The Thrombotic and Arrhythmogenic Risks of Perioperative NSAIDs

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WORLDWIDE, NEARLY 30 MILLION PEOPLE take nonsteroidal anti-inflammatory drugs (NSAIDs) daily. These drugs are highly efficacious for the treatment of both acute and chronic pain. These drugs play an important role in the multimodal analgesia model of perioperative pain management and are an integral component of the 2012 American Society of Anesthesiologists guidelines for the treatment of acute pain in the perioperative setting. Unless contraindicated, these guidelines advocate administration of around-the-clock nonselective NSAIDs, COX-2 selective NSAIDs, and acetaminophen, but do not caution against using NSAIDs in the setting of established cardiovascular (CV) disease.

Although NSAIDs are relatively contraindicated for patients with established CV disease, in the outpatient setting up to 42.3% of patients with a history of a myocardial infarction (MI) received NSAIDs during follow-up clinic visits. The percentage of patients with established CV disease or CV risk factors who receive NSAIDs during the perioperative period currently is unknown. However, it is likely that NSAIDs still are commonly prescribed to patients with established CV disease or CV risk factors who are undergoing surgery, considering that this drug class is widely used for postoperative pain. This issue is of particular importance for the surgical patient because of the increased risk of major adverse cardiac events during the perioperative period. It has been well described that the perioperative period is associated with hemodynamic instability (tachycardia, arrhythmias, hypertension, hypotension), a procoagulant state, and myocardial oxygen supply-demand imbalances.

Despite a plethora of data indicating that NSAIDs may increase CV risk in certain patient groups, this association likely is underappreciated, especially with regard to the short-term perioperative use of these drugs. During the perioperative period, clinicians may opt to administer these agents to patients with CV disease or CV risk factors because of a lack of awareness of the association between NSAIDs and increased CV risk or because of the belief that short-term NSAID use is unlikely to be problematic. However, relatively little currently is known about the individual CV risk profile of each specific NSAID or if a safe treatment period exists. Furthermore, the scope of potential risks posed by NSAIDs remains largely unclear. The purpose of this article is to review NSAID mechanisms and their range of use in the perioperative period, to highlight the significant but underappreciated CV risks of NSAIDs (thrombotic and arrhythmogenic potential), and to provide precautions when considering the perioperative use of NSAIDs in patients with CV disease or significant CV risk factors.

It should be noted that a number of meta-analyses are discussed throughout this review. There are a multitude of advantages and disadvantages to using data derived from a meta-analysis. Overall, meta-analyses that are well-constructed appropriately combine results from multiple studies, allowing the precision and accuracy of a given study’s findings to be improved upon as a greater number of total data are analyzed. This, in turn, may increase the statistical power to detect an effect. However, a poorly constructed meta-analysis can yield results that contradict large multicenter trials or a previous meta-analysis, generate bias due to exclusion of possibly germane studies, contradict results of earlier meta-analyses, or allow for the inclusion of flawed studies.

MECHANISM OF NSAIDs

NSAIDs have a long history of prescription and nonprescription use for their antipyretic, analgesic, and anti-inflammatory properties. Pharmacokinetically, most NSAIDs are absorbed completely when administered orally, have negligible first-pass metabolism, and small volumes of distribution. They undergo hepatic transformation by the CYP-2C8, 2C9, and 2C19 cytochrome, as well as glucuronidation in the liver.

NSAIDs exert their primary effect by inhibiting the enzyme cyclooxygenase (COX) enzyme isoforms. COX is responsible for the synthesis of inflammatory mediators.

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for catalyzing the conversion of arachidonic acid via the lipoxigenase pathway to leukotrienes and the prostaglandin endoperoxidases (PGG₂ and PGH₂). PGH₂ is a predecessor of the biologically active prostaglandins and thromboxanes, and undergoes isomerization to prostanooids, such as thromboxane-A₂ (TXA₂), prostacyclin (PGI₂), PGD₂, PGE₂, and PGF₂α. TXA₂ is particularly important in hemostasis, as it is responsible for activating immature platelets, stimulating platelet aggregation, and vasoconstriction. Prostacyclin, conversely, inhibits platelet aggregation and causes vasodilation (Fig 1).18

COX has 2 common isoforms: COX-1 and COX-2. Both isoforms are regulated and expressed at varying levels in different tissues. COX-1 is ubiquitous in the human body and releases prostaglandins involved in the maintenance of gastrointestinal integrity, vascular homeostasis, and platelet aggregation. COX-2 is undetectable at baseline in most tissues but has increased expression during tissue inflammation (ie, during surgery). COX-2 is a major source of systemic prostacyclin biosynthesis in healthy humans. It is expressed in brain, endothelial cells, microglia, renal macula densa, renal interstitial cells, and intestinal epithelium.19

