REVIEW ARTICLE

Balancing cardiovascular and gastrointestinal risks in patients with osteoarthritis receiving nonsteroidal anti-inflammatory drugs

A summary of guidelines from an international expert group

Wassim Mosleh[1], Michael E. Farkouh[2]

1 Department of Internal Medicine, University at Buffalo, Buffalo, New York, United States
2 Peter Munk Cardiac Centre and the Heart and Stroke Richard Lewar Centre, University of Toronto, Toronto, Ontario, Canada

KEY WORDS

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ABSTRACT

Over the past 2 decades, extensive research has assessed the use of traditional nonsteroidal anti-inflammatory drugs (NSAIDs), and the newer cyclooxygenase-2 (COX-2) inhibitor drugs, in the treatment of chronic pain syndromes. The proper use of NSAIDs has been the subject of significant debate, bringing together multidisciplinary researchers and clinicians to discuss the risks and benefits of these therapies. Current guidelines discussing the proper use of NSAIDs do not address the issue of the risks of COX-2-selective NSAIDs and nonselective NSAIDs for both the gastrointestinal (GI) and cardiovascular (CV) systems in patients on low-dose aspirin. Accordingly, a multidisciplinary expert group was organized to review the current evidence with the aim of developing statements devoted to guide clinicians in making evidence-based and individualized selections of NSAIDs. This review will discuss and summarize the most recent evidence on this topic to give an insight into the most effective and safest therapeutic options, thus preventing serious adverse CV and GI events. NSAIDs should be used cautiously and as infrequently as possible, with nonpharmacological approaches prescribed first. If the use of NSAIDs is required, the choice should balance the possible CV and GI risks.

Correspondence to:
Michael E. Farkouh, MD, MSc, FRCPC, FACC, FAHA, Peter Munk Cardiac Centre and the Heart and Stroke Richard Lewar Centre, University of Toronto, 85 University Avenue, 4N474, Toronto, Ontario M5G 2N2, Canada, phone: +1 416 340 3141, e-mail: michael.farkouh@uhn.ca
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Introduction As population ages and the prevalence of chronic conditions such as osteoarthritis increases, the number of patients suffering from pain is also expected to rise. Over the past 2 decades, extensive research has assessed the use of traditional nonsteroidal anti-inflammatory drugs (NSAIDs), and the newer cyclooxygenase-2 (COX-2) inhibitor drugs, in the treatment of chronic pain syndromes. The proper use of NSAIDs has been the subject of significant debate, bringing together multidisciplinary researchers and clinicians to discuss the risks and benefits of these therapies. In order to help physicians in attaining safe pain management, organizations such as the American Pain Society, American College of Rheumatology,[1] and the European League Against Rheumatism[2] developed different treatment guidelines. Furthermore, the debate on the appropriate use of NSAIDs resulted in important developments and new insights into the safety of NSAIDs, with particular focus on the proper use of these drugs and their safety regarding cardiovascular (CV) and gastrointestinal (GI) risks.

While NSAIDs are effective in pain-relieving medications, their use can lead to adverse reactions involving the CV system and GI tract. GI adverse reactions include dyspepsia, heartburn, peptic ulcer disease, perforation, and bleeding.[3] Therefore, preventive strategies should be in place for patients with upper GI risk, such as the use of the lowest effective dose of a NSAID, a co-therapy with proton pump inhibitors (PPIs), or the use of a COX-2-selective agent.[4,5] However, since the occurrence of CV comorbidity is substantial in patients with osteoarthritis,[6] and a great percentage of patients with osteoarthritis

are simultaneous users of low-dose aspirin,[7] there has been a great focus lately on adverse CV effects of COX-2-selective NSAIDs. This provoked a reassessment of the safety profile of traditional NSAIDs.

