Association of Perioperative Use of Nonsteroidal Anti-Inflammatory Drugs With Postoperative Myocardial Infarction After Total Joint Replacement

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Background and Objectives: Use of nonsteroidal anti-inflammatory drug (NSAIDs) analgesics is controversial because of cardiovascular risk, but perioperative use may be advantageous for total joint replacement. Thus, we performed this single-center observational cohort study to determine any association between NSAID use and postoperative myocardial infarction (POMI).

Methods: All patient admissions undergoing total hip or knee replacement between March 3, 2009, and September 1, 2010, were identified. Nonsteroidal anti-inflammatory drug use was identified. Postoperative myocardial infarction was defined as troponin I level greater than 0.1 ng/mL. Propensity scores were calculated to adjust for bias of receiving NSAIDs and troponin measurements. Propensity scores and other covariates were used in logistic regression to determine the independent association of NSAID use with POMI.

Results: Of the 10,873 arthroplasty admissions, 1518 (14%) had serial troponins measured, and 97 had a POMI (0.9%). Incidence of POMI was 0.8% for the 9,831 who received NSAIDs and 1.8% for the 1,042 (10%) admitted patients who did not receive NSAIDs with a risk difference of −1% with 95% confidence interval (CI) of −0.2% to −1.9%. The adjusted odds ratio (0.95; 95% CI, 0.5–1.8) and relative risk (0.95; 95% CI, 0.5–1.8) indicated that NSAIDs were not significantly associated with the risk of POMI. Mean duration of NSAID use was 3 days. Length of stay (98 versus 115 hours) was significantly reduced in the NSAID group.

Conclusions: Brief perioperative use of NSAIDs was not associated with increased risk for myocardial infarction after total hip and knee replacement; it may provide benefit in length of stay.

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The risk-benefit profile of nonsteroidal anti-inflammatory drugs (NSAIDs) remains controversial.[1] Both nonselective and selective cyclooxygenase[2] inhibitors (COX2I) are associated with cardiovascular risk[2,3] and may impair bone healing and prosthesis fixation for total joint replacement.[4] COX2I agents, especially rofecoxib,[5] have received the most scrutiny for cardiovascular risk, but the US Food and Drug Administration requires a black box warning for cardiovascular risk for all nonselective NSAIDs. Whether the duration of exposure to NSAIDs is a critical feature for development of cardiovascular risk is controversial. Initial analyses of cardiovascular risk with rofecoxib indicated that 7 to 18 months of exposure to rofecoxib were required; however, subsequent analyses indicated increased risk early in treatment and even with the first dose.[6,7] Recent studies have noted that even brief duration of exposure (1 month) to nonselective NSAIDs, such as ketorolac and meloxicam, in some populations is sufficient to increase cardiovascular risk.[8] Thus, documentation of cardiovascular safety during short-term exposure to NSAIDs would be valuable because the occurrence of postoperative myocardial infarction (POMI) is associated with increased mortality,[9] even with relatively small increases in troponin.[10]

Among other uses, NSAIDs are quite beneficial for postoperative analgesia. Nonsteroidal anti-inflammatory drugs have been extensively studied for this application, and multiple meta-analyses have noted that postoperative use of NSAIDs reduces pain scores, opioid use, and opioid-related adverse effects such as nausea.[11,12] Total joint replacements are very common procedures and have high severity of postoperative pain. The speed of rehabilitation and duration of hospital stay are associated with improved analgesia.[13] Thus, perioperative use of NSAIDs may be advantageous for total joint replacements if the risk of POMI is not increased. Our patients undergoing total joint replacement routinely received perioperative NSAIDs, and we analyzed our electronic medical record database to determine the independent association between NSAID use and POMI in a large cohort of patients.

