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

We read with deep interest the article by Priyanka Ballal *et al*,[1] who investigated the risks of joint replacement associated with warfarin in comparison with direct oral anticoagulant (DOAC) usage. The authors concluded that warfarin, a vitamin K antagonist, was associated with a greater risk of KR and HR than DOACs.

However, we noticed that the percentages of patients receiving non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol were 39.3% and 67.8%, respectively, in the knee replacement/hip replacement (KR/HR) group (n=857) and 37.2% and 39.1%, respectively, in the control group (n=3428). Thus, the total analgesic usage was significantly higher in the KR/HR group, indicating more severe pain in the patients in this group. The principal clinical indication for knee and hip replacement is end-stage arthritis, or with persistent severe joint pain[2 3]; the joint pain is generally more severe in end-stage arthritis, and the degree of joint pain can reflect the severity of arthritis. However, the authors did not state the order of administration of analgesics and warfarin. Did warfarin increase the use of analgesics? Or were warfarin and analgesics started at the same time? Or was the analgesic administered before warfarin?

Furthermore, the paracetamol usage rate differed in the two groups (67.8% vs 39.1%). Paracetamol has been confirmed to potentiate the anticoagulant response produced by warfarin,[4] and this potentiation effect is likely to result from the ability of N-acetyl-para-benzoquinoneimine, paracetamol's toxic metabolite, to inhibit the enzymes of the vitamin K cycle.[5] Warfarin's anticoagulant effects also occur through inhibition of vitamin K functioning, which leads to inadequate functioning of Gla proteins and might be associated with the progression of osteoarthritis.

Taken together, these aspects indicate the need to further consider the interaction between paracetamol and warfarin and the influence of paracetamol on the effects of warfarin on osteoarthritis progression.

We respect the significant contributions of the authors and look forward to the follow-up results of this study.

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REFERENCES

1 Ballal P, Peloquin C, Boer CG, *et al*. Warfarin use and risk of knee and hip replacements. *Ann Rheum Dis* 2021;80:605–9.
2 Ferguson RJ, Palmer AJ, Taylor A, *et al*. Hip replacement. *Lancet* 2018;392:1662–71.
3 Price AJ, Alvand A, Troelsen A, *et al*. Knee replacement. *Lancet* 2018;392:1672–82.
4 Mahé I, Bertrand N, Drouet L, *et al*. Interaction between paracetamol and warfarin in patients: a double-blind, placebo-controlled, randomized study. *Haematologica* 2006;91:1621–7.
5 Thijssen HH, Soute BA, Vervoort LM, *et al*. Paracetamol (acetaminophen) warfarin interaction: NAPQI, the toxic metabolite of paracetamol, is an inhibitor of enzymes in the vitamin K cycle. *Thromb Haemost* 2004;92:797–802.