NSAIDs have different levels of specificity for the COX-2 receptor. Nonselective NSAIDs are inhibitors of both COX-1 and COX-2. Given the balanced inhibition of these 2 enzymes, the “profens” (ibuprofen, ketoprofen, flurbiprofen) and naproxen are considered nonselective NSAIDs. COX-2-specific inhibitors have varying degrees of inhibition for the respective isoenzymes. For instance, diclofenac is 18- to 29-fold more potent toward inhibition of the COX-2 enzyme. Celecoxib, valdecoxib, and rofecoxib are 30-, 61-, and 272-fold, respectively, more inhibitory of the COX-2 enzyme compared with the COX-1.21 Benefits of COX-2-specific agents include analgesia comparable to nonselective NSAIDs but with decreased gastroduodenal irritation and toxicity, as COX-1 is directly involved in gastric cytoprotection.22 Additionally, COX-2-selective NSAIDs demonstrate less bronchoconstriction risk in the patient population with aspirin-induced asthma and less depression of platelet function (aggregation and hemostasis).18

**UTILITY OF NSAID USE IN THE PERIOPERATIVE PERIOD**

Surgery and tissue injury initiate an inflammatory response via multiple mediators and receptors that results in primary nociceptive pain as well as possibly inciting neuropathic (chronic) pain syndromes. NSAIDs, because of their effect on inhibiting COX enzymes, possess analgesic, anti-inflammatory, and antipyretic effects. Hence, NSAIDs are used to ameliorate acute and chronic pain preemptively, intraoperatively, and postoperatively, either as a single agent for mild-to-moderate pain or, more commonly, as part of a multimodal analgesic regimen for moderate-to-severe pain.

Ketorolac, the most commonly administered parenteral NSAID in the United States, is used widely to provide perioperative analgesia. Ibuprofen recently has been formulated to allow for parenteral administration and will likely become prescribed commonly in the perioperative period. All NSAIDs, including ketorolac, have been used as analgesics in nearly all major and minor procedure types: Laparoscopic, orthopedic, breast, thoracic, abdominal, gynecologic, urologic, liver, ENT, and cardiac.

The routine strategy of multimodal perioperative analgesia involves utilizing a combination of drugs with different mechanisms of action to optimize analgesia and minimize side effects. Multimodal analgesia frequently includes NSAIDs, acetaminophen, opioids, anticonvulsants, alpha2-agonists, NMDA antagonists, local anesthetics, and GABA agonists. Opioids, because of their potent analgesic effects, are the cornerstone of therapy for significant acute nociceptive pain. However, opioids lack anti-inflammatory properties and frequently are limited by their side effect profile. Hence, NSAIDs commonly are used in combination with opioids to reduce opioid requirements and side effects. A combination of NSAIDs and opioids enhances the overall analgesic quality, minimizes adverse opioid effects, and has opioid-sparing effects.

COX-2-selective agents have been examined in a variety of ways in the perioperative period. Comparing nonselective versus COX-2-selective NSAIDs, a 2004 systematic review by Romsing et al reported that both drug classes provided equivalent and effective postoperative analgesia for both minor and major surgical procedures. A subsequent meta-analysis of 52 randomized placebo-controlled trials examined whether there was an advantage of multimodal analgesia with acetaminophen, nonselective NSAIDs, or COX-2 agents added to morphine patient-controlled analgesia for postoperative pain. In this analysis, all agents showed a significant opioid-sparing effect, but NSAIDs (selective and nonselective) were the only agents that significantly improved 24-hour visual analog score pain scores. Further, NSAID (selective and nonselective) use was associated with a decrease in the

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**Fig 1. Differential effects of nonspecific and COX-2 specific NSAIDs.**
incidence of postoperative nausea and vomiting and sedation. COX-2 agents have demonstrated analgesic efficacy in spine surgery, otolaryngologic surgery, orthopedic surgery, breast surgery, robotic prostatectomy, and gynecologic surgery.

NSAIDs improve the quality of recovery in the postoperative period because they do not contribute to postoperative nausea and vomiting. A 2005 meta-analysis that included 22 prospective, randomized, double-blind studies including 2,307 patients evaluated the risk of morphine adverse effects in patients treated with NSAIDs. The addition of NSAIDs significantly decreased postoperative nausea and vomiting from 30% to 22% (relative risk [RR] = 0.704 [0.590-0.841], p < 0.001). There also was a significant positive reduction in nausea alone (RR = 0.879 [0.785-0.983], p = 0.02), in vomiting alone (RR = 0.678 [0.508-0.906], p = 0.008), and in reduced sedation (RR = 0.714 [0.537-0.950], p = 0.02).

