PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2015; **24**: 647–653
Published online 22 April 2015 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3788

ORIGINAL REPORT

# Non-steroidal anti-inflammatory drug administration after coronary artery bypass surgery: utilization persists despite the boxed warning

Alexander Kulik[1,2]*, Katsiaryna Bykov[1], Niteesh K. Choudhry[1] and Brian T. Bateman[1,3]

[1] *Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[2] *Lynn Heart and Vascular Institute, Boca Raton Regional Hospital, and Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL, USA*
[3] *Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA*

## ABSTRACT

**Purpose** In 2005, the US Food and Drug Administration (FDA) issued a boxed warning against the administration of non-steroidal anti-inflammatory drugs (NSAIDs) after coronary artery bypass graft (CABG) surgery because of cardiovascular safety concerns. We assessed utilization rates before and after the advisory and evaluated predictors of NSAID administration following CABG.

**Methods** We assembled a cohort of 277 576 patients who underwent CABG from 2004 to 2010. Temporal trends in NSAID exposure were evaluated, and predictors of postoperative NSAID use were identified using generalized estimating equations.

**Results** Over the study period, 92 938 CABG patients (33.5%) received NSAIDs following surgery. The frequency of NSAID administration declined steadily over time, from a peak of 38.9% in 2004 to a low of 29.0% in 2010 ($p < 0.0007$). Ketorolac was the most frequent NSAID prescribed, commonly on the first postoperative day. Surgery performed after the boxed warning was independently associated with a 20% lower odds of NSAID administration [odds ratio (OR): 0.80; $p = 0.0003$]. Other factors that predicted a lower odds of NSAID use following surgery included a history of renal disease (OR: 0.33; $p < 0.0001$) and liver disease (OR: 0.66; $p < 0.0001$), and the need for concurrent valve surgery (OR: 0.78; $p < 0.0001$). A mammary graft at the time of surgery increased the odds of NSAID administration (OR: 1.23; $p < 0.0001$).

**Conclusions** The frequency of NSAID administration after CABG has declined since the FDA advisory, yet many patients continue to receive them in recent years. Our data highlight the need for future research initiatives to further define the risks associated with NSAID use in this population. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—analgesia; postoperative care; pain; coronary artery bypass graft (CABG); pharmacoepidemiology

*Received 28 January 2015; Revised 20 March 2015; Accepted 20 March 2015*

## INTRODUCTION

Pain management after coronary artery bypass graft (CABG) surgery remains challenging. Inadequately controlled postoperative pain can raise catecholamine levels, triggering myocardial ischemia, stroke, and bleeding complications.[1] Limiting patient mobility, poorly managed postoperative pain can increase the risk of deep vein thrombosis and pneumonia, in addition to harmful psychological consequences such as insomnia and demoralization.[2] Ultimately, pain that is insufficiently treated can escalate the cost of medical care, with longer stays in the hospital and a greater risk of hospital readmission.[1,2]

Opioids are the most common medications used to control the pain from surgical trauma. However, their administration is associated with troublesome effects, including respiratory depression, sedation, constipation, and nausea. As an adjunct to routine postoperative narcotic administration, non-steroidal anti-inflammatory drugs (NSAIDs) have been promoted as a method of limiting opioid-related adverse effects, as well as facilitating early extubation and mobilization after surgery.[3] NSAIDs also have potential side effects, but several studies from the late 1990s and early 2000s demonstrated that, when administered to

*Correspondence to: A. Kulik, Lynn Heart and Vascular Institute, Boca Raton Regional Hospital, 801 Meadows Road, Suite 104, Boca Raton, FL, 33486 USA. E-mail: alex_kulik@yahoo.com

appropriately selected patients, their use can improve postoperative pain control after CABG without increasing the risk of bleeding or renal complications.[3,4]

Nevertheless, in April 2005, the US Food and Drug Administration (FDA) recommended the labeling for all NSAIDs be modified to include a contraindication "for use in patients in the immediate postoperative setting after CABG surgery".[5] This FDA boxed warning (black box warning) was based upon two studies that evaluated the safety of the cyclooxygenase-2 (COX-2) inhibitors parecoxib and valdecoxib following cardiac surgery. When used in the perioperative period, these agents significantly increased the risk of complications after CABG, including myocardial infarction, stroke, cardiac arrest, and pulmonary embolism.[6,7] Valdecoxib was subsequently removed from the market, and the FDA boxed warning was issued for all NSAIDs after CABG.