METHODS

This single-center observational cohort study was approved by the Hospital for Special Surgery Institutional Review Board. A waiver for individual written consent was granted by the Hospital for Special Surgery institutional review board, and data were collected from electronic patient records (Sunrise Clinical Manager (Sunrise 4.5 SP6), Allscripts Healthcare Solutions, Inc, Chicago, Ill). STROBE guidelines were followed for this study. From March 3, 2009, to September 1, 2010, all 10,873 patient admissions undergoing elective total hip or knee replacement were identified. Only records until hospital discharge were available. Institutional standards for perioperative care were as follows. All patients underwent preoperative medical clearance from an internist with cardiologist consultation and selective testing if they had a history of significant cardiovascular disease. All patients were assessed by an anesthesiologist before surgery either in the preoperative clinic or in the surgical holding area. All NSAIDs and aspirin were stopped the week before surgery in all patients. Other home medications were continued throughout the perioperative period. The intraoperative anesthetic technique was selected by the attending anesthesiologist, and 97% of patients received a neuraxial block.[14] The surgical technique was

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at the discretion of the attending surgeon. Patients were enrolled in standardized clinical pathways. Coumadin was typically used for pharmacologic deep venous thrombosis prophylaxis, and a nomogram[15] was used to dose coumadin to achieve an International Normalized Ratio of 1.8 to 2.5 on postoperative day 4. Physical therapy was initiated either on the afternoon of surgery or on the morning of postoperative day 1, with a target of twice a day ambulation on postoperative day 1 followed by progressively more activity. The total knee replacement pathway included continuous passive motion devices twice a day.

Postoperative analgesia was provided in a standardized fashion by the Acute Pain Service, which was staffed by an anesthesiologist and nurse specialist.[14] Patient-controlled epidural analgesia with 0.06% bupivacaine and hydromorphone (10 μg/mL) or clonidine (1 μg/mL) was typically used, and NSAIDs were routinely included for postoperative analgesia, unless unselected from the standard order set. Meloxicam was the preselected NSAID, per institutional preference of our staff internists, and was administered on the day of surgery in the surgical holding area (15 mg per os for age ≤ 75 years and 7.5 mg for age > 75 years) followed by 7.5 mg per os daily for at least 2 postoperative days. Other NSAID choices were ketorolac (15–30 mg intravenous every 6 to 8 hours) and celecoxib (200 mg every day), depending on surgeon or pain management preference. These were also administered on the day of surgery and continued during the postoperative period.

The primary outcome was POMI defined as a troponin I value greater than 0.1 ng/mL. This value is more than the 99th percentile reference for our assay (Architect Stat Troponin-I; Abbott Laboratories, Abbott Park, Ill) and is suitable for a cutoff to define POMI.[16] Per institutional standards, all patients with known ischemic heart disease or suspicious perioperative course underwent a postoperative rule out myocardial infarction protocol consisting of at least 2 serial troponin I measurements 12 hours apart. All included patient records were electronically searched for troponin measurements performed at any time during the hospital stay.

Statistical Analysis

Two separate bivariate analyses were initially performed to determine whether any differences in perioperative characteristics were apparent between groups that did or did not have a POMI and did or did not receive NSAIDs using either *t* test for continuous variable or χ^2/fisher exact test for discrete variable. Clinical judgment and statistical significance at *P* value of 0.05 in bivariate analyses were used to select variables for the process of multivariable modeling. To adjust for bias of receiving NSAIDs, propensity scores for the likelihood of receiving NSAIDs were calculated using a multivariable logistic regression (propensity model) with covariates including age, sex, type of procedure, preexisting renal (creatinine > 2) and ischemic heart disease, and whether troponin was measured to adjust for detection bias. Two multivariable logistic regression models were then conducted to determine the independent association between POMI and (*a*) any perioperative NSAID use (Any NSAID model) and (*b*) type of NSAIDs (Specific NSAID model), respectively, while also adjusting for age, sex, home cardiovascular medications (β-blockers or statins), underlying cardiovascular risk as measured by revised cardiac risk index, lowest postoperative hemoglobin, and the risk of receiving NSAIDs (propensity score). Revised cardiac risk index was calculated post hoc for statistical analysis and was not clinically used to determine which patients underwent troponin measurements. Backward elimination was used for logistic model selection.

The reliability of these logistic regression models was assessed by a test of model discrimination using the *c* statistic and a test of model calibration with the Hosmer-Lemeshow (H-L) test.[17] The *c* statistic is the same as the area under the receiver operating characteristic curve[18] and is used to measure how well the model discriminates between observed data at different levels of the outcome. A *c* statistic value greater than 0.7 is considered indicative of acceptable discrimination.[19] The H-L test evaluates whether a logistic regression model is well calibrated so that the probability predictions from the model reflect the true occurrence of events in the data. Nonsignificant *P* values ($P \geq 0.05$) for this test are considered indicative of a well-calibrated model.[20] Odds ratio (OR), relative risk (RR), and risk difference were obtained from logistic regression. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Power Analysis