NSAID utility may extend to nonanalgesic anti-inflammatory effects in the perioperative setting. In a recent retrospective analysis, the effect of the administration of different intraoperative analgesics (sufentanil, ketamine, clonidine, and ketorolac) on breast cancer recurrence was examined. Keturolac was the only agent that demonstrated an appreciable association with decreased breast cancer recurrence. This reduced recurrence risk was postulated to be a result of ketorolac’s antiangiogenic properties and opioid-sparing effects. Similarly, in colon cancer patients, short-term preoperative NSAID treatment had a positive effect in terms of downregulating the colon cancer tissue expression of Prominin 1/CD133, a stem cell marker associated with survival prognosis.

THROMBOTIC RISKS OF NSAIDs

Historically, there have been observed associations between nonselective NSAID use and increased blood pressure and congestive heart failure. New data became available with the development of the COX-2-selective agents that demonstrated differences in safety with these agents; of particular concern was their increased CV risk profile. There are 4 seminal studies demonstrating the thrombotic risks of COX-2-selective agents. The first study to raise concerns about the increased thrombotic risk associated with COX-2 inhibitors was the Vioxx Gastrointestinal Outcomes Research trial (VIGOR).

In 301 centers across 22 countries, patients were assigned randomly to receive 50 mg of rofecoxib daily versus 500 mg twice daily naproxen for treatment of rheumatoid arthritis (RA). The primary endpoint was a confirmed clinical upper gastrointestinal bleeding event. The study findings demonstrated significantly less gastrointestinal bleeding with rofecoxib; however, a separate analysis showed a significant decrease in MI in the naproxen group compared with those given rofecoxib (0.1% vs 0.4%, RR = 0.2 [0.1-0.7]), which raised concerns about the CV safety with rofecoxib. Aside from the higher MI risk with rofecoxib, the overall mortality rate and the rate of death from CV causes were similar in both groups. This study was limited, because aspirin users were excluded, CV events were not a primary outcome, and there was no placebo group. The information from this trial contributed to the subsequent withdrawal of rofecoxib.

The VIGOR study was followed by the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial. This trial was designed to determine the effect of 3 years of treatment with rofecoxib on the risk of recurrent neoplastic polyps in patients with a history of colorectal adenomas; eight centers (in 29 countries) enrolled 2,586 patients who were randomized to 25 mg of rofecoxib daily versus placebo. A blinded external committee reviewed serious adverse thrombotic events, and after 18 months, a significant increased relative risk for MI and cerebrovascular accident (CVA) became apparent in the rofecoxib group (RR = 1.92 [1.19-3.1], p = 0.008). Additionally, nonadjudicated investigator-reported congestive heart failure was described in the rofecoxib group compared with the placebo group (hazard ratio [HR] = 4.61 [1.50-18.83]). Limitations of this study included early termination by 2 months and more patients discontinued rofecoxib than placebo due to adverse events.

The third seminal study was the Prevention of Sporadic Colorectal Adenomas with Celecoxib (APC). This randomized double-blind study stratified according to use or nonuse of aspirin for CV prophylaxis and compared 2 doses of celecoxib (200 mg versus 400 mg twice a day) with placebo for the prevention of colorectal adenomas. The investigators reviewed all potentially serious CV events (death from CV causes, MI, CVA, or heart failure) among the 2,035 patients enrolled. Compared with placebo, celecoxib use had a hazard ratio of 2.3 (95% CI, 0.9-5.5) for the 200 mg dose and a hazard ratio of 3.4 (95% CI, 1.4-7.8) for the 400 mg dose. The study group’s data and safety monitoring board recommended early discontinuation of the study. It was concluded that celecoxib was associated with a dose-related increase in major CV complications; however, this study was not adequately powered to specifically look at all possible CV events or to detect a small number of CV events.