The increased CV risk of COX-2-selective inhibitors has been well documented in randomized controlled trials (RCTs) and observational studies. However, substantial evidence suggests that also nonspecific NSAIDs (ns-NSAIDs) may increase this risk.[8] Therefore, the benefits of the anti-inflammatory and analgesic activity of different NSAIDs should be balanced against their possible CV and GI risks concomitantly. Numerous guidelines describe the proper use of NSAIDs[1,5,9,10]; however, none of them look into the risks of ns-NSAIDs and COX-2-selective NSAIDs for both the CV and GI systems in patients taking low-dose aspirin. Accordingly, a multidisciplinary expert group was organized to evaluate the existing evidence with the goal of developing statements devoted to guide clinicians in making evidence-based and individualized selections of NSAIDs, as detailed in the consensus paper by Scarpignato et al.[11] This review uses that study as the basis for discussing and summarizing the most recent evidence on this topic, in order to give an insight for the most effective and safest therapeutic options, thus preventing serious adverse CV and GI events.

In 2011, a series of meetings of a multidisciplinary expert group were held in Amsterdam (Netherlands) and Treviso (Italy), in order to address current issues around CV and GI risk associated with NSAIDs and their appropriate use. This concluded in the Expert Summit meeting (Amsterdam, November 15–16, 2011), where experts voted on 9 clinical evidence-based statements about NSAID-associated CV and GI risks. After in-depth discussions, consensus was reached on all 9 statements based on the modified Delphi consensus process. The outcome of this was a consensus paper by Scarpignato et al,[11] the essence of which will be reviewed below.

Efficacy and cost-effectiveness The debate about whether ns-NSAIDs or COX-2-selective inhibitors should be used in patients with osteoarthritis is frequently controlled by the possible GI and CV events. However, the comparative analgesic and anti-inflammatory efficacy is also important. Comparative effectiveness has been shown in several RCTs.[12-18] For instance, 1 RCT showed that etoricoxib had similar effectiveness as diclofenac in patients with osteoarthritis.[14] Another RCT showed that celecoxib had similar effectiveness to naproxen.[15] In the Celecoxib versus Omeprazole and Diclofenac in Patients with Osteoarthritis and Rheumatoid arthritis (CONDOR) study, there was no difference in the effectiveness of celecoxib and diclofenac in patients with osteoarthritis.[17]

Cost also influences therapeutic choices. Both medication costs and the economic burden on the health care system of NSAID-induced GI or CV events should be taken into account. Using a PPI with a COX-2-selective inhibitor or an ns-NSAID for patients with low and high GI risk is a cost-effective treatment strategy.[19] After the results of the CONDOR study,[16] the economic model of the 2008 National Institute for Health and Care Excellence clinical guideline was updated to include relative risks of adverse events concerning the lower GI tract.[20] The results of the analysis showed that celecoxib plus a PPI is a cost-effective strategy for the treatment of osteoarthritis compared with diclofenac plus a PPI.

Thus, the decision between COX-2-selective inhibitors and ns-NSAIDs does not heavily depend on the efficacy or cost-effectiveness of each, but more so on the GI and CV risk profile of each patient.

Safety **Cardiovascular risk of nonsteroidal anti-inflammatory drugs** The presence of CV comorbidity is common in patients with osteoarthritis and is linked to almost all NSAIDs.[6] Therefore, it is important to investigate the CV adverse events with the use of different NSAIDs in patients with osteoarthritis. A study by Graham et al[21] showed that both ns-NSAIDs and rofecoxib were associated with an increased CV risk of adverse events. Several RCTs and meta-analyses aimed at comparing the association of CV risk of adverse events between ns-NSAIDs and COX-2-selective NSAIDs. On one hand, the Vioxx™ Gastrointestinal Outcomes Research (VIGOR) trial showed that rofecoxib was associated with a greater occurrence of adverse CV events than naproxen in patients not using aspirin.[17] Furthermore, a meta-analysis of all rofecoxib trials demonstrated a great increase in CV events when higher doses where used.[22] This trial introduced an important question regarding CV risk of COX-2-selective inhibitors and their safety compared with ns-NSAIDs. In contrast, in the subsequent years, many other RCTs and meta-analyses emerged to demonstrate that CV events were either higher in ns-NSAIDs, such as naproxen,[23] or equivalent,[8,14,24-27] when compared with COX-2-selective NSAIDs. Three main trials (The Celecoxib Long-term Arthritis Safety Study [CLASS], Therapeutic Arthritis Research and Gastrointestinal Event Trial [TARGET], and Multinational Etoricoxib and Diclofenac Arthritis Long-term trial [MEDAL]) evaluated the safety of a COX-2-selective inhibitor in comparison with a nonselective NSAID.[14,24,28] The CLASS study showed a similar CV risk between celecoxib and ns-NSAIDs.[24] The TARGET trial showed a higher CV event rate in ibuprofen users compared with lumiracoxib users.[28] The MEDAL trials showed that etoricoxib was comparable to diclofenac.[14] Focusing on celecoxib specifically, several studies have shown that it is associated with the same overall CV risk of ns-NSAIDs.[8,27,29,30]

