

Myocardial Infarction and Its Association with the Use of Nonselective NSAIDs: A Nested Case-Control and Time-to-Event Analysis

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Abstract

Objective: In April 2005, the US Food and Drug Administration issued a public health advisory warning to health care clinicians about the cardiovascular (CV) safety of nonsteroidal anti-inflammatory drugs (NSAIDs). Although the warning about cyclooxygenase-2 selective NSAIDs was anticipated, little data exists about the CV safety of nonselective NSAIDs. We analyzed data from a group of NSAID users to determine if specific nonselective agents were associated with an increased risk of myocardial infarctions (MIs) and sudden cardiac death (SCD).

Design: A nested case-control design was used to study NSAID users ages 18 to 84 years. Cases were defined by a hospital admission for MI or an out-of-hospital SCD. Study control subjects were matched for age, sex, current Kaiser Permanente membership, and geographic location (Northern or Southern California). Odds ratios (OR) were estimated using conditional logistic regression.

Results: Our base population included 1,394,764 NSAID users. From this population we identified 8143 cases and 31,496 matched study control subjects. The median time to event was <100 days for all NSAIDs. Two nonselective NSAIDs were associated with increased odds of adverse CV outcomes: indomethacin (OR, 1.27; 95% confidence interval, 1.04–1.56) and naproxen (OR, 1.14; 95% confidence interval, 1.00–1.30).

Conclusion: Our results suggest that some nonselective NSAIDs are associated with an increased risk of MI and SCD. We found the increased risk to be small compared with the risk associated with rofecoxib. Cardiovascular events occurred early in therapy. Caution is warranted with some nonselective NSAIDs, especially those for which other studies have found evidence of risk.

Introduction

Evidence from both epidemiologic and clinical trials confirm that the selective cyclooxygenase-2 (COX-2) inhibitors are associated with an increased risk of adverse cardiovascular (CV) events.¹⁻⁹ However, little is known about the CV risk associated with nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). Despite a lack of evidence, the US Food and Drug Administration (FDA) issued a warning in 2005 that the nonselective NSAIDs may be associated with an increased risk of serious CV events.¹⁰

Interference with the cyclooxygenase enzyme is thought to be the primary mechanism by which NSAIDs exert their pharmacologic action. NSAIDs, as a class, have a broad range of CV effects that may play a role in causing myocardial infarction (MI) and sudden cardiac death (SCD).^{11,12} Fluid retention, elevations in blood pressure, and interference with antihypertensive medications are well-described adverse effects of these drugs.¹³ NSAID effects on the coronary vasculature are mediated by their relative inhibition of the cyclooxygenase enzymes (COX-1 and COX-2). These two enzymes have opposing effects in the coronary vasculature.¹⁴⁻¹⁸ COX-1 exists within the platelets and is responsible for

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production of thromboxane A₂, which induces vasoconstriction and platelet aggregation. The COX-2 enzyme predominates in the endothelial cell of the arterial walls and is responsible for generation of prostacyclin, which inhibits platelet aggregation and causes vasodilation.

There is wide variation within the NSAIDs class of drugs with respect to selectivity for COX-1 and COX-2 isoenzymes.^{19–21} Rofecoxib and celecoxib have a high selectivity for the COX-2 isoenzyme, whereas as drugs such as flurbiprofen and ketorolac have a high affinity for the COX-1 isoenzyme. Because selective COX-2 inhibitors do not interfere with the COX-1 enzyme at therapeutic doses, it is postulated that the imbalance resulting from the preferential blockade results in vasoconstriction and platelet aggregation, leading to stroke and MI. Nonselective NSAIDs, with balanced effects on COX-1 and COX-2, would not be expected to carry an excess risk for MI.

