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The Risk of Acute Myocardial Infarction With Etodolac Is Not Increased Compared to Naproxen: A Historical Cohort Analysis of a Generic COX-2 Selective Inhibitor

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Background: This study compares the risk of acute myocardial infarction among patients exposed to etodolac, naproxen, celecoxib, and rofecoxib.
Methods: A retrospective cohort study in 38 258 veteran patients (26 376 patient-years) measured the adjusted odds ratios of acute myocardial infarction during exposure to etodolac, naproxen, celecoxib, or rofecoxib.
Results: Diagnosis of acute myocardial infarction was confirmed in 100 patients who were exposed to a study nonsteroidal anti-inflammatory drug. Compared to naproxen, the increased risk of acute myocardial infarction was not significant for etodolac (OR = 1.32, $P = .27$), whereas celecoxib (OR = 2.18, 95% CI 1.09-4.35, $P = .03$) and rofecoxib (OR = 2.16, 95 CI 1.04-4.46, $P = .04$) were significant. A post hoc analysis indicates that patients with a prior history of acute myocardial infarction had a significant, 4.26-fold risk for another acute myocardial infarction if taking celecoxib or rofecoxib.
Conclusion: Etodolac is not associated with a statistically increased risk of acute myocardial infarction compared to naproxen.

Keywords: COX-2; celecoxib; rofecoxib; etodolac; naproxen; AMI; cohort; epidemiology

Background

In February 2007, the American Heart Association[1] issued a scientific statement regarding the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for musculoskeletal symptoms in patients with known cardiovascular disease or risk factors for ischemic heart disease. They suggested that after acetaminophen, aspirin, tramadol, and short-term narcotic analgesia have failed to control symptoms, nonacetylated salicylates should be the next step followed by noncyclooxygenase-2 (COX-2) selective NSAIDs, NSAIDs with some COX-2 activity, and finally COX-2 selective NSAIDs. It is further suggested that risk and benefit should be balanced at each step,

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using aspirin and proton pump inhibitors (PPIs) to minimize thrombotic risk and gastrointestinal (GI) bleeding risk, respectively. In 2005, the American College of Rheumatology[2] amended its 2000 guidelines, suggesting that "the risk versus benefit of the specific COX-2 inhibitors favors their continued use in the United States, although patients should be counseled about potential cardiovascular risks." Although all NSAIDs may impose similar cardiovascular risks, some agents appear to be safer than others.

The VIGOR trial[3] first raised a concern that COX-2 agents may be associated with the risk of acute myocardial infarction (AMI), with a significantly higher incidence of AMI with rofecoxib (Vioxx®) compared to naproxen. VIGOR investigators concluded that naproxen, a potent antiplatelet agent, conferred cardioprotection while rofecoxib did not. Several subsequent retrospective studies also found that naproxen is cardioprotective,[4-7] while several others did not.[8-10] Recent meta-analyses suggest that naproxen is cardioneutral.[11,12] In August 2004, similar to the VIGOR trial, lumiracoxib was prospectively compared to naproxen in a cardiotoxicity trial known as TARGET.[13] In the TARGET trial, naproxen was associated with a significantly lower frequency of cardiovascular events compared to lumiracoxib; confirmed AMIs in the lumiracoxib arm were 5-fold higher (ie, 10 events in the lumiracoxib arm and 2 events with naproxen). Within months of the TARGET trial, 2 randomized prospective trials "APPROVe" and "APC" documented an increased cardiovascular risk of the COX-2 inhibitors rofecoxib and celecoxib (Celebrex®) compared to placebo.[14,15] This new information significantly clarified the cardiovascular risk of COX-2 inhibitors, although it remains unclear whether or not adverse cardiovascular events are a COX-2 "class effect."