Of note, the results of the different trials depend on which ns-NSAID was the comparator. Consequently, there are a number of NSAID features besides their COX-2 selectivity.[31] Five

major predictors of CV toxicity were found, including: "1) the degree of COX-2 selectivity; 2) the effect of the NSAID on systolic blood pressure; 3) the half-life of the medication; 4) the dosing of the medication; and 5) the interaction of the NSAID with aspirin in patients at highest CV risk".[32] These predictors of cardiotoxicity were illustrated in the outcome trials. For instance, rofecoxib has greater COX-2 selectivity than celecoxib and was thus found to be associated with greater CV toxicity. Diclofenac and ibuprofen caused an increase in systolic blood pressure in osteoarthritic patients and showed greater cardiotoxicity when compared with celecoxib. Lumiracoxib had a lower effect on blood pressure and a lower half-life, thus demonstrating a better safety profile compared with ibuprofen. Finally, ibuprofen is well known for negatively interacting with aspirin when given concomitantly.

It was also found that while CV risk of high-dose diclofenac and ibuprofen is comparable to that of selective COX-2 agents, high-dose naproxen was associated with less vascular risk than other NSAIDs.[30] However, it is important to note that this benefit towards naproxen is compromised by its greater GI toxicity. Naproxen has double the GI risk of all other ns-NSAIDs.[30] Also, this was based on a nonrandomized comparison between the different agents. Therefore, taking into consideration collective data from meta-analyses, RCTs, and observational studies, the CV risk is generally elevated both for COX-2-selective inhibitors and for ns-NSAIDs. However, the decrease in the rates of upper GI events in COX-2-selective inhibitors was greater than the increase in the rates of CV event (myocardial infarction, vascular death, or stroke), for which there was no difference between COX-2-selective inhibitors and ns-NSAIDs.[33] The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) study is expected to provide key findings about the relative CV safety of celecoxib, naproxen, and ibuprofen, and will be the first RCT to evaluate the comparative CV safety of anti-inflammatory drugs.[34]

Furthermore, there has been a discussion whether or not COX-2-selective inhibitors also restrict the antiplatelet effect of aspirin. All ns-NSAIDs impede thromboxane A_2 synthesis and therefore platelet aggregation,[35-37] except for diclofenac[38] and meloxicam.[39] RCTs show that, in patients on low-dose aspirin, the use of ns-NSAIDs worsens the cardiovascular outcomes, as one study showed an elevated risk of acute myocardial infarction.[40] The TARGET also showed that there was a greater rate of CV events in ibuprofen in comparison with lumiracoxib when used concomitantly with low-dose aspirin.[28] Therefore, since COX-2-selective NSAIDs do not affect COX-1-dependent platelet aggregation,[38,41-44] they should be the first-line anti-inflammatory drugs for patients taking low-dose aspirin for CV prevention.[45] However, this should only be done when their use is unavoidable with other therapies, and their benefits must be balanced with the CV risks unique to each individual patient based on their clinical picture.

Gastrointestinal risks of nonsteroidal anti-inflammatory drugs The use of NSAIDs is associated with an increased risk of adverse events throughout the entire GI tract. Several studies and meta-analyses have documented the GI adverse effects of NSAIDs.[46-48] The majority of these studies have reported adverse events in the upper GI tract, such as perforations, ulcers, and GI bleeding. Therefore, the use of gastroprotective strategies in at-risk patients (patients with a history of GI ulcers, advanced age, use of medications such as low-dose aspirin or anticoagulants, and *Helicobacter pylori* infection)[49] treated with NSAIDs has been adopted by different guidelines.[50,51] However, a recent trend has shown a decrease in upper GI events and a significant increase in lower GI events.[52] In the VIGOR trial, over 40% of the NSAID-related events occurred in the lower GI tract.[53] Yet, NSAID-induced adverse events in the lower GI tract are not prevented by PPIs.[3,54,55]

