Anticoagulation FORUM
Excellence in Thrombosis Care

Clinical FAQ: Drug-Drug Interactions
NSAIDs and OACs

Is it safe to continue an Oral NSAID with an Anticoagulant?

The combined use of NSAIDs and anticoagulants is discouraged given the significant increase in risk of bleeding when used concomitantly. A 2020 meta-analysis found a nearly twofold increased risk of gastrointestinal bleeding (GIB) when warfarin is combined with an NSAID vs warfarin alone.[1] Danish registry reviews evaluating this topic in patients with atrial fibrillation or after venous thrombombolism similarly have found a twofold or higher increased risk of GIB for patients using NSAIDs while on oral anticoagulation.[2-3]

When first encountering a patient with this combination, exploring alternative therapies for pain relief should be a priority. Oral NSAIDs are commonly used for the treatment of osteoarthritis (OA). The 2019 American College of Rheumatology (ACR) OA treatment guidelines recommend topical NSAID use over oral NSAID use due to less systemic exposure. They also strongly or conditionally recommend the use of non-pharmacological interventions (exercise, weight loss, tai chi, yoga, cognitive-behavioral therapy, acupuncture, etc.) and alternative pharmacological therapies (topical capsaicin, acetaminophen, duloxetine, tramadol, intraarticular glucocorticoid injections, etc.) for the treatment of OA depending on affected joint.[4]

If alternative therapies have been exhausted and a patient's quality of life is severely impacted in the absence of oral NSAIDs, shared decision making should be used to determine the best course of action. Patients must be well educated on the risks of the combination and instructed when to seek medical attention if abnormal bleeding does occur. For acute pain, lowest doses and shortest durations of NSAIDs should be used. Choice of anticoagulant should be considered as well. DOACs have a lower bleeding risk compared to warfarin. Among DOACs, apixaban appears to have a more favorable safety profile in terms of GIB while rivaroxaban appears to have the least favorable.[5-6] Additionally, studies have found that when combined with a PPI, the risk of GIB is significantly decreased.[7]

COX selectivity of NSAIDs can be considered as well. In general, NSAIDs with greater COX-2 selectivity (celecoxib, etodolac, meloxicam) are associated with less GIB but have also been associated with an increased risk in CV events and should be used with caution in those with underlying CV disease. A meta-analysis found that upper GIB rates of COX-2 selective agents were similar with that of diclofenac and ibuprofen.[8] Naproxen was not associated with an increased risk of CV events, but had a higer risk of GIB as compared with COX-2 selective agents.[8] Naproxen may also inhibit p-glycoprotein, thereby increasing apixaban exposure.[9]

Anticoagulation FORUM
Excellence in Thrombosis Care

Resources

1. Zapata L, Hansten P, Panic J, et al. Risk of Bleeding with Exposure to Warfarin and Nonsteroidal Anti-Inflammatory Drugs: A Systematic Review and Meta- Analysis. Thromb Haemost. 2020 Jul: 120(7):1066-1074.
2. Olsen A, McGettigan P, Gerds T, et al. Risk of gastrointestinal bleeding associated with oral anticoagulation and nonsteroidal anti-inflammatory drugs in patients with atrial fibrillation: a nationwide study. Eur Heart J Cardiovasc Pharmacother. 2020 Sept 1;6(5):292-300.
3. Petersen SR, Bonnesen K, Grove EL, Pedersen L, Schmidt M. Bleeding risk using non-steroidal anti-inflammatory drugs with anticoagulants after venous thromboembolism: a nationwide Danish study. *European Heart Journal*. 2024;46(1).
4. Kolasinski S, Neogi T, Hochberg M, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care & Research. Feb 2020: 72(2):149-162.
5. Vinogradova Y, Coupland C, Hill T, et al. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. BMJ. 2018;362:k2505.
6. Van Ganse E, Danchin N, Mahe I, et al. Comparative Safety and Effectiveness of Oral Anticoagulants in Non-valvular Atrial Fibrillation: The NAXOS Study. Stroke. 2020;51:2066-2075.
7. Ray WA, Chung CP, Murray KT, et al. Association of Oral Anticoagulants and Proton Pump Inhibitor Cotherapy With Hospitalization for Upper Gastrointestinal Tract Bleeding. *JAMA*. 2018;320(21):2221.
8. Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomized trials. Lancet 2013;9894:769–79.
9. Frost C, Shenker A, Gandhi MD, et al. Evaluation of the effect of naproxen on the pharmacokinetics and pharmacodynamics of apixaban [published online ahead of print April 2, 2014]. Br J Clin Pharmacol. 2014 Oct; 78(4):877-885.

Updated: April 2025 by Rebecca Cope, PharmD, MPH, BCACP
Next Review: April 2026.