We studied a group of NSAID users to investigate whether there is an association between current usage and CV events. We wanted to answer two specific questions: First, are any nonselective NSAIDs associated with a higher rate of CV events? Second, how long are patients exposed to NSAID treatment before CV events occur? Data on selective COX-2 inhibitors have been previously published.³

Methods

Kaiser Permanente (KP) is a nonprofit group-model health care organization offering health maintenance plans and providing integrated health care services to more than six million members in California. The KP membership is racially diverse and similar to the US population with respect to age, education, and household income. Electronic files are maintained on member eligibility, physician office visits, hospitalizations, Emergency Department visits, laboratory results, and outpatient drug dispensing. Mortality data are captured either through hospitalization records or by linking membership information with death certificate data supplied by the California Department of Health, Center for Health Statistics.

For this study, we identified a cohort of KP patients, ages 18 to 84 years, who filled at least one prescription for an NSAID (selective COX-2 inhibitor or nonselective NSAID) between January 1, 1999, and December 31, 2001. We used this cohort of patients to conduct a nested case-control study (cases and study control subjects identified within a cohort of NSAID users).²² Twelve months of KP membership prior to a patients' first NSAID prescription was required for study eligibility. To minimize bias, patients with severe and life-threatening diseases were excluded from the cohort, including those in whom

cancer, renal failure, liver failure, severe respiratory disease, or HIV/AIDS had been diagnosed and those who had undergone organ transplantation. Cohort members were monitored from their date of entry until the end of the study period, disenrollment, or the occurrence of a study endpoint, whichever came first.

Cases were defined as having an admission to the hospital for an MI or the occurrence of SCD outside the hospital setting. An MI endpoint (case event) required that the patient be admitted to the hospital with an ICD-9 (International Statistical Classification of Diseases and Related Health Problems, 9th edition) code 410 (acute MI) or an ICD-9 code 411.1 (intermediate coronary syndrome) as long as there was laboratory documentation of myocardial damage (elevated creatine kinase–MB fraction >7 ng/mL and creatine kinase–MB fraction >3% or elevated troponin I ≥4 ng/mL). Deaths occurring outside the hospital setting were classified as SCD if the underlying cause of death was listed on the death certificate as hypertensive heart disease, ischemic heart disease, conduction disorders, arrhythmias, heart failure, atherosclerotic heart disease, sudden death, or death from an unknown cause.^{2,23}

Cases were matched to a maximum of four study control subjects, randomly selected from the NSAID user cohort, who were active members on the date of the case event

Exposure	n	Percentage women	Age (years) ^a
Cases			
Current	1773	42	67.5
Celecoxib	127	54	70.2
Diclofenac	21	33	65.4
Etodolac	40	45	68.8
Ibuprofen	674	39	66.3
Indomethacin	167	31	67.2
Nabumetone	73	45	68.9
Naproxen	367	43	66.9
Piroxicam	69	49	67.9
Rofecoxib	68	57	71.0
Sulindac	143	44	71.1
Nonsteroidal anti-inflammatory drugs	24	29	64.9
Recent	1712	38	66.7
Remote	4658	37	66.6
Total	8143	38	66.8
Study control subjects			
Current	6557	42	68.6
Recent	6219	39	66.9
Remote	18,720	37	66.4
Total	31,496	38	67.0

^aMean age on the date of the index event.

(index date). Study control subjects were selected on the basis of age, sex, and KP region (Northern or Southern California). The nested case-control design allowed for individuals selected as a control subject for one case to become a case or a control subject for another case at a later date, provided that they remained in the study cohort.²²

NSAID exposure status for cases and control subjects was based on the index date. Exposure classification was determined by the days of medication supply captured from the pharmacy dispensing record. Patients were classified as current users if the duration of their most recent NSAID prescription overlapped the index date. Remote users were those whose medication supply ended more than 60 days before the index date. These patients were used as the reference exposure group because it was unlikely that they were continuing to take the prescription NSAID at the time of the index date. Recent users were those individuals whose NSAID prescriptions ended between 1 and 60 days before the index date.