COX-2-selective NSAIDs also damage the small bowel, but with lower frequency and severity of events than ns-NSAIDs do. This has been validated by a systematic review, which illustrated that COX-2-selective inhibitors showed a significantly lower rate of adverse effects on the small bowel in comparison with ns-NSAIDs.[56] This was true for celecoxib also when an ns-NSAID was used along with a PPI, as shown by capsule-endoscopy studies.[57,58] Celecoxib was found to lead to fewer adverse events within the complete GI tract compared with ns-NSAIDs. As regards the upper GI tract, studies have shown that celecoxib is as safe as using an ns-NSAID plus a PPI.[59] A meta-analysis also showed that the use of COX-2-selective inhibitors results in significantly lower rates of gastroduodenal ulcers and their complications than the use of ns-NSAIDs does.[60] As for the lower GI tract, the CONDOR trial showed that the proportion of patients with clinically significant events throughout the GI tract was significantly greater in patients taking diclofenac in combination with omeprazole than in those taking celecoxib.[16] This was also confirmed by the GI-REASONS trial, which illustrated that the use of celecoxib led to a lower risk of upper and lower GI events than the use of ns-NSAIDs did.[61]

There are limited data on the safety of COX-2-selective inhibitors other than celecoxib for the lower GI tract. Two outcome studies (VIGOR and CONDOR) showed a reduced risk of more serious events in the lower GI tract for rofecoxib and celecoxib[16,53]; however, this benefit was not illustrated for etoricoxib in the MEDAL trial.[62]

Furthermore, while adverse events of the upper GI tract can be diminished by PPIs, their inefficacy in reducing lower GI tract injury should be addressed. The use of COX-2-selective inhibitors could assist in reducing adverse events in the entire GI tract; however, the best preventive

