Correspondence on 'Warfarin use and risk of knee and hip replacements'

Warfarin, the traditional oral anticoagulant (OAC), functions by inhibiting the biological activity of vitamin K, and thus inhibiting the carboxylation of coagulation factors. Meanwhile, warfarin also interacts with the formation of active vitamin K-dependent bone and cartilage proteins, including osteocalcin, matrix Gla protein and Gla-rich protein.[1 2] Therefore, warfarin can be hypothesised to be associated with adverse musculoskeletal events.[2] In contrast, novel OACs (NOACs) act independently of vitamin K.

We have read with great interest the article by Ballal *et al*[3] who conducted a nested case–control study and raised the concern that warfarin was associated with significantly higher risk of hip or knee replacements compared with NOACs (adjusted OR 1.59, 95% CI 1.31 to 1.92). Another cohort study also indicated that vitamin K antagonist was associated with an increased risk of osteoarthritis (OA) incidence and progression (OR 2.50, 95% CI 1.94 to 3.20).[4] As OA is a relatively rare event and current evidence on the OAC-associated OA risk was limited, we aimed to examine the association between OACs and OA risk using the Food and Drug Administration Adverse Event Reporting System (FAERS) data.

We queried FAERS Database using OpenVigil V.2.1 (http://openvigil.sourceforge.net/).[5] Reports of OA events related to OACs from 2004 Q1 to 2020 Q4 were retrieved and analysed. We used Medical Dictionary for Regulatory Activities to identify cases with adverse events of interest. The primary outcome was OA. Secondary outcomes included OA-related composite event, osteoarthropathies and hip or knee replacements. The search terms for adverse events of interest are detailed in online supplemental table S1. We set three pairs of comparison: warfarin versus all other drugs, warfarin versus NOACs (dabigatran, rivaroxaban, apixaban and edoxaban) and NOACs versus all other drugs. Both reporting OR (ROR) and information component (IC) (Bayesian Confidence Propagation Neural Network analysis) were calculated to detect the potential safety signal. A signal was defined as a 95% CI of ROR or exp (IC) >1.[6] The sensitivity analysis was also performed by restricting analysis to reports with patients aged 18 years or older. Analysis was performed in R (V.4.0.3).

We obtained 99 938 reports with warfarin and 207 513 reports with NOACs overall, and OA event was involved in 192 and 170 of them, respectively. The characteristics of warfarin and NOAC-associated OA reports are presented in online supplemental table S2. The reporting of OA was significantly higher with warfarin than all other drugs (1.92 vs 1.35 per 1000 cases; ROR 1.42, 95% CI 1.23 to 1.64; exp (IC) 1.64, 95% CI 1.33 to 2.01) and NOACs (1.92 vs 0.82 per 1000 cases; ROR 2.35, 95% CI 1.91 to 2.89; exp (IC) 2.01, 95% CI 1.56 to 2.58). Warfarin was also reported at disproportionately higher rate regarding OA-related composite event, osteoarthropathies and hip or knee replacement event (table 1). Meanwhile, no signals of disproportionate reporting of OA or joint replacements with NOACs were identified (table 1). When we restricted the analysis to reports of patients aged 18 years or older, no inconsistency with primary analysis was found (online supplemental table S3).

The data mining of FAERS Database found consistent results with recent observational studies,[3 4] which could augment the evidence of warfarin-associated OA and hip or knee replacement risk to some extent. Our study also has several limitations. First, analysis on spontaneous reports is prone to reporting bias, such as under-reporting and Weber effect. Apart from this, data on detailed comorbidities, co-medications and the treatment details are often missing and we could not control confounding bias properly.

To our knowledge, OA cannot be reversed and management on modifiable risk factors is essential. Except for the well-known disadvantage in thromboembolic event prevention, bleeding risk and drug–drug interactions,[7] warfarin may be also associated with higher risk of OA and joint replacements compared with NOACs. The comparison of warfarin versus NOACs on this issue further supports NOACs recommended as the first-line therapy, especially among elderly patients who are also vulnerable to ageing-related musculoskeletal disorders. Notably, although recent correspondence on this topic had a discussion on the use of analgesics between different OAC groups,[8 9]

Table 1 Disproportionality analysis using different measures to identify potential association between different OACs and the risk of OA and joint replacement

	Drug of exposure group		Comparator group			
Outcome of interest	No of cases	No of non-cases	No of cases	No of non-cases	ROR (95% CI)	Exp (IC) (95% CI)
Warfarin vs all other drugs						
OA	192	99 746	10 832	8 011 267	1.42 (1.23 to 1.64)	1.64 (1.33 to 2.01)
OA-related adverse event	254	99 684	12 867	8 009 232	1.59 (1.40 to 1.80)	1.91 (1.60 to 2.29)
Knee or hip replacements	181	99 757	8999	8 013 100	1.62 (1.39 to 1.87)	1.96 (1.58 to 2.42)
Osteoarthropathies	258	99 680	13 149	8 008 950	1.58 (1.39 to 1.78)	1.89 (1.59 to 2.26)
Warfarin vs NOACs						
OA	192	99 746	170	207 343	2.35 (1.91 to 2.89)	2.01 (1.56 to 2.58)
OA-related adverse event	254	99 684	197	207 316	2.68 (2.23 to 3.23)	2.19 (1.75 to 2.73)
Knee or hip replacements	181	99 757	216	207 297	1.74 (1.43 to 2.12)	1.61 (1.25 to 2.08)
Osteoarthropathies	258	99 680	198	207 315	2.71 (2.25 to 3.26)	2.21 (1.77 to 2.75)
NOACs vs all other drugs						
OA	170	207 343	10 854	7 903 670	0.60 (0.51 to 0.69)	0.48 (0.39 to 0.60)
OA-related adverse event	197	207 316	12 924	7 901 600	0.58 (0.50 to 0.67)	0.46 (0.38 to 0.57)
Knee or hip replacements	216	207 297	8964	7 905 560	0.92 (0.80 to 1.05)	0.88 (0.73 to 1.07)
Osteoarthropathies	198	207 315	13 209	7 901 315	0.57 (0.50 to 0.66)	0.45 (0.37 to 0.55)

IC, information component; NOACs, novel OACs; OA, osteoarthritis; OACs, oral anticoagulants; ROR, reporting OR.

limited attention has been paid to patient-reported outcome (ie, joint pain) in previous studies. Also, further large population-based studies are warranted to investigate the duration-response of warfarin-associated OA risk, which plays an important role in making causal inference.[10]

In conclusion, no signals of disproportionate reporting of OA with NOACs were identified, while significantly disproportionate association was found for warfarin. Warfarin's chronic adverse effect by interfacing with off-target vitamin K-dependent proteins deserves health professionals' attention.

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