Lastly was the Alzheimer’s Disease Anti-inflammatory Prevention (ADAPT) trial, which was a randomized blinded placebo-controlled study designed to evaluate naproxen, 220 mg twice a day, versus celecoxib, 200 mg twice a day, versus placebo for the primary prevention of Alzheimer’s disease. After the previously discussed APC trial reported increased CV risks with celecoxib, this study also was suspended when the ADAPT investigators reviewed their available data on adverse CV events in the participants. The reported adverse events included CV or cerebrovascular related death, MI, CVA, congestive heart failure, and transient ischemic attacks. For these adverse events, the ADAPT trial demonstrated a hazard ratio of 1.10 for celecoxib (95% CI, 0.67-1.79) versus 1.63 for naproxen (95% CI, 1.04-2.55). An additional outcome was the need for hypertension treatment that was not present at baseline. They found increased hazard ratios of 1.56 (95% CI, 1.26-1.94) for celecoxib and 1.40 (95% CI, 1.12-1.75) for naproxen for the need for initiation of antihypertensive treatment. The authors concluded that the nonselective NSAID naproxen also may present a certain degree of CV risk. This study was limited by its early termination and CV-related risks were not a primary outcome in the study design.
The exact mechanism of increased thrombosis with COX-2 inhibitors is subject to debate. PGI2 is a known vasodilator as well as a potent inhibitor of platelet aggregation. Hence, NSAID-induced suppression of COX-2-dependent PGI2 formation in the endothelium can both heighten the response to thrombotic and hypertensive stimuli as well as initiate and accelerate atherosclerosis. There is a relative imbalance between TXA2 and PGI2 levels, favoring TXA2 when COX-2 is suppressed, hence, leading to greater vasoconstriction and hypercoagulability. However, the hypothesis that COX-2 is expressed normally by endothelial cells in response to the physical shear stress of blood flow remains disputed. A recent mouse in-vivo thrombosis model did not support the accepted hypothesis, although the study was limited by the use of healthy blood vessel walls. Clinical and experimental data show COX-2-derived PGI2 production is increased in atherosclerosis as in other inflammatory conditions, which may explain negative findings in healthy vessel models. Further evidence of the role of COX-2 in atherogenesis is supported by a study showing that human carriers of a COX-2 gene polymorphism have a reduced risk for MI and stroke. Although the exact mechanism may still be unclear, there is ample clinical evidence demonstrating that almost all NSAIDs have some thrombotic risk associated with their use and that this risk generally increases with both the dose and the in-vitro COX-2 selectivity of the agent.

In 2009, Farkouh et al provided a comprehensive evidence-based review of 8 key clinical trials, 5 meta-analyses, and 5 epidemiologic studies on the subject of the CV safety of NSAIDs (selective and nonselective). Their review sought to clarify the association between NSAID use in patients with RA or OA, and an increased risk of a CV or thrombotic event. Trelle et al examined the CV safety of NSAIDs. Trelle et al examined 31 trials including 116,429 total patients and found that etoricoxib (estimated rate ratio [ERR] = 4.07 [1.23-15.7]) and diclofenac (ERR = 3.98 [1.48-12.70]) were associated with the highest risk of CV death. Of seven NSAIDs evaluated (duration of use ranged from 6-18 months, clinical indications included RA or OA), naproxen was associated with the lowest risk of MI, and ibuprofen was associated with the highest risk of MI (odds ratio [OR] = 2.02 [1.29-1.56] and OR = 4.27 [2.90-6.29], respectively). Use of oral ibuprofen, diclofenac, sulindac, and flurbiprofen all were associated significantly with increased acute MI risk. These concerns have been further strengthened by 2 recent nationwide Danish cohort studies. The first study showed even short-term treatment (7-14 days) with various oral NSAIDs (rofecoxib, celecoxib, ibuprofen, diclofenac) was associated with an increased risk of death and recurrent MI in patients with a history of prior MI. Diclofenac was associated with the highest risk for death or recurrent MI at day 1-7 of treatment (HR = 3.26 [2.57-3.86]). The second study compared 43,608 patients with an index MI against 55,579 controls over a 10-year interval. The authors found that any NSAID use in the index-MI group compared with non-use in the controls was persistently associated with an increased 1-year death risk (HR = 1.59 [1.49-1.69]), a 5-year hazard ratio of 1.63 (95% CI, 1.52-1.74), and an increased 1-year coronary death (HR = 1.30 [1.22-1.39]), and 1-year non-fatal MI (HR = 1.41 [1.28-1.55]).

Although not as well documented in the literature as CV risks, there is also a known risk of stroke (CVA) with NSAID use. Trelle et al examined CVA risk in addition to CV risk and found that there was the highest risk with the use of all NSAIDs (naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib, lumiracoxib). Naproxen was associated with the highest risk of stroke, (rate ratio = 3.36 [1.00-11.6]) followed by diclofenac (rate ratio = 2.86 [1.09-8.36]). Of note, specific duration of use and doses used were not specified. Other recent studies have corroborated the risk of CVA with NSAID use. In a retrospective case-crossover study using a Taiwanese health registry to examine short-term NSAID use and CVA risk, Chang et al identified all ischemic and hemorrhagic CVA patients admitted over a 1-year period in 2006. They also searched a pharmacy prescription database for NSAID use during the case and control periods. For ischemic CVA, there was an increased risk evident for all oral NSAIDs (intermittent and regular use) with the least risk for celecoxib (adjusted odds ratio (OR) = 1.20 [1.00-1.44]) and greatest for ketorolac (OR = 1.90 [1.39-2.60]). Of note, there was a significantly increased risk for ischemic CVA (OR = 3.92 [3.25-4.72]) and hemorrhagic CVA (OR = 5.98 [4.40-8.13]) with parenteral ketorolac given in the 7 days prior to the event. The authors note that the risk of ischemic CVA was attenuated by regular aspirin use, and additionally, there was no increased risk of hemorrhagic CVA in regular aspirin users. Other observational, retrospective studies also have shown an increased risk of CVA associated with rofecoxib, valdecoxib, diclofenac, and indomethacin.

