Interaction Between Low-Dose Aspirin and Nonsteroidal Anti-Inflammatory Drugs Can Compromise Aspirin’s Efficacy in Preventing Venous Thrombosis Following Total Joint Arthroplasty

Eugene Krauss, MD, FAAN, FACS¹,²,³, MaryAnne Cronin, MS, PharmD³, Nancy Dengler, RN, NP³, and Ayal Segal, MD¹,³

Abstract
Total joint arthroplasty is a rapid recovery procedure with patients optimized quickly in preparation for discharge. Two significant postoperative goals are effective pain management and prevention of postoperative venous thromboembolism (VTE). Low-risk patients receive aspirin 81 mg twice daily for VTE prophylaxis; this dosing regimen has been reduced over the past few years from 325 mg to 162 mg to 81 mg twice daily. Unless contraindications exist, all patients receive multimodal pain management that includes the use of celecoxib or meloxicam. Upon reduction of the aspirin dose to 81 mg twice daily, we rapidly identified 2 patients who developed a pulmonary embolus when celecoxib or meloxicam was administered concurrently with aspirin. The interaction between nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin varies among the different NSAIDs. It is also highly dependent on numerous factors, including time of administration, dose of aspirin, and both pharmacodynamics and dose of the NSAID. Real-world outcomes of concomitant administration of NSAIDs with low-dose aspirin led to increased incidence of VTE, possibly due to competitive inhibition of aspirin at platelet receptor sites. This interaction was mitigated by altering the administration times of both agents.

Keywords
celecoxib, nonsteroidal anti-inflammatory drug, drug interaction, low-dose aspirin

Date received: 14 February 2020; revised: 24 March 2020; accepted: 24 March 2020.

Background
Total joint arthroplasty is a rapid recovery procedure with hospital length of stays shortened to 48 hours or less. Patients must be optimized quickly in preparation for discharge home. Two significant postoperative goals are effective pain management and prevention of postoperative venous thromboembolism (VTE).

The Department of Orthopaedic Surgery at Syosset Hospital/Northwell Health System performs over 1200 joint arthroplasties annually. All surgeons follow one standardized pain management and thromboprophylaxis protocol. Patients are risk-stratified for postoperative VTE using the 2013 version of the Caprini Risk Assessment Model.¹ Patients who score 9 or less are categorized as low-risk and receive aspirin enteric coated (EC) 81 mg twice daily for 6 weeks. Patients who score 10 or greater are considered high-risk.² High-risk patients receive apixaban 2.5 mg twice daily for 35 days for total hip arthroplasty (THA) and apixaban 2.5 mg twice daily for 12 days, followed by aspirin EC 81 mg twice daily for 4 weeks for total knee arthroplasty (TKA). All patients are called after postoperative day 60 to assess for any complications.

¹ Syosset Hospital, Northwell Health, New York Orthopaedic and Spine Center, Great Neck, NY, USA
² Zucker School of Medicine at Hofstra/Northwell, Hofstra University School of Medicine, New York Orthopaedic and Spine Center, Great Neck, NY, USA
³ Syosset Hospital, Northwell Health, Syosset, NY, USA

Corresponding Author:
MaryAnne Cronin, Syosset Hospital, Northwell Health, 221 Jericho Turnpike, Syosset, NY 11791, USA.
Email: mcronin@northwell.edu
Multimodal therapy has become the mainstay for postoperative pain management and includes around-the-clock dosing of acetaminophen plus an NSAID. This improves postsurgical pain control, reduces opiate consumption, and improves early mobilization and rehabilitation.5-8 This cocktail of medications has gained popularity not only due to its effectiveness in managing postoperative pain9-11 but also as a means to reduce narcotic consumption in light of the opioid crisis that currently exists in the United States.12

Total joint arthroplasty carries a significant risk of postoperative VTE, which includes deep vein thrombosis (DVT) and PE. National guidelines have recommended mechanical and/or chemical prophylaxis to prevent postoperative VTE.13,14 Over the past decade, new pharmacologic options have been approved for prevention of VTE following arthroplasty.15-17 In addition, resurgence of the time-honored agent, aspirin, has shown efficacy when used in appropriate, lower risk patients.2,18-20 The optimal dose of aspirin, however, is still up for debate within the orthopaedic community.