Previous meta-analyses have reported relative risk of rofecoxib for cardiovascular risk to be approximately 2.3.[3,7,21] On

TABLE 1. Perioperative Characteristics and Association With POMI

Characteristic	POMI (n = 97)	No POMI (n = 10776)
Age,* mean (SD), y	77 (10)	66 (12)
Sex,* M/F, %	58/42	41/59
Weight, mean (SD), kg	78 (19)	83 (25)
Procedure, n (%)		
Unilateral THR	49 (51)	5346 (50)
Bilateral THR	0 (0)	245 (2)
Unilateral TKR	47 (49)	4648 (43)
Bilateral TKR	1 (1)	537 (5)
Preoperative creatinine > 2, %	6.2	0.5
Preoperative Hb < 10, %	2.1	1.4
Preoperative history of CAD, %	62	12
Revised CRI,* n (%)		
0	29 (30)	8392 (78)
1	41 (42)	2020 (19)
≥2	27 (28)	364 (3)
Home medications,* %		
β-blockers	39	17
Statins	5	20
β-blockers and statins	52	15
Neither	4	48
Perioperative NSAIDs,* %		
Meloxicam or ketorolac	72	85
Celecoxib	8	6
Postoperative troponin measured,* %	100	13
Type of analgesia,* %		
PCEA	78	88
IV PCA	14	6
Peripheral/IV PCA	2	1
Unspecified	6	5
Highest postoperative verbal pain score, mean (SD)	3.8 (2.6)	4.1 (2.1)
Lowest postoperative Hb,* mean (SD)	9.0 (1.0)	9.6 (1.3)

*Significantly different between groups by bivariate analysis.

CRI indicates cardiac risk index; PCA, intravenous patient-controlled analgesia; PCEA, patient-controlled epidural analgesia IV; THR, total hip replacement; TKR, total knee replacement.

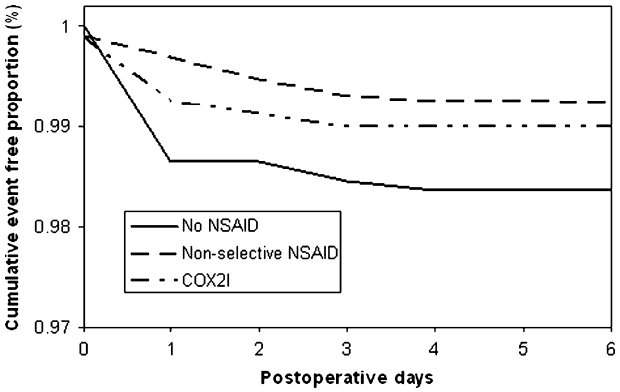

FIGURE 1. Time course for POMI.

the basis of a similar magnitude of effect, our data set has a power of 0.89 to detect the same relative risk for NSAID.

RESULTS

Of the 10,873 arthroplasty admissions, 1,518 (14%) had serial troponins measured and 97 had a POMI (0.9%). There were no fatalities. Table 1 displays perioperative characteristics of those who did or did not experience a POMI. Incidence of POMI was 1.8% for the 1,042 (10%) admitted patients who did not receive NSAIDs, and the time course is displayed in Figure 1. Incidence of POMI was 1.3% for the 610 who received COX2I (celecoxib) and 0.8% for the 9,221 who received nonselective NSAIDs (meloxicam or ketorolac). Figure 2 displays mean with 95% confidence interval unadjusted risk differences for POMI between patients who did and did not receive NSAIDs. Table 2 displays perioperative characteristics of those who did or did not receive NSAIDs. The full-propensity model was reduced by using backward elimination showing that age, preexisting renal disease, and whether troponin was measured were significantly associated with the likelihood of receiving NSAIDs. After adjustment for bias of receiving NSAID use with propensity scores obtained from the reduced-propensity model, both logistic regression models (Any NSAID and Specific NSAID) identified virtually identical independent risk factors for POMI, such as male sex, preexisting β-blocker use, increased revised cardiac risk index, and decreased postoperative hemoglobin (Table 3). Both adjusted ORs and RR indicated that NSAIDs were not significantly associated with the risk of POMI (Table 3). Mean duration of NSAID use was 3 days (SD, 1.3).