In the context of the hypercoagulable and prothrombotic state that peroperative patients experience, the potential thrombotic risks of NSAIDs are magnified, particularly in patients with established CV or cerebrovascular disease who are undergoing surgery. Exacerbating this issue is that many perioperative patients take aspirin for secondary CV prevention, and there is a potential interaction between aspirin and several of the nonselective NSAIDs, in particular ibuprofen. Rimon et al demonstrated in a dog model that celecoxib interfered with the ability of low-dose aspirin (81 mg) to block arachidonic acid-induced platelet aggregation. Further evidence indicates that NSAIDs interfere with the antithrombotic effects of aspirin by competitive inhibition at the receptor binding site of the COX-1 enzyme. One study examined the magnitude and duration of inhibition of platelet aggregation following doses of aspirin (325 mg) or ibuprofen (400 mg) alone or in combination in 10 healthy volunteers. A significant reduction was found in both parameters of platelet aggregation when ibuprofen was given prior to aspirin administration in these normal subjects. These findings also
were demonstrated in a follow-up confirmatory study by the same authors that followed 28 patients who were taking aspirin for secondary CVA prevention and also regularly taking ibuprofen or naproxen. All 28 patients showed no inhibition of platelet aggregation during ongoing aspirin-NSAID use. Removal of the NSAID reliably restored responsiveness for aspirin. Clinically, 13/18 patients (only 18 were willing to be followed long-term) had recurrence of an ischemic event while taking both agents together.88

An additional factor contributing to the increased risk of a CV or cerebrovascular event in the perioperative setting is that many patients on chronic aspirin therapy are advised to stop their aspirin before surgery, although this practice recently has been called into serious question.89 Taking all of these variables into account, a higher risk of postoperative MI or CVA in high-risk patients who are prescribed NSAIDs might be expected, yet there is a paucity of data directly addressing this issue. The first prospective study investigating the safety of COX-2 inhibitors in the perioperative setting evaluated the safety and efficacy of parecoxib and valdecoxib in 462 patients undergoing nonemergent coronary artery bypass grafting (CABG) surgery. Serious adverse events occurred twice as frequently in patients treated with parecoxib or valdecoxib compared with placebo; specifically, there was a nonsignificant trend toward the incidence of cerebrovascular complications and MI.90 A follow-up larger study looked at a primary endpoint of the combined incidence of adverse events in 4 areas (CV events, renal failure, gastrointestinal ulceration, and wound-healing complications) in CABG patients receiving parecoxib/valdecoxib compared with placebo for 10 days postoperatively. The investigators found that CV events (MI, cardiac arrest, CVA, and pulmonary embolus) were more frequent among the patients given parecoxib and valdecoxib compared with placebo (2.0% v 0.5%, risk ratio = 3.7 [1.0-13.5], p = 0.03). This article raised concerns about the perioperative use of these drugs in patients undergoing CABG.91

A follow-up study in 2006 examined the safety of the same 2 drugs in noncardiac surgery and did not find a higher incidence of CV thromboembolic events. However, they articulated the caveat that this study population had a low incidence of known CV disease. The authors recommended these drugs be reserved for patients at low risk for thromboembolic events.73

**NSAIDs AND TACHYARRHYTHMIA RISK**

Until recently, most of the focus on NSAID use and CV risk has revolved around thromboembolic risks, such as MI and CVA, with little attention focused upon the potential risks of cardiac conduction issues. There is now mounting evidence of an association between NSAID use and various tachyarrhythmias. The presence of atrial fibrillation (AF) is an important perioperative risk factor for CV and noncardiac morbidity. Ventricular arrhythmias can be lethal and are the most common cause of sudden cardiac death. Consequently, if real, an association between the use of NSAIDs and atrial or ventricular tachyarrhythmias has important clinical and public health implications and should be an important consideration for the care of patients undergoing surgery. This section provides a comprehensive review of the tachyarrhythmia risks associated with the use of NSAIDs.