Aspirin is an inexpensive VTE treatment option. Aspirin 81 mg is associated with significantly less GI distress and nausea compared with aspirin 325 mg.21,22 Additionally, it has been shown to have improved antiplatelet efficacy in lower doses.23,24 Aspirin 81 mg is rapidly metabolized to an ineffective concentration, with a short half-life of 20 minutes in systemic circulation.25 Its mechanism of action is complete and irreversible inhibition of the synthesis of platelet thromboxane A2 by blocking the activity of platelet cyclooxygenase (COX)-1 throughout dosing intervals.26 This process, however, involves initial reversible binding with weak intrinsic affinity.27

Unlike aspirin, NSAIDs are reversible inhibitors of platelet COX-1, causing partial and intermittent inhibition of platelet thromboxane A2.26 Celecoxib is a COX-2 inhibitor with some inhibitory activity on COX-1. This agent has become our NSAID of choice due to its safer GI profile with effective pain control.

Platelets lack COX-2 and even supratherapeutic doses of COX-2 inhibitors have been shown not to interfere with platelet function.28 Multiple studies have concluded that celecoxib does not demonstrate any significant drug interaction with aspirin.29-31 However, 2 of the 3 studies looked at this interaction with aspirin 300 mg and aspirin 325 mg.29,30 Although the
third study did evaluate the interaction of celecoxib with low-dose aspirin (100 mg), these patients were receiving long-term treatment with aspirin for stable ischemic heart disease when the NSAID was introduced to the regimen. Of interest as well, all study patients were male. To date, no one has studied this treatment of aspirin for stable ischemic heart disease when the dose aspirin (100 mg), these patients were receiving long-term...

A distinct pharmacodynamic (PD) interaction exists whereby traditional NSAIDs that bind to the COX-1 receptor may prevent aspirin’s inhibition of platelets via effective competition, most likely at the level of platelet COX-1. Lawson et al were the first to describe this interaction between aspirin and ibuprofen. Subsequent studies have described a comparable PD interaction when traditional NSAIDs were administered concurrently with aspirin (Table 2). Collectively, the literature has reported an interaction between low-dose aspirin and COX-2 inhibitors in vitro. Rimon et al specifically studied celecoxib’s effect on low-dose aspirin (...)

