic hand and knee OA in the Framingham Offspring cohort, while low dietary vitamin K intake was associated with radiographic knee OA in a Japanese population-based cohort.[10 11] Complementing those radiographic findings, two longitudinal studies also demonstrated an association of low plasma phylloquinone with incidence[12] and progression[13] of cartilage lesions on knee MRI, providing more direct support for a role of vitamin K in cartilage pathology. To more definitively evaluate the role of vitamin K in OA, a randomised controlled trial of vitamin K supplementation versus placebo was conducted in 378 participants who were enrolled without regards to their baseline vitamin K status. There was no difference overall in the prevalence of hand OA between the two arms.[14] However, in a post hoc analysis limited to patients who were vitamin K insufficient at baseline, those in the vitamin K supplementation arm had 47% significantly less joint space narrowing than those receiving placebo, suggesting that for hand OA those with insufficient vitamin K could derive benefit from vitamin K supplementation.[14]

In addition to vitamin K's role in OA through Gla proteins in the bone and cartilage, it might have direct effects on inflammation, which could have relevance for OA.[25] Higher plasma phylloquinone was associated with lower inflammatory burden in two separate cohorts cross-sectionally.[26 27] In contrast, undercarboxylated osteocalcin, a Gla protein, was not associated with inflammation.[26] Since these effects appear to be unrelated to vitamin K's role in gamma-carboxylation, it is unlikely that warfarin would play a role in vitamin K's effects on inflammation.[28] Thus, there might be potential additional benefit to targeting vitamin K in OA beyond warfarin alone.

We recognise that this observational study cannot provide definitive causal insights. However, it is unlikely that a randomised trial of warfarin versus a DOAC for an OA end point would be performed. We dealt with confounding by indication by limiting our sample to adults with atrial fibrillation as this diagnosis warrants anticoagulation, and by including an active comparator arm of DOACs, which are anticoagulants used for the same indication but do not antagonise vitamin K. Our study also has limitations. As with all observational studies, there is potential for residual confounding. We identified exposure to warfarin and DOACs through prescriptions, but these do not necessarily reflect medication adherence. Joint replacement was used as a proxy for end-stage OA. While approximately 97% of KRs are performed for knee OA, HRs can be performed for other reasons, such as hip fracture.[17] We are unable to disentangle putative effects of warfarin on bone density and risk of osteoporotic fracture[29] versus end-stage OA as the reason for HR in this study. Nonetheless, in stratified analyses, warfarin use was associated with risk of KR with a similar magnitude as in the main analysis, and with HR, though with a slightly lower magnitude. Overall, our study provides support for a detrimental effect of warfarin in OA, complementing prior studies examining the effects of vitamin K in OA, and supports the inference that warfarin's effects are due to its role as a vitamin K antagonist.

Given the worldwide prevalence and impact of OA and lack of effective disease-modifying therapies, our study supports the need for a well-powered randomised control trial evaluating vitamin K supplementation in OA. Our study also raises the consideration of preferentially using DOACs rather than warfarin, when appropriately indicated, in people with OA.

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Contributors PB was involved in study design, code selections, drafting the manuscript and critical revision. CP was involved in study design, data analysis and critical revision. CGB was involved in critical revision. TN was involved in conception, study design, data analysis, critical revision and final approval of the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

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Data availability statement Data may be obtained from a third party and are not publicly available. Deidentified data were used for this work. The IMRD dataset used in this work is a subscription-based dataset with a legal contract requiring data to remain onsite and analysed at Boston University Medical Center. We are therefore legally unable to make these data publicly available. We would be able to collaborate with potential external investigators to deal with research questions of interest if appropriate resources are provided. Investigators may contact IMRD for further information about obtaining data.

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