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# NSAIDs, hormonal contraception, and venous thromboembolism

## A harmful drug interaction that deserves more attention

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Venous thromboembolism is a multifactorial disease, involving interactions between inherited and acquired risk factors such as immobilisation, active cancer, trauma or fracture, recent surgery, and—in young women—pregnancy and hormonal contraception.[1] The magnitude of the risk from combined hormonal contraception depends on the dose of oestrogen and type of progestin.[2] Although oestrogen causes hypercoagulability by promoting gene transcription of multiple coagulation factors, the role of progestin is less clear.[3]

In a linked paper, Meaidi and colleagues (doi:10.1136/bmj-2022-074450) studied whether use of non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, diclofenac, and naproxen influences the risk of venous thromboembolism in otherwise healthy women using hormonal contraception.[4] NSAID use has previously been linked to venous thromboembolism,[5] although causality is debated. As most evidence comes from non-randomised studies,[6] unmeasured confounding, particularly confounding by indication, is a concern. Another concern is the potential use of NSAIDs for prodromal symptoms from incipient deep vein thrombosis, but this cannot explain the increased risk in long term users of NSAIDs.[5] The proposed mechanisms linking NSAID use to venous thrombosis include inhibition of cyclo-oxygenase-2 (COX-2) derived prostaglandins, which activate the coagulation system by promoting platelet aggregation and suppressing the expression of thrombomodulin.[7]

Meaidi and colleagues conducted a nationwide cohort study of women of reproductive age (15-49 years) in Denmark during 1996-2017.[4] Within a tax supported universal healthcare system,[8] they linked nationwide registries with patient, population, prescription, cause of death, and medical birth data.[9] The study included more than two million women, of whom 529 704 used NSAIDs while using hormonal contraception.[4] The study had long term follow-up for venous thromboembolic events (n=8710),[10] with accurate censoring at emigration and death.[9] The authors found that a short course of NSAIDs was associated with a higher risk of venous thromboembolism. The risk depended on whether the women were using hormonal contraception and was highest in those receiving high risk hormonal contraception, defined as combined oestrogen and progestin patches, vaginal rings, or tablets containing either 50 µg ethinyl oestradiol, specific progestins (desogestrel, gestodene, or drospirenone), or the anti-androgen cyproterone.[4]

The reported relative risks for NSAID associated venous thromboembolism were higher than reported in a meta-analysis of previous studies (pooled risk ratio 1.80).[6] In Meaidi and colleagues' study, NSAID use in young women not using hormonal contraception was associated with a sevenfold increased event rate. Relative risks are, however, often influenced (confounded) by the baseline risk.[11] Healthy young women have a low baseline risk, which likely contributed to the observed higher relative risk.[4]

In absolute terms, NSAID use was associated with four extra events per week per 100 000 women not using hormonal contraception, and 23 extra events in women using high risk hormonal contraception.[4] The study examined statistical interaction (by interaction coefficients) but not biological interaction or synergism.[12] Synergism can be assessed by estimating the difference in rate differences, known as the interaction contrast, comparing event rates among women using high risk or low risk hormonal contraception with or without NSAID use.[13] On this basis, NSAIDs appeared to interact with high risk hormonal contraception to increase the rate of venous thromboembolism substantially beyond that explained by their additive effects.

Among individual NSAIDs, the association was strongest for the older COX-2 inhibitor diclofenac (12-fold increased risk in women not using hormonal contraception).[14] These data add to existing evidence[11 15] and concerns[16] about the cardiovascular safety of diclofenac. Meaidi and colleagues did not explore the effect of dose,[4] but other data suggest that cardiovascular risks in users of high dose and low dose diclofenac are comparable.[17] Owing to safety concerns,[11] diclofenac has been withdrawn as an over-the-counter drug in several Nordic countries.[18] Nonetheless, it is among the most commonly used NSAIDs worldwide and remains available over-the-counter in most countries.[19]

In summary, the study by Meaidi and colleagues[4] provides good evidence that NSAIDs are associated with an increased risk of venous thromboembolism in women of reproductive age. A key finding was the interaction between NSAIDs and high risk hormonal contraception that showed an increased risk of venous thromboembolism in a synergistic manner. Although the absolute risk of venous thromboembolism within the first week after NSAID initiation remained low, even in women using high risk hormonal contraception, the association is of public health importance considering the high prevalence of NSAID use and hormonal contraception in young women.