### Table 2. Literature Review Describing Interaction Between Aspirin and NSAIDs.

| Authors         | Method                                                                 | Conclusions                                                                 |
|-----------------|------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Lawson et al    | Coadministration of aspirin 81 mg once daily with acetaminophen (1000 mg), ibuprofen (400 mg), diclofenac (75 mg), or rofecoxib (25 mg). The NSAIDs were administered either 2 hours before or 2 hours after the aspirin. | The concomitant administration of ibuprofen, but not rofecoxib, acetaminophen, or diclofenac antagonized the irreversible platelet inhibition induced by aspirin. The effect of ibuprofen could be bypassed by administering aspirin 2 hours before a single dose of ibuprofen; however, when multiple doses of ibuprofen were given, these competitive effects were seen. |
| MacDonald et al | Review of an anonymous database for 7107 patients who received low-dose aspirin (<325 mg) alone, aspirin plus ibuprofen, aspirin plus diclofenac, aspirin plus other NSAID | Statistically and clinically significant increased risk of mortality in users of aspirin plus ibuprofen compared with users of aspirin alone. No such increased risk was noted in users of aspirin plus diclofenac or other NSAIDs. |
| Capone et al    | Interaction between aspirin 100 mg and naproxen 500 mg twice daily in healthy patients in vitro and ex vivo | Naproxen interfered with the irreversible inhibitory effect of aspirin on platelet COX-1. Naproxen combined with aspirin might undermine the sustained inhibition of platelet COX-1 necessary for cardioprotection by aspirin. |
| Gladding et al  | Interaction between aspirin 300 mg and naproxen, tiaprofenic acid, ibuprofen, indomethacin, sulindac, and celecoxib. NSAIDs were given 2 hours prior to the aspirin. | Ibuprofen, indomethacin, naproxen, or tiaprofenic acid all block the antplatelet effect of aspirin. Sulindac and celecoxib did not demonstrate any significant antplatelet effect or reduce the antplatelet effect of aspirin. |
| Wilner et al    | Healthy volunteers received celecoxib (400 mg/d) or placebo for 4 days. On day 5, they also received a single 325 mg dose of aspirin with either 200 mg celecoxib or placebo. | There was also no significant difference in the effect of aspirin on platelet aggregation due to ADP, collagen, or arachidonic acid between the groups. Therefore, these data indicate that celecoxib does not alter the effects of aspirin on platelet function. |
| Renda et al     | Twenty-four patients who were undergoing long-term treatment with aspirin (100 mg daily) for cardioprotection were coadministered celecoxib 200 mg twice daily, ibuprofen 600 mg 3 times daily, or placebo for 7 days | Unlike ibuprofen, celecoxib did not interfere with the inhibition of platelet COX-1 activity and function by aspirin despite a comparable suppression of COX-2 ex vivo in patients with osteoarthritis and stable ischemic heart disease. |
| Rimon et al     | In vitro and in vivo analysis (in dogs) of the effect of celecoxib administered at 8 AM and 5 PM with aspirin 81 mg administered at 12 PM | In vivo results indicated that celecoxib could interfere with the action of aspirin on COX-1 in vivo, and in the dog model, celecoxib did interfere with the effect of low-dose aspirin. |
| Saxena et al    | In vitro analysis in healthy volunteers. Aspirin either alone or in combination with ibuprofen, naproxen, oxaprozin, diclofenac, ketorolac, flufenamic acid, piroxicam, dipyramone, and celecoxib. | Unlike ibuprofen, celecoxib did not interfere with the inhibition of platelet COX-1 and aspirin despite a comparable suppression of COX-2 ex vivo in patients with osteoarthritis and stable ischemic heart disease. |
| Ruzov et al     | Ex vivo interaction between celecoxib and aspirin for COX-1 binding and measured resulting antplatelet effects. Data were then analyzed using PK/PD modeling to predict in vivo platelet aggregation for different doses and administration schedules for aspirin and celecoxib. | Celecoxib (100 mg twice daily) can attenuate to a limited extent the in vivo antplatelet effects of low-dose aspirin. This interaction can be substantial during the first few days of aspirin initiation in patients already treated with celecoxib and cannot be prevented by separating administration times. However, at high doses celecoxib will compete efficiently with low-dose aspirin and may be mitigated by changing administration times. |

Abbreviations: ADP, adenosine 5'-diphosphate; COX-1, cyclooxygenase 1; NSAIDs, nonsteroidal anti-inflammatory drugs; PK/PD, pharmacokinetics/pharmacodynamics.
determined that celecoxib binds tightly to the regulatory sub-unit of the COX-1 enzyme and does interfere with aspirin’s ability to inactivate COX-1.