It remains unknown whether NSAID utilization rates after CABG have changed since the boxed warning was issued, although some groups have reported their continued use to select cardiac surgery patients.[8–10] Therefore, in this study, we examined the utilization patterns of NSAIDS before and after the FDA advisory and evaluated the predictors of postoperative NSAID administration early after CABG.

## METHODS

### *Data source*

The study cohort was derived from the Premier Research Database, a repository of hospital administrative data. This features a complete census of inpatients from approximately 400 hospitals in the USA. The database contains information about daily charges for all medications, procedures, and diagnostic tests conducted during each hospitalization, as well as patient demographic and hospital characteristics, discharge diagnoses, and discharge status (including death). Validated Premier data have been extensively used to study medication use and health outcomes in the perioperative period.[11] The use of this database for research was approved by the Institutional Review Board of the Brigham and Women's Hospital, Boston, MA; and a Data Use Agreement was in place.

### *Cohort*

We included all patients who, during the course of hospital stay, underwent a CABG operation between 1 January 2004 and 31 December 2010. Patients who underwent more than one CABG operation (i.e. redo CABG) during the time interval of the study ($n = 673$, 0.2%) were maintained in the cohort, with each CABG hospitalization tabulated separately in the analysis.

### *Exposure to non-steroidal anti-inflammatory drugs*

Postoperative NSAID exposure was defined as hospital charges for ibuprofen, indomethacin, naproxen, diclofenac, etodolac, ketorolac, meloxicam, celecoxib, rofecoxib, or valdecoxib, starting the day after surgery and until day of hospital discharge. Exposure patterns were assessed for overall NSAID use, COX-2 inhibitors only, and at the individual drug level. Exposure to NSAID medication on the day of surgery (day 0) was not included in the data analysis because it could not be conclusively established that treatment on day 0 started in the postoperative period, rather than that occurring before surgery or in the operating room as preemptive analgesia (49 951 patients exposed on day 0, 97% ketorolac).

### *Patient and hospital characteristics*

We identified four groups of potential predictors of NSAID exposure, focusing on demographic characteristics (age and gender), surgery characteristics, chronic comorbid conditions, and hospital characteristics. The surgery characteristics included the following: urgency of surgery, the day of surgery (relative to hospital admission date), the number of bypass grafts, the use of a mammary graft, a history of previous CABG, the use of cardiopulmonary bypass, the need for blood transfusion and the number of packed red blood cells dispensed on the day of surgery, the need for concurrent valve surgery, and the month and year of surgery.

Chronic comorbid conditions were identified using discharge diagnoses, including chronic liver disease, chronic obstructive pulmonary disease, malignancy, prior myocardial infarction, prior stroke, chronic renal disease, chronic hematologic conditions, carotid artery stenosis, rheumatoid arthritis, and diabetes mellitus. Although these conditions were recorded as discharge diagnoses, all are chronic diseases that would be present prior to hospital admission.

Hospital characteristics were also assessed, including whether a patient was treated at a teaching hospital accredited by the Association of American Medical Colleges, and whether the hospital was urban or rural in location. The annualized volume of CABG surgeries performed by each hospital was estimated by dividing the total number of CABG surgeries for each hospital during the study time period by the number of years that each hospital performed one or more CABG operations. Hospitals were ranked in order of



DOI: 10.1002/pds

annualized volume and were then categorized into low (below 110/year), medium (110–225/year), and high (above 225/year) tertiles of volume.[12]

### *Statistical analysis*

Standard descriptive statistical analyses were used. Continuous data are presented as a mean ± standard deviation, and categorical data are presented as proportions. Temporal trends in NSAID exposure were evaluated, focusing on the day of administration after surgery and the different types of individual NSAIDs. In addition, the frequency of NSAID use (and COX-2 inhibitors only) during each year of the study period was assessed, with analysis of variance (ANOVA) and logistic regression employed to explore the relationship between administration rate and year. Comparisons were performed using chi-squared and *t*-tests, as appropriate, between patients who were and were not exposed to NSAIDs. Independent predictors of postoperative NSAID use were identified by using generalized estimating equations (GEEs) adjusting for clustering at the hospital level, using a logit link function with binary distributed errors. All baseline characteristics were incorporated into the GEE analysis, including demographic characteristics, surgery characteristics, chronic comorbid conditions, and hospital characteristics. As the FDA boxed warning was issued in April 2005, whether surgery was performed before or after this date was incorporated as a covariate into the analysis to determine if the warning was associated with a change in NSAID use. Odds ratios (ORs) are presented with 95% confidence intervals (CI). All analyses were performed with SAS software, version 9.3 (SAS Institute, Cary, NC, USA).