Etodolac is an NSAID with moderate COX-2 selectivity in vitro[16] and in vivo.[17–19] Etodolac has a favorable GI safety profile and its cardiotoxicity has been evaluated by 2 nonadjudicated retrospective study designs. In 2002, Solomon et al performed a case–control study to evaluate the risk of AMI associated with a battery of NSAIDs, including 93 patients receiving etodolac.[4] Their findings were equivocal (odds ratio (OR) = 1.28, 95% confidence interval (CI): 1.00-1.64) in evaluation of the association between etodolac use and cardiovascular risk. In 2006, Motsko et al performed a cohort study, evaluating the risk of etodolac-related AMIs in Texas veteran patients over a 3-year period. Motsko et al noted that the risk of AMI was significantly increased in patients taking celecoxib or rofecoxib but not in patients taking etodolac, when compared to ibuprofen.[20] They noted a particular spike in risk in patients who had been on celecoxib or rofecoxib for greater than 180 days or in patients greater than 65 years old. Thus, by *International Classification of Diseases, Ninth Revision* (*ICD-9*) code review, the cardiovascular risk associated with etodolac appears to be different than other COX-2 selective NSAIDs. The objective of this investigation is to evaluate the potential cardiovascular toxicity of etodolac in a high-risk male veteran population using an adjudicated-AMI cohort model over a 6-year period.

Methods

Study Design and Population

The study was approved by the Institutional Review Board at the Dallas VA Medical Center. This was a historical cohort study designed to compare the risk of AMI with etodolac to that of naproxen. A total of 2 COX-2 selective drugs (celecoxib and rofecoxib), at doses commonly used in clinical practice, were used for comparison as positive controls. Study participants were male patients at the Dallas Veterans Affairs (VA) Medical Center who (1) received outpatient prescriptions for etodolac $\geq$ 800 mg/d, naproxen $\geq$ 1000 mg/d, celecoxib $\geq$ 200 mg/d, or rofecoxib $\geq$ 12.5 mg/d between October 1, 1998 and September 30, 2004; and (2) were not concurrently taking any other NSAID, except for aspirin. Patients' exposure was censored from the study after they (1) developed an AMI, (2) discontinued use of the study drug, or (3) died. The study period ended on September 30, 2004.

Patient Inclusion Criteria

Data were extracted from the computerized patient record system, clinical laboratory, and pharmacy transaction database at the VA Medical Center at Dallas, Texas. Women were excluded from this study because they were a small proportion (<10%) of our VA patient population. Patients were coded as diagnosed with diseases based on the following *ICD-9* codes: 411, 413-414 (coronary artery disease), 36.11-36.14 or V45.81-V45.82 (previous coronary revascularization), 410 or 412 (previous myocardial

infarction). Other diseases evaluated from the *ICD-9* code included: 428 (congestive heart failure; CHF), 250 (diabetes mellitus), 401 (hypertension), and 272 (hyperlipidemia). Patients were coded positive for chronic antiplatelet therapy use if they received antiplatelet drug prescriptions for $\geq$ 75% of the study drug's exposure period. Notably, patients at the Dallas VA Medical Center who are prescribed aspirin receive it at no charge. Thus, there is a strong incentive for patients to obtain their aspirin as a prescription, making it likely that the current study design captured aspirin exposure. Patients were included in the study if they were taking an antiplatelet agent: aspirin, ticlopidine, clopidogrel, or extended-release dipyridamole/aspirin. Patients taking antiplatelet agents concurrent with one of the study drugs were coded for use, and agents were included in the analysis as covariates.

Definition of AMI Diagnosis

All patients who received a prescription for a study NSAID during the study period and had (1) troponin I or T > 0.01 ng/mL, or (2) a muscle-brain (MB) fraction (creatine kinase-MB [CK-MB]) of > 5% of the total CK measurement, or (3) an *ICD-9* code diagnosis of AMI were reviewed by 2 cardiologists (JJW and ESB). Reviewers were blinded to NSAID drug exposure status. Diagnostic standards for AMI were chosen according to established criteria for cardiovascular outcomes.[13] Patients were excluded if they had sepsis syndrome, pulmonary embolism, trauma, acute renal failure, prolonged noncardiac hypotension (eg, GI hemorrhage), nonischemic cardiac arrests, stimulant or cocaine use. Patients with elevated cardiac enzymes and CHF were only included in the study cohort if they had other ischemic signs (rest angina, ischemic electrocardiogram changes, coronary revascularization; Table 1).