These conflicting results investigating the interaction between celecoxib and aspirin may be due to several factors. Gurbel et al concluded that the interaction between NSAIDs and aspirin is variable and depends on the dose of aspirin, dose of NSAID, and dose timing. Additionally, in vivo and ex vivo results are not always reflective of the complexity of thrombosis mechanisms. Gurbel et al evaluated celecoxib 200 mg once daily with various aspirin doses and suggested that the interaction can be substantial during the first day of aspirin administration in patients already treated with celecoxib, and it cannot be prevented by separating administration times of the drugs. For a patient treated chronically with low-dose aspirin, the addition of celecoxib 200 mg once daily is not expected to mitigate aspirin’s antiplatelet effects. At high doses, however, celecoxib is able to compete efficiently with aspirin for COX-1 binding in vivo and can interfere with the antiplatelet effects of low-dose aspirin. Saxena et al confirmed these findings and showed increasing interference with higher celecoxib concentration. Finally, Hohlfeld et al noted discrepancies between aspirin and NSAIDs with respect to both half-life and binding affinity; they concluded that based on half-life, ASA would be inactivated prior to COX enzyme binding, and the presence of an NSAID with ASA would prevent the access of ASA to platelet receptor sites due to differences in binding affinity.

Our low-risk patients currently receive aspirin EC 81 mg twice daily for VTE prophylaxis. Unless contraindications exist, all patients receive multimodal pain management that includes the use of celecoxib 200mg every 12 hours or meloxicam 15mg once daily. We did not see the same PD interaction when NSAIDs were administered with aspirin 325 mg twice daily or aspirin 162 mg twice daily. However, upon reduction of aspirin dose to 81 mg twice daily, we rapidly identified 2 patients who developed a PE when celecoxib or meloxicam was administered concurrently with aspirin after total joint arthroplasty.

Emerging evidence supports the theory that the timing of NSAID and aspirin administration appears to influence the degree of interaction. Gurbel et al recommended administering naproxen at least 2 hours after an aspirin dose to diminish the interaction. Following this recommendation, the dosing schedule was altered for our postoperative arthroplasty patients with EC aspirin scheduled for 0600 and 1800 administration daily. Celecoxib is administered at 0900 and 2100; meloxicam is administered at 0900 daily. Patients are educated prior to discharge on the importance of continuing this practice at home and are specifically instructed to take aspirin at least 2 hours before the NSAID; they are given patient-specific medication calendars with times of administration listed for the duration of therapy. After initiating this dosing schedule, only 2 VTE events were noted postoperatively in the low-risk group over the following year. A detailed review revealed that both were female THA patients and both took the aspirin at the same time each day as the NSAID (1 on celecoxib and 1 on meloxicam).

**Conclusion**

The interaction between NSAIDs and low-dose aspirin varies among the different NSAIDs. It is highly dependent on numerous factors, including time of administration, dose of aspirin, and both PD and dose of the NSAID. Concurrent administration of aspirin and NSAIDs is common in clinical practice and remains an area for further research. Acetaminophen has never shown any interaction with aspirin and is safe to give concurrently with aspirin.

Real-world outcomes of concomitant administration of NSAIDs with low-dose aspirin led to increased incidence of VTE, possibly due to competitive inhibition of aspirin at platelet receptor sites. This interaction was mitigated by altering administration times of both agents. Patients prescribed low-dose aspirin and NSAIDs, including the COX-2 inhibitor celecoxib, must be educated to modify dosing regimens so that aspirin is administered at least 2 hours prior to the NSAID. This adjustment in timing of administration has shown efficacy to minimize interference of the antiplatelet effects of low-dose aspirin.

This is a case study manuscript. Information collected is part of department annual performance improvement metrics. Informed consent for patient information to be published in this article was not obtained because patient information is de-identified.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