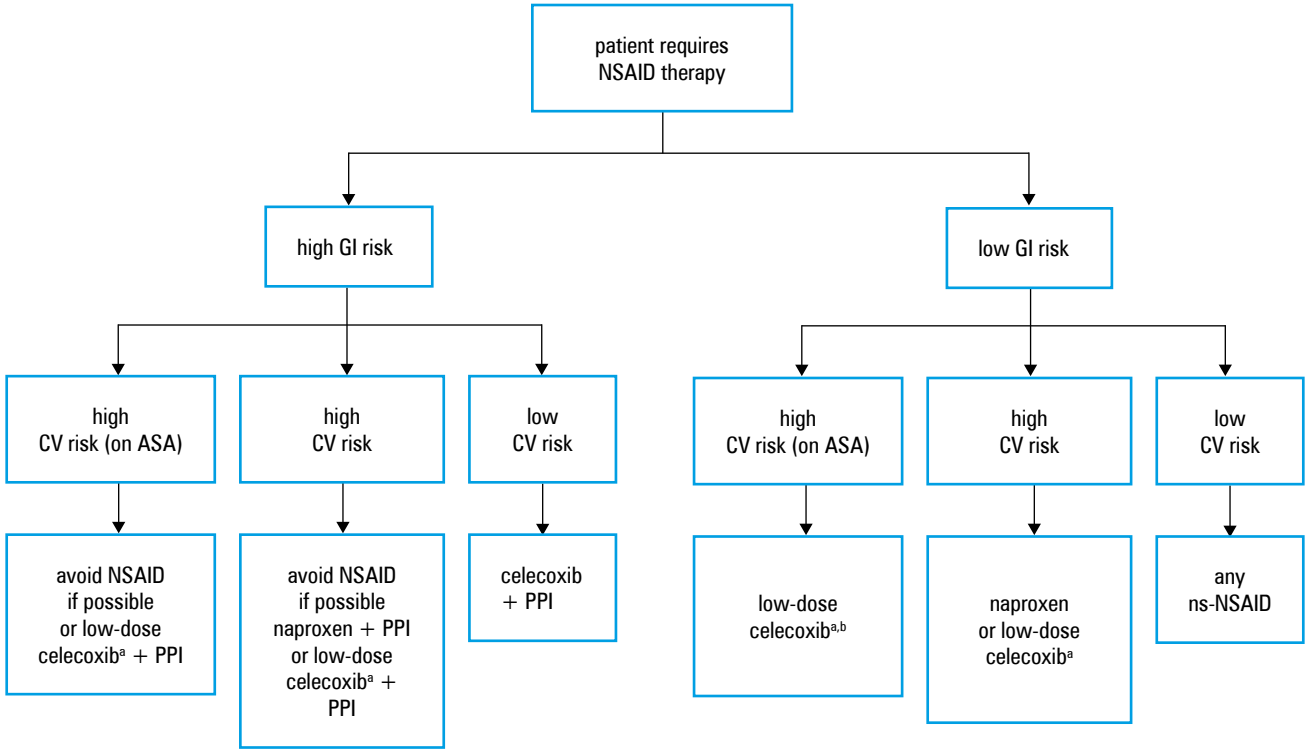

FIGURE 1 Algorithm for long-term nonsteroidal anti-inflammatory drug therapy according to patient's gastrointestinal and cardiovascular risk factors. Adapted from Scarpignato et al.[11]

Helicobacter pylori infection should be tested and treated, if present, in patients with peptic ulcer history.

a 200 mg once daily; **b** in selected patients, gastroprotection with a PPI may be indicated

Abbreviations: ASA, acetylsalicylic acid; CV, cardiovascular; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor

method for adverse events in the lower GI tract in NSAID users remains to be identified.

What is of particular importance to cardiovascular patients is that a combination of celecoxib and low-dose aspirin also reduces the risk of adverse events in the upper GI tract, in comparison with ns-NSAIDs combined with low-dose aspirin.[63-66] The risk of upper GI events due to the use of ns-NSAIDs is aggravated by a simultaneous use of low-dose aspirin.[67] A study found that combining celecoxib and low-dose aspirin was associated with a lower risk than the use of ns-NSAIDs in combination with low-dose aspirin was.[63] Similarly, a meta-analysis showed that the relative risk of ulcer, bleeding, and perforation in patients using low-dose aspirin with COX-2-selective inhibitors and low-dose aspirin with ns-NSAIDs was 0.72 (95% confidence interval, 0.62–0.95).[60] However, conflicting data were reported in the MEDAL program, which compared etoricoxib with diclofenac in patients with osteoarthritis and rheumatoid arthritis taking low-dose aspirin, as it showed no significant difference between the 2 anti-inflammatory drugs.[68]

In essence, COX-2-selective agents are safer for the upper GI than ns-NSAIDs are; however, evidence remains inconclusive with regards to their individual tolerability by the lower GI tract. While adverse events in the lower GI tract were significantly reduced with the use of celecoxib and rofecoxib in comparison with the use of ns-NSAIDs, this was not observed for etoricoxib. Also, as shown by the CONDOR and GI-REASONS trials, celecoxib has a better GI safety profile in the entire GI tract compared with diclofenac plus omeprazole.

Putting it all together The definitive systematic overview by the Coxib and traditional NSAID Trialists' (CNT) Collaboration confirmed that naproxen did not increase the rate of major cardiovascular events as opposed to all other NSAIDs and may be ideal to use in CV patients if tolerated by the GI tract. It is a must read for all practitioners.[30]

This is where a dilemma arises and where clinicians must weigh the risks and benefits to patients. The superiority of celecoxib, given its tolerability in the whole GI tract as described above, advocates its use along with a PPI as the best approach for reducing the rate of lower and upper GI adverse events in high-risk GI patients. An algorithm as a general guidance for the use of NSAID therapy considering GI and CV risks was proposed by Scarpignato et al,[11] as illustrated in FIGURE 1. The prior recommendations for minimizing the use of non-naproxen ns-NSAIDs when ns-NSAIDS are recommended in favor of naproxen should still hold and is an important but controversial interpretation of this algorithm. FIGURE 2 illustrates data from the CNT, showing that naproxen is safer than non-naproxen ns-NSAIDs with regards to CV risk, and the greater GI protective effects of coxibs over ns-NSAIDs.