## RESULTS

### *Patient cohort*

The study cohort consisted of 277 576 patients who underwent CABG between 2004 and 2010. Table 1 describes the characteristics of patients in the study. The mean age of the cohort was 66.0 ± 10.9 years, and 71.4% of patients were male. Diabetes mellitus was the most common comorbidity, present in 39.6% of patients. The majority of patients underwent surgery at an urban hospital (93.4%), and most were cared for at a teaching facility (54.7%). Most patients underwent on-pump CABG (82.0%), receiving an average of 3.2 ± 1.1 bypass grafts, and 13.8% of patients had concurrent valve surgery. The mean transfusion requirement was 1.4 ± 3.2 units of packed red blood

Table 1. Patient characteristics

| Characteristic | Overall cohort (*N* = 277 576) | No NSAID exposure (*N* = 184 638) | NSAID exposure (N = 92 938) | *p* value |
|---|---|---|---|---|
| Patient characteristics | | | | |
| Age (years, mean ± SD) | 66.0 ± 10.9 | 67.6 ± 10.6 | 62.7 ± 10.8 | <0.0001 |
| Female gender | 79 373 (28.6%) | 54 678 (29.6%) | 24 695 (26.6%) | <0.0001 |
| Diabetes mellitus | 109 812 (39.6%) | 76 139 (41.2%) | 33 673 (36.2%) | <0.0001 |
| Chronic obstructive pulmonary disease | 66 940 (24.1%) | 46 132 (25.0%) | 20 808 (22.4%) | <0.0001 |
| Previous myocardial infarction | 41 845 (15.1%) | 27 557 (14.9%) | 14 288 (15.4%) | 0.008 |
| Gastro-esophageal reflux disease | 47 975 (17.3%) | 31 016 (16.8%) | 16 959 (18.2%) | <0.0001 |
| Renal disease | 26 170 (9.4%) | 23 003 (12.5%) | 3167 (3.4%) | <0.0001 |
| Carotid artery stenosis | 16 042 (5.8%) | 11 738 (6.4%) | 4304 (4.6%) | <0.0001 |
| Previous stroke | 12 894 (4.6%) | 9350 (5.1%) | 3544 (3.8%) | <0.0001 |
| Cancer | 27 228 (9.8%) | 19 744 (10.7%) | 7484 (8.0%) | <0.0001 |
| Liver disease | 4186 (1.5%) | 3294 (1.8%) | 892 (1.0%) | <0.0001 |
| Rheumatoid arthritis | 3313 (1.2%) | 2222 (1.2%) | 1091 (1.2%) | 0.8 |
| Hematologic disease | 1327 (0.5%) | 968 (0.5%) | 359 (0.4%) | <0.0001 |
| Hospital characteristics | | | | |
| Teaching hospital | 151 830 (54.7%) | 103 707 (56.2%) | 48 123 (51.8%) | <0.0001 |
| Urban hospital | 259 271 (93.4%) | 172 613 (93.5%) | 86 658 (93.2%) | 0.05 |
| High-volume hospital (>226 cases per year) | 180 573 (65.1%) | 118 967 (64.4%) | 61 606 (66.3%) | <0.0001 |
| Surgical characteristics | | | | |
| Urgent or emergent surgery | 143 854 (51.8%) | 96 861 (52.5%) | 46 993 (50.6%) | <0.0001 |
| Preoperative hospital length of stay (days, mean ± SD) | 2.3 ± 3.1 | 2.4 ± 3.2 | 2.0 ± 2.7 | <0.0001 |
| Number of bypasses (mean ± SD) | 3.2 ± 1.1 | 3.1 ± 1.1 | 3.2 ± 1.1 | <0.0001 |
| Mammary artery bypass | 233 619 (84.2%) | 152 302 (82.5%) | 81 317 (87.5%) | <0.0001 |
| Redo-CABG | 5783 (2.1%) | 4074 (2.2%) | 1709 (1.8%) | <0.0001 |
| Use of cardiopulmonary bypass | 227 691 (82.0%) | 153 200 (83.0%) | 74 491 (80.2%) | <0.0001 |
| Concurrent valve surgery | 38 335 (13.8%) | 29 809 (16.1%) | 8526 (9.2%) | <0.0001 |
| Need for blood transfusion (on day of surgery) | 97 306 (35.1%) | 71 161 (38.5%) | 26 145 (28.1%) | <0.0001 |
| Number of packed red blood cell transfusions (mean ± SD) | 1.4 ± 3.2 | 1.6 ± 3.5 | 0.9 ± 2.3 | <0.0001 |