**ORCID iD**

MaryAnne Cronin https://orcid.org/0000-0002-7498-1564

**References**

1. Illinois Medical Society. 2013. https://www.venousdisease.com/caprini-dvt-risk-assessment.pdf.
2. Krauss ES, Segal A, Cronin M, et al. Implementation and validation of the 2013 Caprini score for risk stratification of arthroplasty patients in the prevention of venous thrombosis. Clin Appl Thromb Hemost. 2019;25:1-9. doi:10.1177/1076029619838066.
3. Parvizi J, Ceylan HH, Kucukdurmaz F, et al. Venous thromboembolism following hip and knee arthroplasty. The role of aspirin. J Bone Joint Surg Am. 2017;99(1):961-972.
4. Li C, Hirsh J, Sloane D, et al. Aspirin response variability after major orthopedic surgery. Thromb Res. 2012;130(2):216-220. doi:10.1016/j.thromres.2012.04.006.
5. Soffin EM, Wu CL. Regional and multimodal analgesia to reduce opioid use after total joint arthroplasty: a narrative review. HSSJ. 2019;15(1):57-65. doi:10.1007/s11420-018-9652-2.
6. Manworren R. Multimodal pain management and the future of a personalized medicine approach to pain. AORN J. 2015;101(3):308-314.
7. Li J, Ma Y, Xiao L. Postoperative pain management in total knee arthroplasty. Orthopaedic Surg. 2019;11(5):755-761. doi:10.1111/ots.12535.

8. Lee SK, Lee JW, Choy WS. Is multimodal analgesia as effective as postoperative patient-controlled analgesia following upper extremity surgery? Orthop Traumatol Surg Res. 2013;99(8):895-901. doi:10.1016/j.otsr.2013.09.005.

9. Gritsenko K, Khelemsky Y, Kaye AD, Vadivelu N, Urman RD. Multimodal therapy in perioperative analgesia. Best Pract Res Clin Anaesthesiol. 2014;28(1):59-79.

10. Halawi M, Grant SA, Bolognesi MP. Multimodal analgesia for total joint arthroplasty. Orthopedics 2015;38(7):e616-e625.

11. Chen J, Zhu W, Zhang Z, et al. Efficacy of celecoxib for acute pain management following total hip arthroplasty in elderly patients: a prospective, randomized, placebo-control trial. Expe Ther Med. 2015;10(2):737-742.

12. Morris BJ, Mir HR. The opioid epidemic: impact on orthopaedic surgery. J Am Acad Orthop Surg. 2015;23(5):267-271.

13. Johanson NA, Lachiewicz PF, Lieberman JR, et al. American academy of orthopaedic surgeons clinical guideline on prevention of pulmonary embolism in patients undergoing total hip or knee arthroplasty. Adopted by the American Academy of Orthopaedic Surgeons Board of Directors. 2007 prevention of symptomatic pulmonary embolism in patients undergoing total hip or knee arthroplasty. J Am Acad Orthop Surg. 2009;17:183-196. doi:10.2106/JBJS.1.00511.

14. Ytter YF, Francis C, Johanson N, et al. Prevention of VTE in orthopedic surgery patients: anti-thrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(suppl 2):e278S-e325S. doi:10.1378/chest.11-2404.

15. Xarelto (rivaroxaban) [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2011.

16. Eliquis (apixaban) [package insert]. Princeton, NJ: Bristol-Myer Squibb; 2012.

17. Pradaxa (dabigatran etexilate mesylate) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; 2019.

18. Parvisi J, Ceylan HH, Kucukdurmaz F, Merli G, Tuncay I, Beverland D. Venous thromboembolism following hip and knee arthroplasty. The role of aspirin. J Bone Joint Surg Am. 2017;99(11):961-972.

19. Odeh K, Doran J, Yu S, Bolz N, Bosco J, Iori R. Risk-stratified venous thromboembolism prophylaxis after total joint arthroplasty: aspirin and sequential pneumatic compression devices vs aggressive chemoprophylaxis. J Arthroplasty 2016;31(9 suppl):S78-S82.

20. Ogonda L, Hill J, Doran E, Dennison J, Stevenson M, Beverland D. Aspirin for thromboprophylaxis after primary lower limb arthroplasty. The role of aspirin. J Bone Joint Surg Am. 2017;99(11):961-972.