Drug Exposure

Patient days of study drug exposure were determined by totaling the days of study drug exposure (date the prescription was filled through the last day's supply[18,21]), or until an AMI, patient death, or study termination (September 30, 2004). Also, days of concurrent use of a confounding agent (other NSAIDs) were censored for the NSAID exposure calculation.

Table 1. Diagnostic Criteria for New Myocardial Infarction

Inclusion Criteria

Elevation of either troponin I, troponin T, or muscle-brain (MB) fraction of creatine kinase (CK-MB) in association with at least one of the following:

- Chest pain
- Electrocardiogram findings indicative of myocardial ischemia or infarction (ST segment depression or elevation)
- Cardiac catheterization findings requiring surgical or percutaneous revascularization

Exclusion Criteria

Myocardial infarctions which met the defined criteria but occurred in the setting of

- Sepsis, gastrointestinal bleeding, trauma or hypotension induced by other critical illness
- Amphetamine or cocaine abuse
- Recent (<72 hours) surgery

Statistical Analysis

Probabilities were calculated using χ^2 tests, unpaired t tests, and logistic regression analysis using SAS (Statistical Analysis System V9.1, 2005, Cary, NC). Logistic regression probabilities were calculated using the following formula:

$$\text{probability} = 1/(1+e^{(-a + bx + \ldots)}),$$

where e is antilog$_e$, a is the intercept, and b is the scaled logistic regression coefficient. The OR was computed using the standardized estimate of the logistic regression coefficient β, where $\beta = b \times (S_x/S_y)$, and the OR $= e^{\beta}$, where S_x and S_y are standard deviations for independent and dependent variables, respectively, and e is antilog$_e$. For all analyses, statistical significance was set a priori at $\leq .05$.

Results

Study Population and NSAID Use

A total of 38 601 male veteran patients received prescriptions for etodolac, naproxen, celecoxib, or rofecoxib from October 1, 1998 to September 30, 2004. The average age of the study cohort was 58 $\pm$ 13 years. Patients with limited exposure to study NSAIDs and who were taking other NSAIDs concomitantly were excluded (n = 343), leaving 38 258 patients in the study group. Of these, 25 656 patients took etodolac, 16 276 naproxen, 2997 celecoxib, and 2828 rofecoxib. More than one of the study NSAIDs

Table 2. Baseline Characteristics

	Naproxen (n = 16 276)	Etodolac[a] (n = 25 656)	Celecoxib[a] (n = 2997)	Rofecoxib[a] (n = 2828)
Age (years), mean ± SD	55.6 ± 13.2	58.2 ± 13.7	64.2 ± 12.6	63.4 ± 12.8
Diabetes mellitus (%)	16.3	17.5	21.2	22.6
Hypertension (%)	43.1	46.4	59.1	60.2
Hyperlipidemia (%)	25.8	29.3	37.6	42.6
Prior congestive heart failure (%)	4.21	5.22	10.1	8.35
Coronary artery disease (%)	14.1	16.5	24.4	21.3
History of myocardial infarction (%)	2.43	3.15	4.94	3.47
Prior coronary revascularization (%)	3.77	4.77	8.27	7.28
Antiplatelet therapy (%)	24.6	24.8[b]	23.1[b]	23.2[b]

[a] $P < .01$ compared to naproxen unless otherwise specified.
[b] $P > .05$ compared to naproxen.

was used as monotherapy by 8423 patients during the 6-year period.

Coronary artery disease, coronary revascularization, and CHF were more frequent in rofecoxib and celecoxib patients compared to naproxen study participants (Table 2). Traditionally recognized risk factors for AMI (advanced age, diabetes, hyperlipidemia, and hypertension) were also significantly more frequent among celecoxib and rofecoxib exposed patients. The prevalence of traditional risk factors and preexisting coronary artery disease or heart failure among etodolac patients was intermediate between naproxen and the celecoxib and rofecoxib groups (Table 2).