NSAID, non-steroidal anti-inflammatory drug; CABG, coronary artery bypass graft.



DOI: 10.1002/pds

cells on the day of surgery, but most patients (64.9%) did not require perioperative blood transfusion.

### *NSAID exposure*

Over the entire study period, 92 938 CABG patients (33.5%) received NSAIDs following surgery. The frequency of NSAID administration declined steadily during the time period of the study, from a peak of 38.9% in 2004 to a low of 29.0% in 2010 (Figure 1, $p < 0.0007$ ANOVA, $p < 0.0001$ logistic regression). Before the boxed warning, 38.3% patients received NSAIDS, compared with 32.3% patients after the FDA advisory was issued in April 2005 ($p < 0.0001$). As illustrated in Figure 1, the administration of COX-2 inhibitors dropped from 4.1% in 2004 to 0.3% after the boxed warning was announced ($p < 0.0001$).

Of the patients who received NSAIDs after surgery, ketorolac (89.2%) and ibuprofen (12.9%) were the most common (Figure 2), with some patients receiving more than one type in the postoperative period (percentages total more than 100%). The average duration of NSAID treatment in the postoperative period was $2.2 \pm 1.6$ days among NSAID-exposed patients, and 25% of NSAID-treated patients received them for 3 days or longer. The most frequent time of NSAID initiation was the first day after surgery, with 25.6% of patients having their therapy initiated on postoperative day 1 (Figure 3). Among patients who were exposed to NSAIDs on postoperative day 1, 95.7% received ketorolac. Ketorolac-treated patients received on average $4.2 \pm 4.1$ doses of this medication.

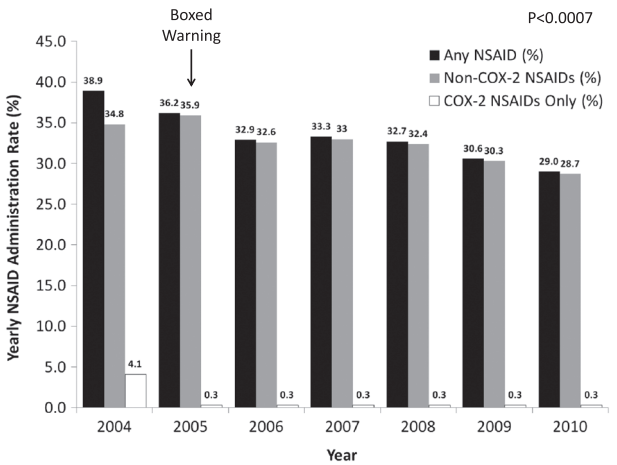


Figure 1. Frequency of non-steroidal anti-inflammatory drug (NSAID) use during each year of study time period, stratified by type. The frequency of NSAID administration declined steadily during the time period of the study ($p < 0.0007$). In contrast to the slow decline in the use of non-cyclooxygenase-2 (non-COX-2) NSAIDs, a dramatic decline was noted for the utilization of COX-2 inhibitors after the boxed warning was issued in April 2005