21. Feldstein MJ, Low SL, Chen AF, Woodward LA, Hozack WJ. A comparison of two dosing regimens of ASA following total hip and knee arthroplasties. J Arthroplasty. 2017;32(9 suppl):S157-S161. doi:10.1016/j.arth.2017.01.009.

22. Victor L, Serebruany VL, Steinhuhl SR, et al. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. Am J Cardiol. 2005;95(10):1218-1222. doi:10.1016/j.amjcard.2005.01.049.

23. Becattini C, Agnelli G. Aspirin for prevention and treatment of venous thromboembolism. Blood Rev. 2014;28(3):103-108. doi:10.1016/j.blre.2014.03.003.

24. Brighton TA, Eikelboom JW, Mann K, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med. 2012;367(21):1979-1987. doi:10.1056/NEJMoai1210384.

25. Patrick J, Dillaha L, Armas D, Sessa WC. A randomized trial to assess the pharmacodynamics and pharmacokinetics of a single dose of an extended-release aspirin formulation. Postgrad Med 2015;127(6):573-580.

26. Capone ML, Sciulli MG, Tacconelli S, et al. Pharmacodynamic interaction of naproxen with low-dose aspirin in healthy subjects. Am Coll Cardiol. 2005;45(8):1295-1301. doi:10.1016/j.jacc.2005.01.045.

27. Ouellet M, Riendeau D, Percival D. A high level of cyclooxygenase-2 inhibitor selectivity is associated with a reduced interference of platelet cyclooxygenase-1 inactivation by aspirin. Proc Natl Acad Sci U S A. 2001;98(25):14583-14588.

28. Ekman EF, Koman LA. Acute pain following musculoskeletal injuries and orthopaedic surgery: mechanisms and management. Instr Course Lect. 2005;54:21-33.

29. Gladding PA, Webster MW, Farrell HB, Irene SLZ, Park R, Ruine N. The antiplatelet effect of six non-steroidal anti-inflammatory drugs and their pharmacodynamic interaction with aspirin in healthy volunteers. Am J Cardiol. 2008;101(7):1060-1063.

30. Wilner KD, Rushing M, Walden C, et al. Celecoxib does not affect the antiplatelet activity of aspirin in healthy volunteers. J Clin Pharmacol. 2002;42(9):1027-1030.

31. Renda G, Tacconelli S, Capone ML, et al. Celecoxib, ibuprofen, and the antiplatelet effect of aspirin in patients with osteoarthritis and ischemic heart disease. Clin Pharmacol Ther. 2006;80(3):264-274.

32. Saxena A, Balaramnavar VM, Hohlfeld H, Saxena AK. Drug/drug interaction of common NSAIDs with antiplatelet effect of aspirin in human platelets. Eur J Pharmacol. 2013;721(1-3):215-224. doi:10.1016/j.ejphar.2013.09.032.

33. Lawson FC, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med. 2001; 345(25):1809-1817.

34. MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. Lancet. 2003;361(9357):573-574.

35. Rimon G, Sidhu R, Lauver DA, et al. Coxibs interfere with the action of aspirin by binding tightly to one monomer of cyclooxygenase-1. PNAS. 2010;107(1):28-33.

36. Ruzov M, Rimon G, Pikovsky O, Stepensky D. Celecoxib interferes with the limited extent with aspirin-mediated inhibition of platelets aggregation. Br J Clin Pharmacol 2015;81(2):316-326.

37. Gurbel P, Tantry U, Weisman S. A narrative review of the cardiovascular risks associated with concomitant aspirin and NSAID use. J Thromb Thrombolysis. 2019;47(1):16-30. doi:10.1007/s11239-018-1764-5.

38. Hohlfeld T, Saxena A, Schrö R. High on treatment platelet reactivity against aspirin by non-steroidal anti-inflammatory drugs—pharmacological mechanisms and clinical relevance [Published online of print December 13, 2012]. Thromb Haemost. 2013; 109(5):825-833. doi:10.1160/TH12-07-0532.