### Atrial Tachyarrhythmia Risk

Atrial fibrillation, the most common atrial arrhythmia and the most common cardiac arrhythmia overall, currently affects more than 2 million Americans and is associated with an increased long-term risk of stroke, heart failure, and death.92 93 Three recent retrospective studies suggested that NSAID use may increase the risk for the development of AF.93 95 The first of these studies used an extensive United Kingdom primary care database to perform a retrospective nested case-control analysis to estimate the risk for first-time chronic AF and paroxysmal AF among users of NSAIDs.92 Five-hundred sixty patients between 40 and 89 years old who had a diagnosis of new AF in 1996 were identified. The AF was further subclassified as chronic if it persisted for more than 1 week in duration, or paroxysmal if it reverted to sinus rhythm within 1 week. The investigators found that NSAID use was associated with a statistically significant 44% increased risk for developing chronic AF.92 The increased relative risk occurred for all NSAIDs and was noted to be present irrespective of treatment duration, although the risk was highest among long-term users; the relative risk associated with NSAID use for fewer than 30 days was 1.04 (95% CI, 0.59-1.83), for 30 days or more was 1.57 (95% CI, 1.15-2.15), and for 1 year or more was 1.80 (95% CI, 1.20-2.72).

A second retrospective population-based case-control study identified 32,602 people in the Danish National Registry of Patients with a first diagnosis of AF or atrial flutter between 1999 and 2008.93 Each subject was compared with 10 age- and gender-matched controls (n = 325,918) without AF or atrial flutter who were selected randomly from the Danish population. Patients were classified as current or recent NSAID users; current users were further subclassified as new (first ever prescription within 60 days of diagnosis date) or long-term users. After adjustment for several confounders, the investigators found that both selective and nonselective NSAID use were associated with an increased risk of AF or atrial flutter. In contrast to the findings of De Caterina et al, the association with AF and atrial flutter was strongest for new users, with a 46% increased risk for nonselective NSAIDs (AOR = 1.46 [1.33-1.62]) and 71% increased risk for COX-2 inhibitors (AOR = 1.71 [1.56-1.88]) compared with non-NSAID users. Those rates were even higher for NSAID users who had started the medication within 60 days of AF or atrial flutter onset. The highest risk occurred in elderly patients and in those with chronic kidney disease or RA. The authors concluded that an increased risk of developing AF or atrial flutter should be taken into account when prescribing NSAIDs.

The third recent observational study was derived from the Taiwanese National Health Insurance Research Database.93 From 2000-2009, 80,080 patients were divided between 7,280 with new-onset AF and a matched cohort of 10 controls without AF on the same date as the index patient (those with new-onset AF); included were all possible NSAIDs (selective and nonselective). Results showed that new (first-ever NSAID use within 30 days of AF onset) users had a significantly increased risk for AF development (OR = 1.651 [1.384-1.971], p < 0.001). From the subgroup analyses, individuals with a heart failure history had the greatest risk (OR = 1.920 [1.485-2.483]). Furthermore, even in patients under 65 without
significant comorbidities, there was a significant risk of new-onset AF with new NSAID use (OR = 1.125 [1.068-1.439], p = 0.001).93

It is important to note that because of their anti-inflammatory properties, the question of whether NSAIDs might offer protection against the development of AF postoperatively has been postulated. A recent randomized double-blind placebo-controlled trial involving 161 patients evaluated the use of naproxen versus placebo for the prevention of AF after CABG surgery. Although the duration of AF appeared to be decreased in the patients taking naproxen, the authors failed to show a reduction in the incidence of postoperative AF, and there was a higher incidence of acute kidney injury in the treatment arm. The authors concluded that the routine use of naproxen after CABG for the prevention of AF cannot be supported.96

A potential association between NSAIDs and atrial tachyarrhythmias, regardless of the duration of treatment, should be an important consideration in the care of surgical patients, because many surgical patients take NSAIDs on a chronic basis and/or often are administered NSAIDs during the perioperative period or may be encouraged to continue taking these medications throughout the postoperative period and beyond.

Based on the available literature, a link between NSAIDs and AF, even if real, is not tantamount to a cause and effect relation; preexisting inflammatory and other clinical conditions also may already exist within patients, both increasing their chances for AF and NSAID prescriptions.97 Yet regardless of whether the link represents an indirect association or a causal relationship, any association between NSAIDs and AF has important broad clinical implications. This is especially germane for perioperative practitioners who frequently encounter patients chronically taking these medications and who also routinely administer these medications as de novo therapy.