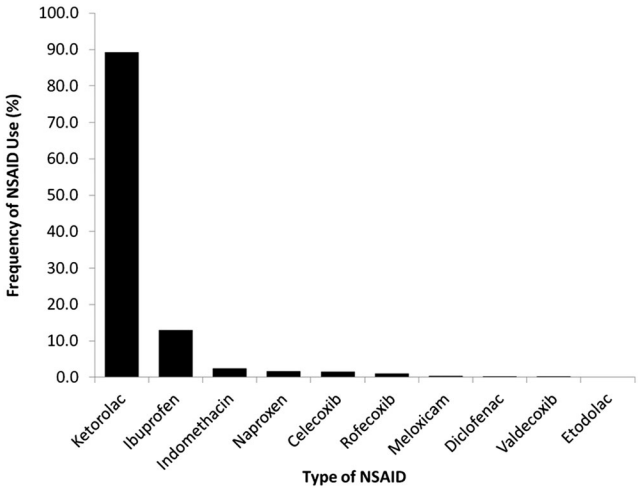


Figure 2. Individual non-steroidal anti-inflammatory drugs (NSAIDs) administered during the study time period. Ketorolac was the most commonly used NSAID in this cohort

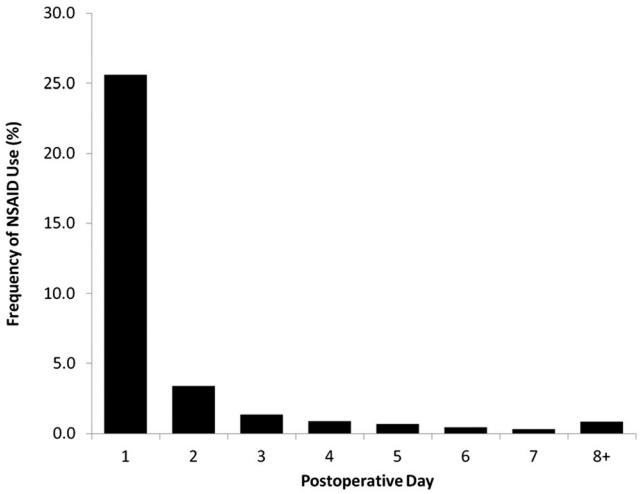


Figure 3. Initiation of non-steroidal anti-inflammatory drugs (NSAIDs) for the entire study population stratified by postoperative day after CABG. The first postoperative day was the most common time for NSAID initiation following surgery

### *Characteristics of NSAID-treated patients*

Table 1 describes the characteristics of the patients that did and did not receive NSAIDs after CABG. Compared with patients who were not treated with NSAIDs, those who were administered NSAIDs were more commonly men and were significantly younger ($p < 0.0001$). NSAID patients were less commonly treated at a teaching hospital and had fewer preoperative comorbidities such as diabetes, stroke, and renal insufficiency ($p < 0.0001$). At the time of surgery, NSAID-treated patients more often received a mammary bypass graft and less often underwent concurrent



DOI: 10.1002/pds

valve surgery ($p < 0.0001$). In the perioperative period, patients who received NSAIDs were administered less blood transfusions following the operation ($p < 0.0001$).

### *Predictors of NSAID use*

After adjusting for patient-related, procedure-related, and hospital-related characteristics using GEEs, surgery performed after April 2005 (timing of boxed warning) was independently associated with a lower odds of NSAID administration in the postoperative period (OR: 0.80; 95%CI: 0.71, 0.90; $p = 0.0003$). Other strong factors (Table 2) that were independently associated with a lower odds of NSAID use following surgery include a history of renal disease (OR: 0.33; 95%CI: 0.30, 0.36; $p < 0.0001$), liver disease (OR: 0.66; 95% CI: 0.61, 0.72; $p < 0.0001$), and the need for concurrent valve surgery (OR: 0.78; 95%CI: 0.72, 0.83; $p < 0.0001$). Factors that independently predicted a greater use of NSAIDs after surgery included the use of a mammary graft at the time of surgery (OR: 1.23; 95% CI: 1.13, 1.34; $p < 0.0001$) and a history of rheumatoid arthritis (OR: 1.11; 95%CI: 1.02, 1.20; $p = 0.01$).