The *c* statistic values for the 3 logistic regression models were estimated to be greater than 0.7 (propensity model $c = 0.75$, any NSAID model $c = 0.9$, Specific NSAID model $c = 0.9$), indicating acceptable discrimination. No significant differences were found between the predicted and the observed probabilities of receiving NSAID through the propensity model ($P = 0.59$) and the probabilities of having POMI through the Any NSAID

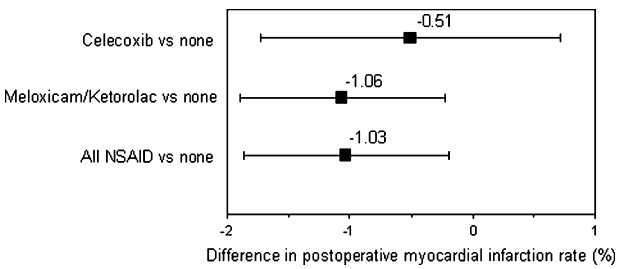

FIGURE 2. Unadjusted risk difference for POMI.

TABLE 2. Perioperative Characteristics and Association With Perioperative Nonselective NSAIDs and COX2I

Characteristic	None (n = 1042)	Any NSAIDs (9221 + 610) Nonselective NSAIDs (n = 9221)	Any NSAIDs (9221 + 610) COX2I (n = 610)
Age, mean (SD), y	69 (12)	66 (12)	65 (12)
Sex,* M/F, %	46/54	41/59	42/58
Weight, mean (SD), kg	83 (21)	83 (25)	84 (21)
Procedure,* n (%)			
Unilateral THR	507 (49)	4541 (49)	347 (57)
Bilateral THR	9 (1)	220 (3)	16 (3)
Unilateral TKR	490 (47)	3983 (43)	222 (36)
Bilateral TKR	36 (3)	477 (5)	25 (4)
Preoperative creatinine > 2,* %	3.7	0.2	0.2
Preoperative Hb < 10, %	2.6	1.2	2.0
Preoperative history of CAD,* %	18.4	12.2	12.0
Revised CRI, n (%)			
0	709 (68)	7240 (79)	472 (77)
1	248 (24)	1692 (18)	121 (20)
≥2	85 (8)	289 (3)	17 (3)
Home medications, %			
β-blockers	22	17	16
Statins	18	20	18
β-blockers and statins	23	15	16
Neither	37	48	50
Postoperative troponin measured, %			
POMI,* %	1.8	0.8	1.3
Duration of NSAID or COX2I, mean (SD), d	N/A	3 (0.7)	5 (2)
Postoperative troponin measured,* %	23	13	15
Type of analgesia, %			
PCEA	65	94	37
IV PCA	29	3	9
Peripheral/IV PCA	4	1	1
Unspecified	2	2	53
Lowest postoperative Hb,* mean (SD)	9.3 (1.3)	9.6 (1.3)	9.7 (1.4)
Postoperative blood transfusion, %	51	44	33
Highest postoperative creatinine,* mean (SD)	1.1 (0.9)	0.9 (0.3)	0.9 (0.3)
Highest postoperative verbal pain score,* mean (SD)	4.4 (2.2)	4.1 (2.1)	4.0 (2.2)
Length of hospital stay,* mean (SD), h	115 (42)	98 (30)	99 (35)

*Significantly different between any NSAID versus no NSAID by bivariate analysis.

THR indicates total hip replacement; TKR, total knee replacement.

TABLE 3. Association Between Perioperative Nonselective and COX2I NSAID Use and POMI Adjusted for Risk of Being on NSAID With Propensity Score

Risk Factor	OR (95% CI)	RR (95% CI)
Any NSAID†	0.95 (0.5–1.8)	0.95 (0.5–1.8)
Nonselective NSAID (meloxicam or ketorolac)	0.9 (0.5–1.7)	0.9 (0.5–1.8)
COX2I (celecoxib)	1.4 (0.5–4)	1.4 (0.5–3.9)
Preexisting β-blocker use	11.5 (4–33.5)*	
Preexisting statin use	1.7 (0.4–6.8)	
Preexisting both β-blocker and statin use	11.6 (4–34)*	
Sex (male versus female)	1.9 (1.2–3.1)*	
Revised cardiac risk index of 1 versus 0	3.5 (1.9–6.2)*	
Revised cardiac risk index of ≥ 2 versus 0	6 (2.9–12.5)*	
Postoperative lowest hemoglobin, per dg/mL	0.72 (0.6–0.9)*	
Propensity score	0.08 (0.02–0.4)*	

*Statistically significant ($P < 0.05$) by logistic regression.