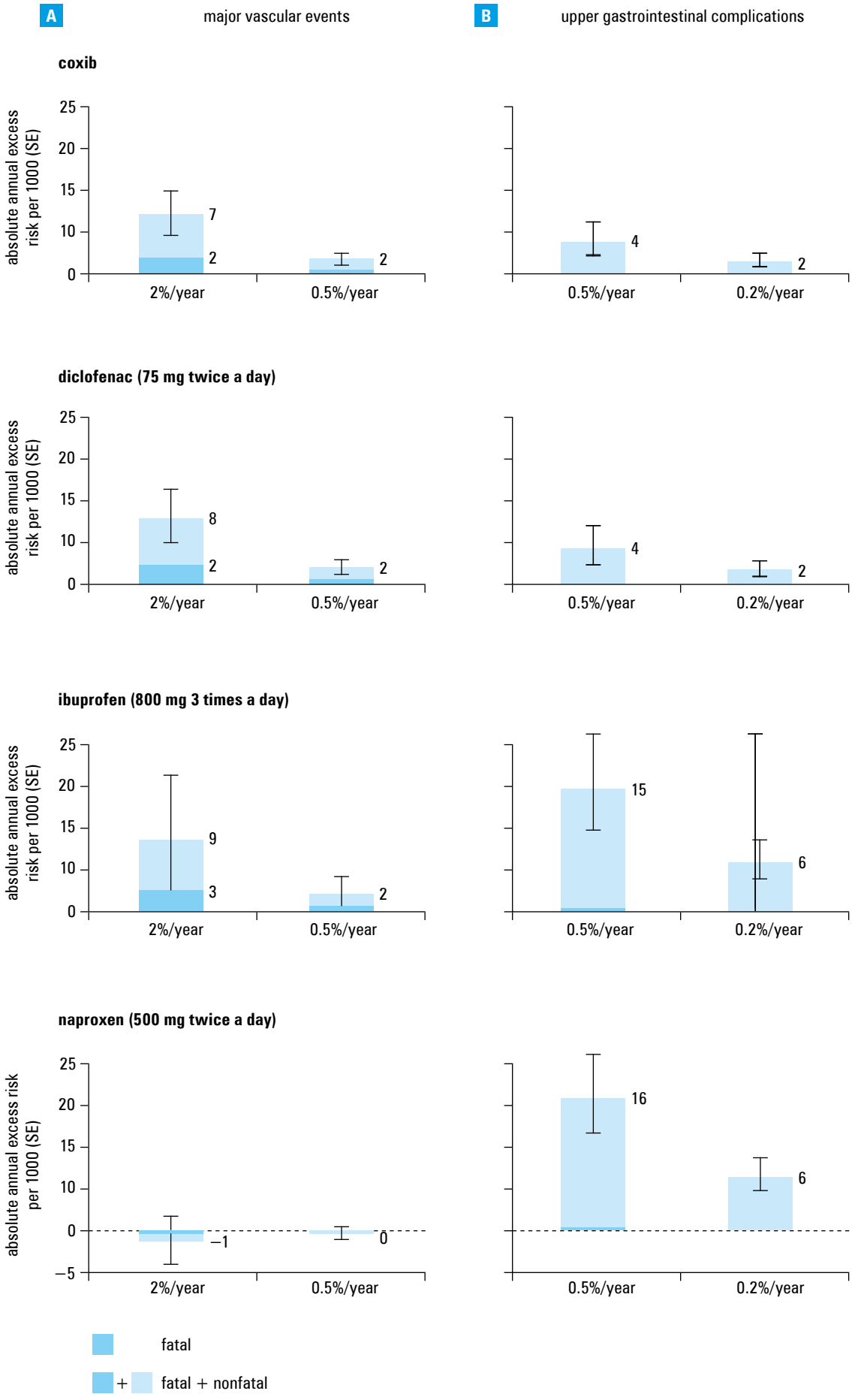

FIGURE 2 Annual absolute effects per 1000 of coxibs and nonselective nonsteroidal anti-inflammatory drugs, including naproxen, at different baseline risks of major vascular events (**A**) and upper gastrointestinal complications (**B**). Adapted from Bhala et al.[30]
Abbreviations: SE, standard error

The CNT findings summarize over 300 000 patients of experience with patient-level data and clearly need to be taken into account. It is necessary to consider this overview when critically evaluating the current consensus document.