## DISCUSSION

Pain control after cardiac surgery is a critical issue for clinicians and patients alike. Poorly managed pain after surgery can compromise the cardiovascular, respiratory, and immune systems and ultimately increase the cost of medical care.[1,2] Moreover, pain that is inadequately controlled and more intense during the first postoperative week can predict the development of chronic persistent pain in the months and years after CABG, with important consequences for long-term patient functioning and quality of life.[13] Narcotics represent the medications most commonly administered to alleviate postoperative pain, but their use can be associated with challenging side effects, particularly when used in high doses for the severe pain that can exist early following cardiac surgery. As an adjunct to opioids, the administration of intravenous or oral NSAIDs may help improve pain control, reduce opioid-related nausea and sedation, and facilitate early extubation and mobilization after CABG.[3]

Table 2. Independent predictors of postoperative NSAID use

| Characteristic | Odds ratio | 95% confidence interval | *p* value |
|---|---|---|---|
| Increased use | | | |
| Mammary graft | 1.23 | 1.13, 1.34 | <0.0001 |
| Rheumatoid arthritis | 1.11 | 1.02, 1.20 | 0.01 |
| Decreased use | | | |
| Surgery after April 2005 | 0.80 | 0.71, 0.90 | 0.0003 |
| Renal disease | 0.33 | 0.30, 0.36 | <0.0001 |
| Liver disease | 0.66 | 0.61, 0.72 | <0.0001 |
| Concurrent valve surgery | 0.78 | 0.72, 0.83 | <0.0001 |
| Diabetes mellitus | 0.83 | 0.81, 0.86 | <0.0001 |
| Previous stroke | 0.85 | 0.81, 0.89 | <0.0001 |
| Carotid artery stenosis | 0.91 | 0.87, 0.96 | 0.0003 |
| Chronic obstructive pulmonary disease | 0.92 | 0.88, 0.96 | <0.0001 |
| Packed red blood cells (per additional unit) | 0.95 | 0.93, 0.96 | <0.0001 |
| Cancer | 0.95 | 0.92, 0.99 | 0.006 |
| Older age (per additional year) | 0.96 | 0.96, 0.97 | <0.0001 |
| Longer preoperative length of stay (per additional day) | 0.98 | 0.97, 0.99 | <0.0001 |

Despite the demonstration of their safety and efficacy in several CABG studies,[3,4] an FDA boxed warning was issued in 2005 recommending against the use of all NSAIDs in the immediate perioperative setting after cardiac surgery.[5] This warning came as a result of studies involving the COX-2 inhibitors valdecoxib and parecoxib, whereby 10–14 days of treatment with these agents led to an increased incidence of cerebrovascular complications, renal dysfunction, myocardial infarction, and difficulty with sternal wound healing.[6,7] Support for the boxed warning was likely strengthened by reports from other patient populations published around the same time that highlighted the cardiovascular risk associated with NSAIDs and COX-2 inhibitors.[14] This safety concern is believed to be related to an imbalance between prostacyclin and thromboxane A2 production, leading to an increased risk of thrombotic events.[14]

In our large, nationally representative, hospital-based cohort study of 277 576 patients who underwent CABG between 2004 and 2010, we detected a slow and steady decline in the rate of perioperative NSAID administration, from a peak of 38.9% in 2004 to a low of 29.0% in 2010 ($p < 0.0007$). Surgery performed after April 2005, when the boxed warning was issued, was independently associated with a lower odds of NSAID administration in our study (OR: 0.80; 95% CI: 0.71, 0.90; $p = 0.0003$). While a reduction in NSAID use was seen, including a dramatic decline in the use of COX-2 inhibitors, we were surprised to note that nearly 30% of CABG patients continue to receive NSAIDs after surgery despite the FDA advisory, even in recent years.

Previous reports on the impact of FDA boxed warnings have documented varied effects on ensuing prescription rates in clinical practice.[15] Dramatic declines were noted with some medications, such as the prescription of antidepressants among adolescents,[16] whereas other studies have reported less impressive



DOI: 10.1002/pds

effects of boxed warnings on prescription patterns.[15] With relatively high rates of NSAID administration seen in our study, even 5 years after the warning was issued, we speculate this may represent a lack of knowledge dissemination of the FDA advisory to the cardiac surgery community. Alternatively, our data may reflect simple disregard or disagreement from clinicians regarding the FDA's opinion on the perioperative risk associated with NSAIDs.[8–10] Recent reports have illustrated varying cardiovascular risks associated with each individual NSAID and the absence of a uniform class effect,[17,18] suggesting that the harmful perioperative effects noted with valdecoxib and parecoxib[6,7] may not necessarily be generalizable to all NSAIDs after cardiac surgery.[3,4,8–10]