†Calculated from the logistic regression Any NSAID model in Methods. All other values were calculated from the logistic regression Specific NSAID model in Methods and were virtually identical with values calculated from the Any NSAID model.

CI indicates confidence interval.

model ($P = 0.9$) and the Specific NSAID model ($P = 0.94$) for the H-L test.

DISCUSSION

Our study indicates that brief perioperative exposure to NSAIDs had an RR of 0.95 with 95% confidence interval of 0.5 to 1.8 compared with patients not receiving NSAIDs for risk for POMI. All NSAIDs (selective and nonselective) are considered to potentially increase the risk of cardiovascular complications. COX2I agents, especially rofecoxib, were the first to come under scrutiny. In September 2004, rofecoxib was voluntarily withdrawn from the global market. Multiple randomized controlled trials (RCTs) and meta-analyses have documented increased cardiovascular risk from use of rofecoxib (RR from 1.3 to 2.2).[5,7,21] Although initial analysis indicated that cardiovascular risk only increased after months of exposure, subsequent analyses indicated that increased risk occurs early in treatment and likely with the first dose.[6,7] Mechanisms for increased cardiovascular risk with COX2I agents are speculative and include prostacyclin-thromboxane imbalance leading to prothrombotic effects of the platelet-endothelium interface. Other potential mechanisms that also apply to nonselective NSAIDs are inhibition of protective effects of myocardial preconditioning and impairment of renal function leading to fluid retention, hypertension, and heart failure.[22]

Celecoxib is the only commercially available COX2I remaining, and increased risk of cardiovascular complications with celecoxib is controversial. Celecoxib has less COX2I selectivity than rofecoxib, and systematic reviews of observational studies[3] and RCTs[23] did not note increased cardiovascular risk (fatal and nonfatal cardiac and cerebral vascular events) with celecoxib in relatively low-risk patients. A large observational study from the United Kingdom also did not note increased risk associated with current use of celecoxib in 9218 cases of first-ever diagnosis of myocardial infarction.[24] However, an observational study based on a nationwide Danish clinical registry noted an increased risk of death or reinfarction with use of celecoxib (hazard ratio, 2.57) after acute myocardial infarction.[25] A recent meta-analysis of 6 large RCTs studying celecoxib noted an increased risk of combined cardiovascular complications with twice a day dosing or with 400-mg daily dosing (hazard ratios, 1.1–3.1) of celecoxib.[26] These recent studies suggest that, perhaps with larger doses or in high-risk populations, celecoxib may be associated with increased cardiovascular risk. Celecoxib (primarily 200 mg once a day) was used in ~5% of our admitted patients and was not associated with increased risk of POMI. Use of a smaller dose and once-a-day dosing to allow partial recovery of normal functions of the cyclooxygenase system may have prevented an increase in risk. Our study provides confirmation of the lack of association of brief perioperative use of celecoxib with POMI.

Cardiovascular risk from nonselective NSAIDs remains controversial because there are no large, long-term trials specifically studying these end points.[27] The previously mentioned systematic review of observational studies[3] noted increased cardiovascular risk with diclofenac (RR, 1.4) in mostly low-risk medical populations. The large observational study from the United Kingdom also noted increased risk associated with the current use of diclofenac (OR, 1.55) or ibuprofen (OR, 1.22) in 9,218 cases of first-ever diagnosis of myocardial infarction.[24] In addition, the observational study based on a nationwide Danish clinical registry noted increased risk of death or reinfarction with the use of multiple types of NSAIDs (hazard ratios from 1.29 to 2.4) after acute myocardial infarction.[25] The risk from duration of exposure to nonselective NSAIDs is uncertain and has not been well studied. Furthermore, a recent observational study in Spain noted that current use of NSAIDs, including ketorolac and meloxicam, for as brief as 1 month was associated (OR, 1.64) with acute coronary syndrome in 2954 patients hospitalized for this event.[8] Perioperative nonselective NSAIDs, meloxicam or ketorolac, were used in 85% of our admissions without significant association with POMI, thus providing supportive data for the safety of brief exposure to NSAIDs. Interestingly, 1 previous randomized controlled trial reported less frequent episodes of myocardial ischemia as measured by ST segment depression with use of ketorolac after total joint replacement,[28] although there was only a single myocardial infarction in each group. Of note, meloxicam can be considered a nonselective or selective NSAID depending on dose. Although the FDA label considers meloxicam to be primarily an NSAID, at smaller doses meloxicam assumes more selective COX2 inhibition similar to celecoxib.[2]