Nonsteroidal Anti-Inflammatory Drug Use and Incidence of AMI

Among patients in the study cohort (n = 38 258 patients), 1693 patients had an elevated troponin, CK-MB, or an *ICD-9* code for AMI. Medical records were available for 1 657 patients (98%) meeting at least one of the study criteria, and were evaluated. A total of 36 patients were excluded from the study cohort because of insufficient documentation. The medical record was required to clearly confirm or refute the coded AMI diagnosis for inclusion in the present investigation as an adjudicated AMI (Figure 1). Acute myocardial infarction diagnosis was confirmed in 426 patients, and 100 had study NSAID exposure within 3 days of hospitalization for AMI (Figure 1). Adjudicated AMIs were defined as events in the subsequent analyses.

Acute myocardial infarction incidence per patient-year was lowest among naproxen patients (0.28%), followed by etodolac (0.39%), celecoxib (0.46%), and rofecoxib (0.61%). Differences in unadjusted incidences of AMI among drug-exposure groups were only statistically significant for rofecoxib compared to naproxen, $P = .04$ (Figure 2). Time to event (ie, diagnosis of an AMI) plotted against cumulative AMI incidence rates for each of the 4 study NSAIDs increased linearly over time (Figure 3). Notably, rates for celecoxib and rofecoxib were higher at 24 months than for etodolac and naproxen.

Logistic regression (Type III sums of squares, direct and stepwise) analysis found that significant independent predictors of AMI were: previous AMI ($P < .01$), age ≥ 50 ($P < .01$), coronary artery disease ($P < .01$), rofecoxib ($P = .04$), and celecoxib ($P = .03$) use (Figure 4). Etodolac use was not associated with a significantly increased AMI risk (OR = 1.32, 95% CI 0.81-2.16, $P = .27$), compared to naproxen. A power analysis of the adjusted odds ratio for etodolac (OR = 1.32, Figure 4) obtained from the logistic regression revealed 80.2% power (2-tailed test, $\alpha < .05$). In contrast, rofecoxib (OR = 2.16, 95% CI 1.04-4.35, $P = .04$) and celecoxib (OR = 2.18, 95% CI 1.09-4.46, $P = .03$) were associated with a statistically increased risk for AMI compared to naproxen. Duration of NSAID exposure was not associated with increased AMI risk.

Stepwise analysis indicated that CHF was not significantly associated and was eliminated from the model. Tobacco use and family history of coronary artery disease could not be directly assessed because they are not electronically available. Therefore, to assess possible association between tobacco use and family history with the risk of AMI, we performed a