Postoperative pain following CABG occurs as a result of surgical trauma and inflammation to the thoracic cage and parietal pleura. Pain is normally transient, with maximal intensity between the day of surgery and postoperative day 3.[4] NSAIDs block the synthesis of prostaglandins through the inhibition of COX-1 and COX-2, thus lowering the production of acute inflammatory response mediators and reducing peripheral nociception. NSAIDs may also contribute through a central analgesic mechanism by inhibiting the prostaglandin synthesis within the spinal cord.[4] In this study, we noted that NSAIDs were most commonly initiated early after surgery, with the highest rate (25.6%) observed on postoperative day 1 when the pain is most intense. Young patients with relatively few comorbidities were more likely to receive NSAIDs, particularly if the mammary artery was harvested from the chest wall during surgery, which was the strongest predictor of NSAID administration in this cohort (OR: 1.23; 95%CI: 1.13, 1.34; $p < 0.0001$).

Ketorolac was the most commonly used NSAID in our population. Of the patients who received NSAIDs after surgery, 89.2% received ketorolac, representing 95.7% of those exposed to NSAIDs on postoperative day 1. Several studies have previously demonstrated the safety and efficacy of ketorolac in the perioperative period.[19,20] In contrast to the risk identified with COX-2 inhibitors,[6,7] ketorolac may not have the same harmful postoperative effects as other NSAIDs, because ketorolac acts mainly as a COX-1 inhibitor without COX-2 selectivity (COX-1/COX-2 ratio 0.36).[21] Within the cardiac surgery literature, the results from two relatively small patient series support the cardiovascular safety of ketorolac when administered for a relatively short duration in the postoperative period, with some suggestion that ketorolac administration may even improve graft patency and lead to survival benefits following CABG.[8–10]

By inhibiting COX-1 and prostaglandin synthesis, NSAIDs may contribute to bleeding and renal complications after surgery.[4,22] In addition to the year of surgery, other factors noted in our study that predicted lower odds of NSAID use included a history of renal disease, liver disease, and older age. Moreover, NSAIDs were less likely to be administered to patients who required more extensive surgery with concurrent CABG and valve operations, those who required more blood transfusion in the perioperative period, and those who required several days of preoperative medical stabilization before surgery. In essence, it appears that clinicians were less likely to administer NSAIDs to older patients with a greater burden of comorbidities, presumably to reduce the risk of NSAID-associated complications after surgery such as renal dysfunction or gastrointestinal hemorrhage. On the other hand, patients with rheumatoid arthritis had a greater likelihood of receiving NSAIDs after CABG, which may reflect the frequent use of these medications in this patient population or the resumption of preoperative medication regimens.

To our knowledge, this is the largest study to date to evaluate the use of NSAIDs after CABG and the first to assess the impact of the FDA boxed warning on their postoperative administration. By using a large database and robust statistical methods, we believe that our study provides the best current evaluation of NSAID use following CABG. Notwithstanding the study findings, the results must be interpreted in the context of the limitations inherent in its design. First, we did not specifically examine the efficacy of NSAIDs for postoperative pain control in this study, as this has been well documented previously and was not the goal of the current analysis.[3,4] Second, we used the Premier Database, which contains data on the utilization of medications, laboratory tests, and procedures. However, the information is collected for billing purposes and therefore lacks detailed clinical information (such as postoperative pain intensity) and the reasons for physicians' prescription choices. Complete Premier data were available only for the years 2004–2010, restricting the time span for analysis. Despite the statistical adjustments employed in this study, including the use of GEE analysis, it remains possible that unmeasured or unknown confounders may have influenced the results. Finally, and most importantly, we did not evaluate the safety of administering NSAIDs in the perioperative period after CABG in this study. Recent series involving small groups of patients have demonstrated reasonable safety associated with their perioperative use,[8–10] but a large-scale study remains an important direction for future research.



DOI: 10.1002/pds

In conclusion, our analysis reveals that approximately one-third of patients receive NSAIDs after CABG, with ketorolac being the most common agent used. Younger patients who receive a mammary graft are more likely to receive NSAIDs after CABG, whereas older patients with more extensive comorbidities and those who undergo more complex surgeries are less likely to receive them. The frequency of NSAID administration after CABG has declined since the FDA boxed warning was issued in 2005, but surprisingly, many patients continue to receive NSAIDs, even in recent years. Our data call into question whether the cardiac surgery community has embraced the FDA advisory. We believe future research initiatives are needed to further define the risks associated with NSAID administration to the CABG population and to provide continued justification for the boxed warning.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

### KEY POINTS

- The frequency of NSAID administration after CABG has declined since the Food and Drug Administration boxed warning in 2005; despite the advisory, many patients continue to receive them in recent years.