Ventricular Tachyarrhythmia Risk

To date, evidence associating NSAID use to an increased risk of ventricular arrhythmias includes a meta-analysis,92 an anecdotal description of cases published in letter form,98 and a study of post-cardiac surgery patients (associating NSAID use to an increased incidence of sudden CV death from all causes, including ventricular fibrillation).91 Furthermore, a large prospective randomized trial, while failing to find a direct association between NSAID use and tachyarrhythmias, found an increased incidence of CV death.65

In a 2006 study, Zhang et al demonstrated an association between the now-withdrawn rofecoxib and an increased risk of ventricular tachyarrhythmias.92 Their meta-analysis, which included 114 randomized clinical trials and involved 116,094 patients, examined the incidence of CV events in all randomized controlled trials of COX-2 inhibitors published through 2006. Among other findings, the authors discovered that rofecoxib was associated with a statistically significant increased risk of cardiac arrhythmias (RR = 2.90 [1.07-7.88]). Ventricular fibrillation (20%), cardiac arrest (27%), and sudden cardiac death (33%) accounted for most of the arrhythmia events in the analysis. In this study, the increased risk of arrhythmias appeared to be limited to rofecoxib, as no class-wide CV risks were identified. This study, among others, ultimately prompted the withdrawal of rofecoxib from the market.

Although only an anecdotal report of 3 cases, Pathak et al described an association between the use of celecoxib and the development of torsade de pointes.98 In all 3 cases, torsade de pointes developed within several days of the initiation of celecoxib, and there was no recurrence following its discontinuation. Two of the patients had a history of long-QT syndrome, and the other had a history of asymptomatic premature ventricular contractions. According to the authors, these cases suggest a possible link between celecoxib and the occurrence of torsade de pointes. They concluded that caution should be used when considering the administration of celecoxib to patients at high risk for developing torsade de pointes and especially in patients with known long-QT syndrome. Adding to this case series, a 2012 prospective study examined heart rate-corrected QT interval [QTc] prolongation in nearly 500 noncardiac surgical patients. It found that ketorolac was only 1 of 3 anesthetic or analgesic drugs administered intraoperatively that had a significant QTc prolonging effect; 58% of those given ketorolac had a study-specified significant (>30 msec) increase in QTc prolongation.99

Nussmeier et al performed a randomized prospective double-blind study of 1,671 patients to evaluate the use of parecoxib and valdecoxib for 10 days after CABG surgery.91 Although the occurrence of ventricular arrhythmias was not a predefined endpoint per se, sudden death from cardiac causes was included as an endpoint. Compared with the control group, the group treated with valdecoxib plus parecoxib had a significantly higher incidence of CV events, including MI and cardiac death (RR = 3.7 [1.0-13.5]). Of the patients who suffered cardiac death in the valdecoxib plus parecoxib treatment arm, one death each was caused by cardiac arrest, ventricular fibrillation, MI, or pulmonary embolus. The authors concluded that selective COX-2 inhibitors should be avoided in patients undergoing CABG.

Solomon et al reviewed all potentially serious CV events among 2,035 patients with a history of colorectal neoplasia who were enrolled in the randomized double-blind Adenoma Prevention with Celecoxib Trial.65 The study compared 2 doses of celecoxib with placebo for the prevention of colorectal adenomas. They found that over a follow-up period of approximately 3 years, celecoxib was associated with a dose-related increase in the composite endpoint of death from CV causes, including MI, stroke, or heart failure, as compared with placebo (HR = 2.3 [0.9-5.5]). However, in this study there was no apparent increase in the individual risk of an arrhythmia with celecoxib use.

To date, rofecoxib is the only NSAID to which a direct and convincing link to ventricular arrhythmias exists.92 Of note, celecoxib has been found, at least in vitro, to inhibit hERG, an ion channel that plays a significant role in mediating cardiac action potential repolarization and therefore prolonging the QT interval.100 However, it is not possible to say with certainty that a similar association with other NSAIDs, particularly the currently available COX-2 inhibitors, does not exist. Given the seriousness and magnitude of the findings that led to the withdrawal of rofecoxib, it is important that further studies be carried out to prove that a similar link with 1 of the other drugs
Table 1. Studies Demonstrating Risk and Benefit Associated with Different NSAIDs