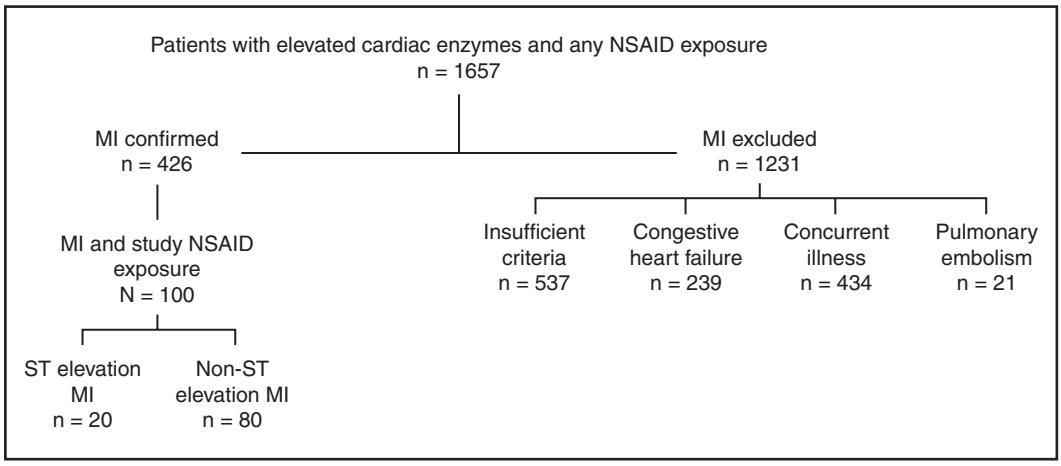


Figure 1. Results of adjudication of patients with elevated cardiac enzymes or *ICD-9* diagnosis of MI and any NSAID exposure. *ICD-9* indicates *International Classification of Diseases, Ninth Revision;* MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug.

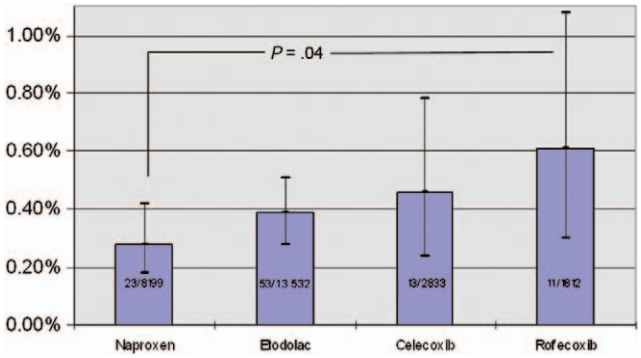


Figure 2. Unadjusted incidence of myocardial infarction per patient year by drug.

random sample (n = 400) of patients divided equally between patients who had an AMI (n = 200) and patients who did not have an AMI (n = 200). Prevalence of tobacco use in the AMI group was not meaningfully different from patients without AMI (46.5% vs 41.5%, respectively). Family history of AMI was reported by 22.5% of AMI patients and 13.5% of patients without AMI (data not shown). Logistic regression analysis of the random sample revealed that smoking and family history differences were not associated with the risk for AMI in the sample of 400 study patients. Study drug effects on the risk for AMI were consistent with the study cohort sample analysis. The high prevalence of tobacco use and family history of coronary artery disease indicate that the study cohort sample is biased toward high-risk patients in the VA population.

A *post hoc* logistic regression evaluated the interaction of prior history of AMI and etodolac, or, a prior history of AMI and the COX-2 group (rofecoxib and celecoxib). In the group with a history of AMI, etodolac was not associated with another AMI (OR = 0.5, 95% CI 0.12-2.1), but the COX-2 group had a 4.26-fold increased risk for another AMI (95% CI 1.17-15.6; Figure 5). In contrast, patients without a previous history of AMI had no significant increase in the risk of a subsequent AMI for any of the NSAIDs.

Discussion

A number of studies have reported on the cardiovascular risk associated with COX-2 selective inhibitors and traditional NSAIDs.[3,7,8,10,13-15,17,20] These studies have reached different conclusions about the cardiovascular effects of COX-2 NSAIDs. This is partly related to differences in the level of COX-2 selective inhibition among COX-2 and traditional NSAIDs. Etodolac falls in the category of "NSAIDs with some COX-2 activity." We have previously demonstrated the relatively safe GI profile of etodolac in veterans, a group at high risk for GI events. This article suggests that the cardiovascular risk of etodolac is similar to that of naproxen and that a standard logistic regression, which isolates the individual effects of all variables, demonstrates a consistently higher risk for the COX-2s (rofecoxib and celecoxib). However, a post hoc analysis suggests that the elevated AMI risk