Beginning 365 days before the index date, we collected CV risk factors for cases and control subjects. Prior hospitalizations were grouped into the following

categories on the basis of diagnosis-related group coding: major CV events (MI, cardiac arrest, and revascularization procedures), angina, congestive heart failure (CHF), other ischemic heart disease (atherosclerosis and ischemia), cardiac arrhythmias, other CV hospitalizations (major CV procedures, peripheral vascular disease, valve disease, cerebrovascular disease, and peripheral vascular procedures), and non-CV hospitalizations. We captured Emergency Department visits for CV and non-CV reasons, same-day hospitalizations for medical procedures, and outpatient diagnoses for tobacco use. Prescription use was recorded for thiazide diuretics, loop diuretics, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, calcium channel blockers, beta-blockers, digoxin, nitrates, antiarrhythmics, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (statins), fibrates, niacin, antiplatelet agents (ticlopidine, clopidogrel), anticoagulants (warfarin, low-molecular-weight heparin), insulin, and oral hypoglycemics.

Conditional logistic regression was used to estimate the odds ratios and 95% confidence intervals. Non-selective NSAIDs with 20 or more currently exposed

Table 2. Percentage prior hospitalizations: cases and study control subjects in the year prior to the index date

Exposure	n	Major cardiovascular event ^a	Angina	Congestive heart failure	Other ischemic heart disease ^b	Arrhythmia	Other cardiovascular event ^c	Hospitalization for noncardiovascular event	Emergency Department cardiovascular event	Emergency Department noncardiovascular event
Cases										
Current	1773	3.3	2.3	2.8	4.1	1.8	3.0	15.0	3.0	32.4
Celecoxib	127	3.1	2.4	3.1	3.1	3.1	1.6	15.0	2.4	45.7
Diclofenac	21	—	—	9.5	4.8	—	4.8	19.0	4.8	38.1
Etodolac	40	2.5	—	—	5.0	—	—	15.0	2.5	35.0
Ibuprofen	674	2.7	2.2	2.7	4.5	1.3	3.3	15.7	3.0	30.3
Indomethacin	167	7.8	1.8	4.8	4.2	3.0	6.6	17.4	7.2	32.3
Nabumetone	73	2.7	2.7	2.7	4.1	4.1	4.1	16.4	8.2	39.7
Naproxen	367	3.0	2.7	1.6	3.0	1.6	1.1	12.5	0.8	30.5
Piroxicam	69	7.2	1.4	1.4	2.9	1.4	1.4	14.5	2.9	29.0
Rofecoxib	68	2.9	1.5	5.9	7.4	2.9	5.9	19.1	2.8	42.6
Sulindac	143	1.4	3.5	2.8	4.2	0.7	3.5	11.2	2.1	27.3
Nonsteroidal anti-inflammatory drugs	24	—	—	4.2	4.2	4.2	—	20.8	4.2	33.3
Recent	1712	3.3	3.2	3.4	2.8	2.0	2.8	17.2	4.4	36.7
Remote	4658	1.9	2.9	3.8	5.0	2.6	4.4	17.3	4.5	33.8
Total	8143	2.5	2.8	3.5	4.3	2.3	3.7	16.8	4.1	34.1
Study controls subjects										
Current	6557	0.5	0.8	0.4	0.7	0.5	0.6	8.0	0.7	19.6
Recent	6219	0.5	1.0	0.4	0.4	0.6	1.0	7.5	0.9	23.9
Remote	18720	0.4	0.8	0.3	0.6	0.7	1.1	8.1	0.9	22.2
Total	31496	0.4	0.9	0.3	0.6	0.6	0.9	8.0	0.9	22.0

^aMyocardial infarction, cardiac arrest, and revascularization procedures.

^bAtherosclerosis and ischemia (except myocardial infarction).

^cMajor cardiovascular procedures, peripheral vascular disease, valve disease, and vascular procedures.

case events were analyzed individually. The remaining NSAIDs were placed into a single group.

In analyzing time to event, we selected cases and control subjects classified as currently exposed to NSAIDs. For these patients, we determined continuous NSAID exposure for the preceding 365 days. Exposure was defined as continuous if gaps between prescription refill dates did not exceed 50% of the days' supply. For example, if a patient received an NSAID prescription for a 30-day (one-month) supply, exposure was classified as continuous if the next prescription was filled within 45 days (1.5 months) of the previous dispense date. Median time to event and interquartile ranges are reported using box-plots.

Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC). The institutional review boards of both the Northern and Southern Divisions of KP California approved this study.

Results

During the study period, 8143 cases were identified and matched to 31,496 control subjects from

our population of 1,394,764 NSAID users. The cases included 6635 patients admitted to the hospital for MI and 1508 with SCD. Eleven percent (n = 702) of patients hospitalized for MI died during their hospital stay. Demographic information for cases and control subjects are shown in Table 1. In all groups except for the group taking selective COX-2 inhibitors (celecoxib, 54% women; rofecoxib, 57% women), the case-patients were predominantly men.

The distribution of CV risk factors by specific NSAID are presented in Table 2 (hospitalizations and emergency care) and Table 3 (prescription use). Although percentages varied between the individual NSAIDs, cases had higher overall rates for CV risk factors compared with study control subjects. In most instances, the prevalence of risk factors in cases was several orders of magnitude higher than in control subjects. This was not unexpected, given the study design and the criteria used to define cases.

We identified eight nonselective NSAIDs and two COX-2 inhibitors with sufficient CV events during the three-year study period to include in the multivariate regression

Table 3. Percentage prior medications: cases and study control subjects in the year before the index date

Exposure	n	Anti-platelets ^a	Anti-coagulants ^b	Anti-arrhythmics ^c	Anti-diabetics ^d	Anti-hypertensives ^e	Loop diuretics ^f	Digoxin	Nitrates	Anti-hyperlipidemics ^g
Cases										
Current	1773	4.3	4.7	2.5	30.1	73.0	21.5	9.5	31.4	33.4
Celecoxib	127	5.5	10.2	3.9	25.2	78.0	24.4	15.0	33.9	36.2
Diclofenac	21	-	4.8	4.8	28.6	90.5	19.0	4.8	47.6	47.6
Etodolac	40	5.0	7.5	2.5	17.5	70.0	7.5	5.0	32.5	42.5
Ibuprofen	674	3.9	4.0	2.4	32.8	72.0	20.6	7.7	31.0	31.9
Indomethacin	167	12.0	6.6	1.8	25.7	79.6	32.9	16.2	38.3	38.3
Nabumetone	73	2.7	1.4	1.4	35.6	75.3	28.8	11.0	28.8	38.4
Naproxen	367	3.0	2.7	1.9	29.7	66.8	17.2	8.4	25.3	30.0
Piroxicam	69	1.4	4.3	5.8	24.6	71.0	24.6	7.2	26.1	27.5
Rofecoxib	68	5.9	10.3	5.9	26.5	80.9	25.0	5.9	35.3	45.6
Sulindac	143	1.4	3.5	2.1	32.2	76.9	19.6	9.8	37.1	30.1
Nonsteroidal anti-inflammatory drugs	24	4.2	12.5	—	37.5	70.8	16.7	20.8	33.3	37.5
Recent	1712	4.8	5.6	2.7	25.2	71.0	21.3	9.8	28.4	33.9
Remote	4658	5.9	6.7	2.7	26.4	70.0	20.8	10.2	28.8	34.9
Total	8143	5.3	6.1	2.7	27.0	70.9	21.0	9.9	29.3	34.4
Controls										
Current	6557	1.2	2.8	1.2	12.8	54.7	8.7	3.7	9.8	20.5
Recent	6219	1.3	2.6	0.8	11.3	50.6	6.5	3.3	8.9	19.6
Remote	18,720	1.5	3.6	1.1	11.7	46.5	6.6	3.6	7.8	18.7
Total	31,496	1.4	3.2	1.1	11.9	49.0	7.0	3.6	8.4	19.3

^aTiclopidine and clopidogrel.

^bHeparin, low-molecular-weight heparin, and warfarin.

^cMexiletine, procainamide, propafenone, flecainide, esmolol, ibutilide, dofetilide, quinidine, and adenosine.