These data raise important concerns about using NSAIDs, particularly diclofenac, and high risk hormonal contraception concomitantly. Healthcare authorities and regulators should include these

findings in their safety assessment of available over-the-counter diclofenac, and women using hormonal contraception and their clinicians should consider alternatives to NSAIDs for analgesia.[16] If treatment with NSAIDs is needed, agents other than diclofenac seem preferable, along with lower risk hormonal contraceptives such as progestin only tablets, implants, or intrauterine devices.

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1 Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol* 2015;12:-74. doi: 10.1038/nrcardio.2015.83 pmid: 26076949

2 Stegeman BH, de Bastos M, Rosendaal FR, etal. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. *BMJ* 2013;347:. doi: 10.1136/bmj.f5298 pmid: 24030561

3 Tchaikovski SN, Rosing J. Mechanisms of estrogen-induced venous thromboembolism. *Thromb Res* 2010;126:-11. doi: 10.1016/j.thromres.2010.01.045 pmid: 20163835

4 Meaidi A, Mascolo A, Sessa M, etal. Venous thromboembolism with use of hormonal contraception and non-steroidal anti-inflammatory drugs: nationwide cohort study. *BMJ* 2023;382:e074450.

5 Schmidt M, Christiansen CF, Horváth-Puhó E, Glynn RJ, Rothman KJ, Sørensen HT. Non-steroidal anti-inflammatory drug use and risk of venous thromboembolism. *J Thromb Haemost* 2011;9:-33. doi: 10.1111/j.1538-7836.2011.04354.x pmid: 21592304

6 Ungprasert P, Srivali N, Wijarnpreecha K, Charoenpong P, Knight EL. Non-steroidal anti-inflammatory drugs and risk of venous thromboembolism: a systematic review and meta-analysis. *Rheumatology (Oxford)* 2015;54:-42. doi: 10.1093/rheumatology/keu408 pmid: 25252703

7 Grosser T, Yu Y, Fitzgerald GA. Emotion recollected in tranquility: lessons learned from the COX-2 saga. *Annu Rev Med* 2010;61:-33. doi: 10.1146/annurev-med-011209-153129 pmid: 20059330

8 Schmidt M, Schmidt SAJ, Adelborg K, etal. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019;11:-91. doi: 10.2147/CLEP.S179083 pmid: 31372058

9 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;29:-9. doi: 10.1007/s10654-014-9930-3 pmid: 24965263

10 Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:-90. doi: 10.2147/CLEP.S91125 pmid: 26604824

11 Schmidt M, Sørensen HT, Pedersen L. Diclofenac use and cardiovascular risks: series of nationwide cohort studies. *BMJ* 2018;362:-10. doi: 10.1136/bmj.k3426 pmid: 30181258

12 VanderWeele TJ. Sufficient cause interactions and statistical interactions. *Epidemiology* 2009;20:-13. doi: 10.1097/EDE.0b013e31818f69e7 pmid: 19234396

13 Schmidt M, Horváth-Puhó E, Ording AG, Bøtker HE, Lash TL, Sørensen HT. The interaction effect of cardiac and non-cardiac comorbidity on myocardial infarction mortality: A nationwide cohort study. *Int J Cardiol* 2020;308:-8. doi: 10.1016/j.ijcard.2020.01.059 pmid: 32057473

14 Bonnesen K, Schmidt M. Recategorization of Non-Aspirin Nonsteroidal Anti-inflammatory Drugs According to Clinical Relevance: Abandoning the Traditional NSAID Terminology. *Can J Cardiol* 2021;37:-7. doi: 10.1016/j.cjca.2021.06.014 pmid: 34182020

15 Bhala N, Emberson J, Merhi A, etalCoxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013;382:-79. doi: 10.1016/S0140-6736(13)60900-9 pmid: 23726390

16 Schmidt M, Lamberts M, Olsen AM, etal. Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J* 2016;37:-23. doi: 10.1093/eurheartj/ehv505 pmid: 26984863

17 Schmidt M, Arendt-Nielsen L, Hauge E-M, Sørensen HT, Pedersen L. High- vs. low-dose diclofenac and cardiovascular risks: a target trial emulation. *Eur Heart J Cardiovasc Pharmacother* 2023;9:-61. doi: 10.1093/ehjcvp/pvad018 pmid: 36921986

18 Kristensen KB, Karlstad Ø, Martikainen JE, etal. Nonaspirin Nonsteroidal Antiinflammatory Drug Use in the Nordic Countries from a Cardiovascular Risk Perspective, 2000-2016: A Drug Utilization Study. *Pharmacotherapy* 2019;39:-60. doi: 10.1002/phar.2217 pmid: 30636337

19 McGettigan P, Henry D. Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries. *PLoS Med* 2013;10:e1001388. doi: 10.1371/journal.pmed.1001388 pmid: 23424288