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<th>Risk</th>
<th>Ibuprofen</th>
<th>Piroxicam</th>
<th>Naproxen</th>
<th>Indomethacin</th>
<th>Ketorolac</th>
<th>Diclofenac</th>
<th>Celecoxib</th>
<th>Valdecoxib</th>
<th>Rofecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI risk</td>
<td>Yes (75)</td>
<td>No (75)</td>
<td>Yes (78)</td>
<td>No (75)</td>
<td>Yes (9,13,65,75)</td>
<td>Yes (75)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVA risk</td>
<td>Yes (75)</td>
<td>Yes (73,75)</td>
<td>Yes (83)</td>
<td>Yes (72,79,81)</td>
<td>Yes (72,75)</td>
<td>Yes (75)</td>
<td>Yes (82)</td>
<td>Yes (75)</td>
<td></td>
</tr>
<tr>
<td>Increase thrombotic</td>
<td></td>
<td>Yes (85)</td>
<td>No (85)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No (87)</td>
</tr>
<tr>
<td>risk by interaction</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>with aspirin</td>
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<td></td>
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<tr>
<td>Perioperative risk of MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes in CABG patients (90,91)</td>
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<tr>
<td>Perioperative risk of CVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes in CABG patients (90,91)</td>
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<tr>
<td>Perioperative risk of PE</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes in CABG patients (90,91)</td>
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</tr>
<tr>
<td>Atrial tachyarrhythmia risk</td>
<td>Yes (94,95)</td>
<td>Yes (94)</td>
<td>Yes (95,96)</td>
<td>Yes (91,92,94)</td>
<td>Yes (92,94,95)</td>
<td>No (92)</td>
<td>Yes (94)</td>
<td>Yes (92,95)</td>
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<td>Ventricular</td>
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<td>3 case reports of torsades (98)</td>
<td>Yes (92)</td>
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<td>tachyarrhythmia risk</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Yes (65)</td>
<td></td>
<td>Yes (65,92)</td>
</tr>
<tr>
<td>Nonperioperative death</td>
<td></td>
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<td></td>
<td></td>
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<td>Benefits for cancer patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reduce CD133 colon cancer prognostic marker (61)</td>
<td>Reduce CD133 colon cancer prognostic marker (61)</td>
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<td></td>
<td></td>
<td></td>
<td>Reduced breast cancer recurrence (27,60)</td>
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</tbody>
</table>

Abbreviations: MI, myocardial infarction; CVA, cerebrovascular accident; PE, pulmonary embolism; RR, relative risk; IV, intravenous; OR, odds ratio; CABG, coronary artery bypass grafting.
does not exist. Additional trials, such as the ongoing PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen) may help further delineate the CV risk profile of these drugs and address the potential issue of tachyarrhythmia risk.101

CONCLUSIONS

It is likely that the full spectrum of NSAID-associated CV risks, particularly with respect to the short-term use of these drugs, remains underappreciated and has yet to be fully elucidated. On the basis of the available evidence, it appears that the benefits of using NSAIDs during the perioperative period may not always outweigh the risks for patients with CV disease or with CV risk factors (see Table 1).

It is the authors’ contention that NSAIDs should be used with caution in the perioperative setting in patients with CV disease or in those who are at high risk for CV or cerebrovascular disease. Various regulatory bodies, including the United States Food and Drug Administration, have posted warnings regarding the potential CV risks of NSAIDs,102 similar warnings have been posted by regulatory bodies in the United Kingdom103 and Australia.104 Clinicians caring for patients on NSAIDs or prescribing NSAID therapy, regardless of the intended duration of treatment, should be aware of the possible associations between these medications and an increased risk of CV events (especially CV thrombotic events, atrial tachyarrhythmias, and ventricular tachyarrhythmias) during the perioperative period. Based on the most current literature, it is clear that almost all NSAIDs are associated with some thrombotic tendency. This heightened CV risk becomes especially pronounced with increasing degrees of NSAID selectivity for the COX-2 receptor. Furthermore, there is limited but noteworthy evidence that NSAIDs are associated with significant arrhythmogenic potential as well.

Until the association is better understood, it is incumbent upon clinicians in the perioperative setting to carefully weigh the risks and benefits prior to administering NSAIDs to certain patient populations. These include those patients with (1) risk factors for CV disease, (2) established CV disease, (3) a history of arrhythrias, or (4) the propensity to develop an atrial or ventricular tachyarrhythmia. Additionally, clinicians should also note that certain NSAIDs likely negate the protective effect of aspirin (which most patients with established CV are prescribed), further compounding the thrombotic milieu seen in the perioperative setting in this at-risk patient population.

There are still a number of areas regarding the CV risk profile of the perioperative use of NSAIDs that warrant further investigation. All available analgesics have potentially serious side effects; the ideal would be to fully understand which drugs have optimal efficacy with maximal safety for perioperative patients of differing CV-risk classes. This area of research could be expanded to examine how patients undergoing cancer surgery with varying degrees of CV risk fare long-term with various analgesic regimens (ie, comparing cancer recurrence versus CV morbidity and mortality). Future research should also examine possible differences in the perioperative CV risks of ketorolac versus intravenous ibuprofen.

REFERENCES