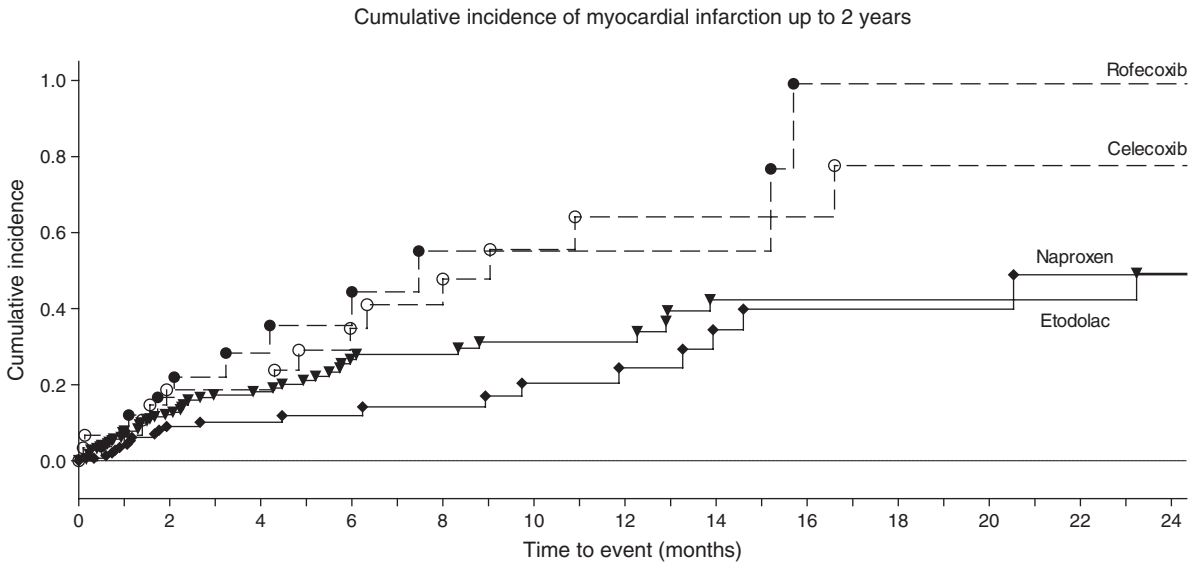


Figure 3. Cumulative incidence of myocardial infarction up to 2 years by study drug.

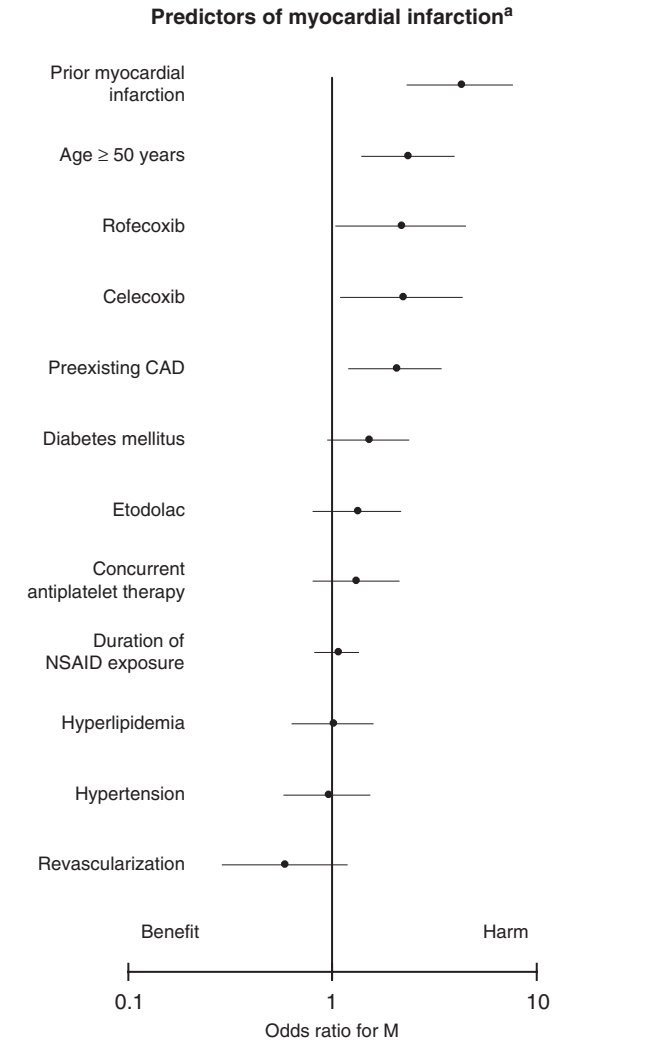
from the COX-2s is the result of heterogeneity; that is, patients without a prior AMI are mixed with patients that had a prior AMI. The use of COX-2 should be avoided in patients with a prior history of AMI. In contrast, patients without a history of AMI may not be at increased risk for AMI from concomitant administration of COX-2 selective NSAIDs. These data are similar to recently published findings by Solomon and colleagues where they contrast low-risk patients to high risk patients.[22]