^dInsulin, sulfonylureas, metformin, and thiazolidinediones.

^eAngiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, calcium channel blockers, β -blockers.

^fFurosemide, bumetanide, ethacrynic acid.

^g3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (statins), fibrates, niacin antiplatelets, anticoagulants, antiarrhythmics, antidiabetics, antihypertensives, loop diuretics, and antihyperlipidemics.

analysis. Ten other nonselective NSAIDs have low usage within KP California and were grouped together. This NSAID group had a combined 24 case events and included the following drugs (number of cases): diflunisal (2), fenoprofen (0), flurbiprofen (2), ketoprofen (1), ketorolac (4), meclofenamate (10), mefenamic acid (0), meloxicam (0), oxaprozin (0), and tolmetin (5).

Table 4 lists the adjusted odds ratios (OR) and the 95% confidence intervals (CIs) for the NSAIDs included in the analysis. The point estimates were close to 1.0 for all of the nonselective NSAIDs. Two nonselective NSAIDs (indomethacin: OR, 1.27, and 95% CI, 1.04–1.56; naproxen: OR, 1.14, and 95% CI, 1.00–1.30) were associated with a small but statistically significant increase in adverse CV outcomes.

The median time to event was <100 days for all of the NSAIDs we studied. Figure 1 provides a visual representation of the median time, the interquartile range, and the upper and lower extremes for a few selected drugs. These data suggest that the vast majority of CV events occurred within the first eight months of continuous exposure.

Discussion

We studied a group of NSAID users to determine if specific nonselective NSAIDs were associated with a higher risk of adverse CV outcomes. Our results suggest that indomethacin and naproxen may be associated with

a small but significant increased risk of CV endpoints compared with remote use of NSAIDs. The additional risk seen with indomethacin and naproxen (27% and 14%, respectively) is much lower than the threefold increase seen with high-dose rofecoxib. In this study, celecoxib was not associated with an increased CV risk. This is consistent with results from previous epidemiologic studies^{4-6,24-28} but is not consistent with some clinical trial results.^{7,9} One possible explanation for this difference is the fact that celecoxib users in our population were generally receiving low doses of the drug (68% of the patients were taking ≤ 200 mg/d of celecoxib).

Our results also suggest that MIs and SCDs occur earlier in the course of therapy than has been previously reported.⁵ The median time to event was <100 days for all of the NSAIDs we studied.

In April 2005, the FDA issued a report stating that nonselective NSAIDs may be associated with adverse CV events.¹⁰ The agency developed a patient medication guide, to be provided each time a prescription NSAID is dispensed, informing patients that “NSAID medicines may increase the chance of a heart attack or stroke that can lead to death.”²⁹ The agency also required labeling changes for over-the-counter NSAIDs sold without a prescription.³⁰ These actions were mandated even though the FDA recognized that there were little data and no long-term placebo-controlled clinical trials to adequately assess CV risk. Patients and physicians were left with questions and very little data about nonselective NSAIDs’ CV risk and how best to manage pain and inflammation with these drugs.

Our results provide information on the comparative safety of several nonselective NSAIDs. We elected to test individual drugs, versus grouping all of the nonselective NSAIDs together, because each of these drugs has a different pharmacologic profile with respect to cyclooxygenase inhibition, nitric oxide metabolism, and the risk for inducing hypertension and fluid retention.

Epidemiologic studies published since 2000, looking at MI risk and NSAID exposure,^{2,4,23-28,31-35} have focused on selective COX-2 inhibitors and report results on only one or two nonselective agents. Some of these studies included small numbers of patients,^{26,31} had restricted populations based on age or socioeconomic status,^{2,23,24,27,28,33,35} or used hospital admissions for MI as their only endpoint,^{4,24,27,28,32-35} limiting the ability to generalize the results to other groups.