## ETHICS STATEMENT

The use of the Premier database for research was approved by the Institutional Review Board of the Brigham and Women's Hospital, and the need for informed consent had been waived.

## REFERENCES


1. Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. *Anesth Analg* 2007; **105**: 205–21.
2. Apfelbaum JL, Chen C, Mehta SS, *et al.* Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg* 2003; **97**: 534–40.
3. Bainbridge D, Cheng DC, Martin JE, *et al.* NSAID-analgesia, pain control and morbidity in cardiothoracic surgery. *Can J Anaesth* 2006; **53**: 46–59.
4. Kulik A, Ruel M, Bourke ME, *et al.* Postoperative naproxen after coronary artery bypass surgery: a double-blind randomized controlled trial. *Eur J Cardiothorac Surg* 2004; **26**: 694–700.
5. FDA U.S. Food and Drug Administration (4 April 2005), Public Health Advisory—FDA Announces Important Changes and Additional Warnings for COX-2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). *Available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm150314.htm *Accessed October 19, 2012*.
6. Ott E, Nussmeier NA, Duke PC, *et al.* Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 2003; **125**: 1481–92.
7. Nussmeier NA, Whelton AA, Brown MT, *et al.* Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005; **352**: 1081–91.
8. Oliveri L, Jerzewski K, Kulik A. Black box warning: is ketorolac safe for use after cardiac surgery? *J Cardiothorac Vasc Anesth* 2014; **28**: 274–9.
9. Engoren MC, Habib RH, Zacharias A, *et al.* Postoperative analgesia with ketorolac is associated with decreased mortality after isolated coronary artery bypass graft surgery in patients already receiving aspirin: a propensity-matched study. *J Cardiothorac Vasc Anesth* 2007; **21**: 820–6.
10. Engoren M, Hadaway J, Schwann TA, *et al.* Ketorolac improves graft patency after coronary artery bypass grafting: a propensity-matched analysis. *Ann Thorac Surg* 2011; **92**: 603–9.
11. Kulik A, Rassen JA, Myers J, *et al.* Comparative effectiveness of preventative therapy for venous thromboembolism after coronary artery bypass graft surgery. *Circ Cardiovasc Interv* 2012; **5**: 590–6.
12. Kulik A, Brookhart MA, Levin R, *et al.* Impact of statin use on outcomes after coronary artery bypass graft surgery. *Circulation* 2008; **118**: 1785–92.
13. Choiniere M, Watt-Watson J, Victor JC, *et al.* Prevalence of and risk factors for persistent postoperative nonanginal pain after cardiac surgery: a 2-year prospective multicentre study. *CMAJ* 2014; **186**: E213–23.
14. Fitzgerald GA. Coxibs and cardiovascular disease. *N Engl J Med* 2004; **351**: 1709–11.
15. Piening S, Haaijer-Ruskamp FM, de Vries JT, *et al.* Impact of safety-related regulatory action on clinical practice: a systematic review. *Drug Saf* 2012; **35**: 373–85.
16. Olfson M, Marcus SC, Druss BG. Effects of Food and Drug Administration warnings on antidepressant use in a national sample. *Arch Gen Psychiatry* 2008; **65**: 94–101.
17. Ray WA, Varas-Lorenzo C, Chung CP, *et al.* Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. *Circ Cardiovasc Qual Outcomes* 2009; **2**: 155–63.
18. Trelle S, Reichenbach S, Wandel S, *et al.*. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011; **342**: c7086.
19. Litvak KM, McEvoy GK. Ketorolac, an injectable nonnarcotic analgesic. *Clin Pharm* 1990; **9**: 921–35.
20. Gillis JC, Brogden RN. Ketorolac. A reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. *Drugs* 1997; **53**: 139–88.
21. Kulkarni SK, Jain NK, Singh A. Cyclooxygenase isoenzymes and newer therapeutic potential for selective COX-2 inhibitors. *Methods Find Exp Clin Pharmacol* 2000; **22**: 291–8.
22. Lee A, Cooper MC, Craig JC, *et al.* Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function. *Cochrane Database Syst Rev* 2004: CD002765.