Several studies' results suggest that naproxen may have the lowest risk of AMI among traditional NSAIDs.[3-7,11-13] A meta-analysis in *BMJ*[11] showed that "high dose ibuprofen (800 mg three times daily) and high dose diclofenac (75 mg twice daily) were each associated with an increased risk of vascular events, but that the risks of high dose naproxen (500 mg twice daily) were substantially smaller." Similarly, a meta-analysis in *JAMA*[12] also showed a summary relative risk for naproxen to be 0.99 (0.89-1.09;16 studies). Naproxen also had a low rate of AMIs in the present study. However, naproxen is associated with a higher risk of GI bleeding or perforations compared to COX-2 selective NSAIDs. The 2 major adverse effects of NSAIDs and COX-2 inhibitors (GI and cardiotoxicity) are minimized with etodolac. Therefore, etodolac may be preferred for patients at increased risk for NSAID-related GI and cardiovascular complications. In patients with no prior history of AMI, celecoxib may be an acceptable alternative.

Competing theories explain the GI and cardiovascular risk associated with NSAID use. One leading theory is driven by the degree of COX-2 selectivity. An increased degree of COX-2 selectivity is associated with GI safety, but it is also associated with increased risk of AMI.[23] It is interesting that etodolac is less likely to cause GI ulceration[16-18] and that it is not associated with AMI, based on a prior,[20] and the present investigation. Pharmacokinetic differences among COX-2 agents (eg, half-life) may explain etodolac's favorable cardiovascular profile. Etodolac has a relatively short half-life (6 hours) compared to celecoxib (11 hours) and rofecoxib (17 hours).

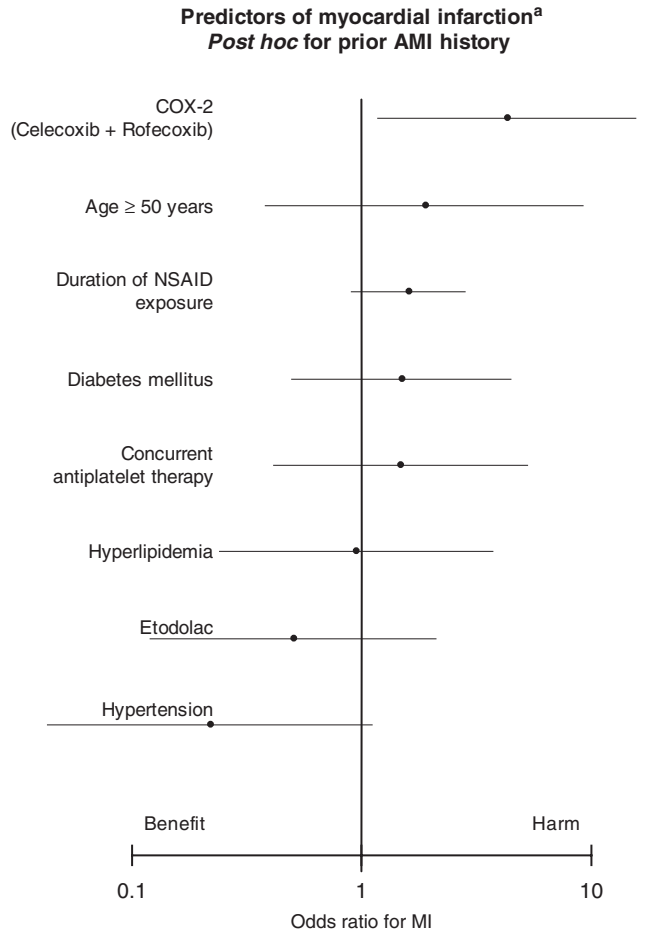
In addition to drug effects, a previous diagnosis of coronary artery disease, age $\geq$ 50 years, and a history of AMI were associated with an increased risk for AMI in the current study. A history of AMI increased the likelihood of another AMI 4-fold compared to patients with no medical history of AMI, consistent with a prior investigation which reported a 5-fold increased risk for AMI in patients with prior MI histories.[24] Hypertension (P = not significant [NS]), diabetes (P = .09), and hyperlipidemia (P = NS) were not statistically significantly associated with an increased risk for AMI, suggesting history of an AMI is a strong surrogate for these 3 well-known risk factors. Revascularization procedures trended toward a protective effect OR = 0.58 95% CI (0.29-1.18) against AMIs, regardless of NSAID type.