Essentially, for patients with low GI and CV risk, naproxen may be used, especially if used chronically and intermittently. However, in patients with high GI and CV risk, one must consider the risk-to-benefit ratio of ns-NSAIDs and COX-2-selective inhibitors, as outlined above. It is also vital that when using any NSAID, either COX-2-selective or ns-NSAID, one must consider giving these drugs at the lowest effective dose and at the lowest frequency. Low-dose celecoxib (200 mg once daily) is considered the safest in patients with high GI and CV risk if NSAIDs are needed and the patient takes low-dose aspirin. In patients with low GI but high CV risk, naproxen is considered the preferred option, given its reduced CV risk relative to other ns-NSAIDs. However, taking into consideration the existing evidence, low-dose celecoxib may also be appropriate.[25,69-73] In patients who have high GI risk and low CV risk, a COX-2-selective inhibitor without a PPI or an ns-NSAID along with a PPI seems to be comparable in terms of upper GI tract protection. In patients with high CV and GI risk, assuming the use of NSAIDs is unavoidable, the therapeutic method depends on whether the patient is on low-dose aspirin or not. If the patient is not on low-dose aspirin, either low-dose celecoxib or naproxen could be used in combination with a PPI. If the patient is on low-dose aspirin, celecoxib is the best option.

In conclusion, NSAIDs should be used cautiously and as infrequently as possible with nonpharmacological approaches being prescribed first.

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ARTYKUŁ POGLĄDOWY

Stosowanie niesteroidowych leków przeciwzapalnych w chorobie zwyrodnieniowej stawów – jak zrównoważyć ryzyko sercowo-naczyniowe i ryzyko żołądkowo-jelitowe

Podsumowanie wytycznych międzynarodowej grupy ekspertów

Wassim Mosleh[1], Michael E. Farkouh[2]

1 Department of Internal Medicine, University at Buffalo, Buffalo, Nowy Jork, Stany Zjednoczone
2 Peter Munk Cardiac Centre and the Heart and Stroke Richard Lewar Centre, University of Toronto, Toronto, Ontario, Kanada

SŁOWA KLUCZOWE

choroba zwyrodnieniowa stawów, inhibitory cyklooksygenazy 2, niesteroidowe leki przeciwzapalne, ryzyko sercowo-naczyniowe, ryzyko żołądkowo-jelitowe

STRESZCZENIE

W ostatnim 20-leciu w wielu badaniach oceniano stosowanie tradycyjnych niesteroidowych leków przeciwzapalnych (NSLPZ) oraz nowszych inhibitorów cyklooksygenazy 2 (COX-2) w leczeniu przewlekłych zespołów bólowych. Prawidłowe stosowanie NSLPZ stało się przedmiotem szerokiej debaty na temat zagrożeń i korzyści związanych z takim leczeniem, w której brali udział badacze z wielu dyscyplin naukowych i lekarze praktycy. Dotychczasowe wytyczne stosowania NSLPZ nie odnoszą się do ryzyka sercowo-naczyniowego (RSN) i ryzyka żołądkowo-jelitowego (RŻJ) związanego ze stosowaniem NSLPZ swoistych dla COX-2, czy też nieswoistych, z kwasem acetylosalicylowym w małej dawce włącznie. W związku z tym wielodyscyplinarna grupa ekspertów podjęła się przeglądu piśmiennictwa, aby sformułować wskazówki dla lekarzy dotyczące opartego na danych naukowych wyboru NSLPZ dla indywidualnych pacjentów. W niniejszym przeglądzie omawiamy i podsumowujemy najnowsze dane naukowe na ten temat, pozwalające wybierać najskuteczniejsze i najbezpieczniejsze opcje terapeutyczne, a tym samym unikać poważnych powikłań ze strony układu krążenia i przewodu pokarmowego. NSLPZ należy stosować ostrożnie i najrzadziej jak to możliwe, preferując najpierw metody niefarmakologiczne. Jeśli zastosowanie NSLPZ jest konieczne, w wyborze leku należy uwzględnić RSN i RŻJ.

Adres do korespondencji:
Michael E. Farkouh, MD, MSc, FRCPC, FACC, FAHA, Peter Munk Cardiac Centre and the Heart and Stroke Richard Lewar Centre, University of Toronto, 85 University Avenue, 4N474, Toronto, Ontario M5G 2N2, Kanada, tel.: +1 416 340-3141, e-mail: michael.farkouh@uhn.ca
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