Logistic regression identified several other risk factors for POMI that confirm previous findings. Male sex,[29] increased revised cardiac risk index,[30] and severity of postoperative anemia[31] have been previously identified as risk factors, and the causative nature of these risk factors has reasonable pathophysiology. Preexisting use of β-blockers, either alone or in combination with statins, was also identified as a risk factor. This most likely represents a positive association with the presence and severity of ischemic heart disease rather than β-blockers causing POMI.

Other recognized risks from perioperative use of NSAIDs include bleeding and renal impairment.[12] However, these risks are typically minimized with brief use of small doses of NSAIDs. Use of NSAIDs in our data set was not associated with increased need for postoperative transfusion, lower postoperative hemoglobin values, or higher postoperative creatinine values than for those patients who did not receive NSAIDs. These were not considered primary outcomes, and comparisons were not adjusted for covariates. But overall, our study confirmed the low risk of

bleeding or acute renal impairment from brief perioperative use of NSAIDs.

Perioperative use of NSAIDs has well-recognized benefits. Meta-analyses indicate that postoperative pain scores are reduced (approximately 1/10 on VAS), opioid use is reduced (30%–50%), postoperative nausea and vomiting are reduced (12%–32%), and sedation is reduced (29%) with the use of NSAIDs.[11,12] Adequate control of postoperative pain and adverse effects are considered a key feature for fast-track postoperative recovery pathways that are used for total joint replacement.[32] The ability to safely use NSAIDs as a key component of fast-track recovery has general applicability because total hip and knee replacements are commonly performed procedures. For example, the latest data set (2009) from the Health Care Cost and Utilization Project reported nearly 436,000 total hip replacements and 679,000 total knee replacements in the United States alone (available at: http://hcupnet.ahrq.gov/HCUPnet.jsp?Id=03D9A39FD206A7D2&Form=DispTab&GoTo=SelDXPR&JS=Y. Accessed August 8, 2011). These procedures have significant postoperative pain and may especially benefit from the improved analgesia and adverse effect profiles from perioperative use of NSAIDs because improved analgesia has been shown to hasten rehabilitation and decrease length of hospital stay.[13,33,34] Accordingly, our data noted a significantly shorter length of hospital stay with the use of NSAIDs in an unadjusted fashion. Pain scores were also statistically lower with NSAIDs, but the difference was unlikely to have significant clinical impact.

Although our data included a large cohort, there are limitations. As is typical of any single-center observational study, institutional biases may occur and differences between groups are inferential. We attempted to control for as many covariates as possible with propensity scores and logistic regression. However, future multicenter RCTs will be needed to confirm our observations. Total joint replacements are considered moderate-risk procedures with an expected incidence of 1% to 5% for cardiac morbidity.[35] Our rate of POMI (0.9% in 10,873 admissions) was as expected and comparable to previous large clinical surveys (5,000–15,000) of total joint replacement that reported rates ranging from 0.2% to 1.5%.[29,36] Our cohort has the potential of healthy user bias because our mortality rate was 0%. Detection bias is a potential because only selected patients underwent troponin measurements as opposed to the ideal of universal measurement,[9] and we attempted to adjust for this confounder in our propensity analysis. We are unable to determine whether patients who had their aspirin stopped before surgery are at a different risk because our database does not allow identification of this subset. Although pharmacological effects of aspirin and NSAIDs should be washed out after discontinuation for a week, it is possible that long-term preoperative use of these agents may have biased our findings. In addition, perioperative administration of aspirin for 1 week before and 3 days after noncardiac surgery in high-risk patients has been shown to reduce the risk of POMI during the first month after surgery (RR, 0.8).[37]

In conclusion, the use of NSAIDs in our large cohort of total joint replacement patients was not associated with increased risk of POMI. Previous benefits of NSAIDs for postoperative analgesia, such as improved pain scores and shorter length of stay, were confirmed.

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