Similar to other studies, the present study found no protective effect for AMI with antiplatelet



[a]odds ratio (95%): MI 4.21 (2.32-7.66); age ≥ 50 2.32 (1.38-3.92); rofecoxib 2.16 (1.04-4.46); celecoxib 2.18 (1.09-4.35); CAD 2.03 (1.21-3.42); diabetes 1.49 (0.95-2.35); etodolac 1.32 (0.81-2.16); antiplatelet therapy 1.3 (0.80-2.13); NSAID exposure 1.05 (0.82-1.35); hyperlipidemia 0.99 (0.63-1.57); hypertension 0.94 (0.58-1.51); revascularization 0.58 (0.29-1.18).

Figure 4. Predictors of myocardial infarction. CAD indicates coronary artery disease; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug.



[a]odds ratio (95% CI): COX-2 (celecoxib + rofecixib) 4.26 (1.17-15.6); age ≥ 50 1.88 (0.38-9.26); NSAID exposure 1.59 (0.90-2.82); diabetes 1.49 (0.50-4.49); antiplatelet therapy 1.47 (0.41-5.27); hyperlipidemia 0.94 (0.24-3.74); etodolac 0.50 (0.12-2.10); hypertension 0.22 (0.04-1.11).

Figure 5. Predictors of myocardial infarction in patients with a previous MI. COX-2 indicates cyclooxygenase-2; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug.

therapy, even among COX-2 patients.[14,15] Antiplatelet therapy is possibly a surrogate for high cardiovascular risk patients. Alternatively, the thrombogenic cardiovascular effect of COX-2 NSAIDs may be more potent than concurrent antiplatelet therapy.

The present investigation has several limitations. First, some patients in the study cohort may have been treated for an AMI outside of the VA system. In a study of nearly 40 000 patients, however, the effect of missed events should be evenly (randomly) distributed among treatment groups. Second, inaccurate coding of cardiovascular risk factors in medical records may have masked the contribution of known risk factors. Also, smoking and family history of cardiovascular disease were only assessed indirectly in a subsample of the study cohort.

In clinical practice, most patients with musculoskeletal symptoms will have inadequate relief from acetaminophen. Additionally, acetaminophen in higher doses (and in patients with hepatic disease) has the potential to cause hepatotoxicity. Thus, we cannot abstain from the use of NSAIDs. The present analysis suggests that etodolac may provide a very favorable risk:benefit profile with regard to both GI events (as shown in our previous study in the same cohort) and a relatively favorable cardiovascular risk profile (as shown in this article). Patients without a prior history of AMI may use celecoxib as an alternative.

Conclusion

The risk of AMI was not increased among adult male VA patients who took etodolac compared to those taking naproxen. In contrast, the risk of AMI in male VA patients who took rofecoxib and celecoxib was increased 2-fold. A post hoc analysis suggests that COX-2 selective NSAIDs only pose a significant risk for AMI in patients who have had a prior AMI.

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