Our study has several other advantages over previous epidemiologic studies. First, KP membership is relatively diverse with respect to age and ethnicity. Our primary endpoint included SCD as well as hospitaliza-

Table 4. Risk of acute myocardial infarction with the use of various NSAIDs

NSAID exposure group	Cases	Study control subjects	Adjusted odds ratio ^a	95% confidence interval	p
Remote use	4658	18720	1.00	Comparator	
Current use (cases)	1773	6557			
Celecoxib	127	496	0.87	(0.69–1.08)	0.21
Diclofenac	21	54	1.72	(0.98–3.01)	0.06
Etodolac	40	129	1.34	(0.91–1.98)	0.14
Ibuprofen	674	2588	1.08	(0.97–1.20)	0.15
Indomethacin	167	471	1.27	(1.04–1.56)	0.02
Nabumetone	73	248	1.09	(0.81–1.47)	0.56
Naproxen	367	1416	1.14	(1.00–1.30)	0.05
Piroxicam	69	335	0.87	(0.66–1.15)	0.33
Rofecoxib ≤ 25 mg/d	58	188	1.23	(0.89–1.74)	0.21
Rofecoxib > 25 mg/d	10	8	3.01	(1.10–8.31)	0.03
Sulindac	143	531	1.18	(0.95–1.45)	0.13
NSAIDs ^b	24	92	1.11	(0.67–1.81)	0.69
Recent use	1711	6219	1.15	(1.07–1.23)	<0.01

^aAdjusted for age, sex, Health Plan region, major cardiovascular events, angina, heart failure, other ischemic heart disease, cardiac arrhythmias, noncardiac hospitalization, other cardiovascular hospitalizations, antiplatelets, anticoagulants, antiarrhythmics, antidiabetics, antihypertensives, loop diuretics, and antihyperlipidemics.

^bNSAIDs: diflunisal, flurbiprofen, ketoprofen, ketorolac, meloxicam, oxaprozin, and tolmetin.

tions for MI, which is important, considering that SCD accounted for 18.5% of the CV events. Furthermore, we restricted the analysis to only those nonselective NSAIDs with a sufficient number of case events, which helped reduce error around the point estimates.

Several limitations exist with our study. We are not able to capture all of the known CV risk factors from our electronic databases (ie, smoking history, family history of MI, and use of low-dose aspirin). Our systems also do not capture use of over-the-counter NSAIDs. To assess these issues, a telephone survey of study control patients was undertaken for the previous study, which found no difference in aspirin use, over-the-counter NSAID use, smoking history, or a family history of MI in first-degree relatives between different groups of NSAID users.³ These results are similar to data cited by Solomon et al,⁴ who noted that a Medicare Current Beneficiary Survey found no difference in body mass index, tobacco use, aspirin use, annual household income, and educational attainment between users of nonselective NSAIDs and users of selective COX-2 inhibitors. Although these data were not captured electronically, it does not appear to occur preferentially within any one group of NSAID users and therefore is unlikely to bias the results.

A statistical limitation exists with our results in that the excess risk associated with naproxen and indomethacin is small; therefore, unmeasured residual confounding may affect point estimates and the level of significance. If all of the CV events or covariates are not captured, residual confounding can have a significant effect on results.

Our results suggest that the risk of adverse CV events associated with nonselective NSAIDs is small relative to a drug such as rofecoxib. This information is important to patients and physicians. It is unlikely that long-term controlled safety studies will be conducted with nonselective NSAIDs, because they are available as generic products. Therefore, we need to rely on well-conducted epidemiologic studies as a means of identifying risk.

One exception to this is a recently initiated study, the PRECISION trial,³⁶ funded by Pfizer Pharmaceuticals, the manufacturer of Celebrex, which is investigating CV risk and the general safety of celecoxib, ibuprofen, and naproxen. The results from PRECISION will not be available for several years, and the study includes only three drugs from the NSAID class.

More work needs to be done to understand the CV risk associated with the NSAID class in general and nonselective NSAIDs in particular. This should be a priority, given the large number of NSAID prescriptions dispensed annually in the United States, which is estimated to be in excess of 100 million.³⁷ Until

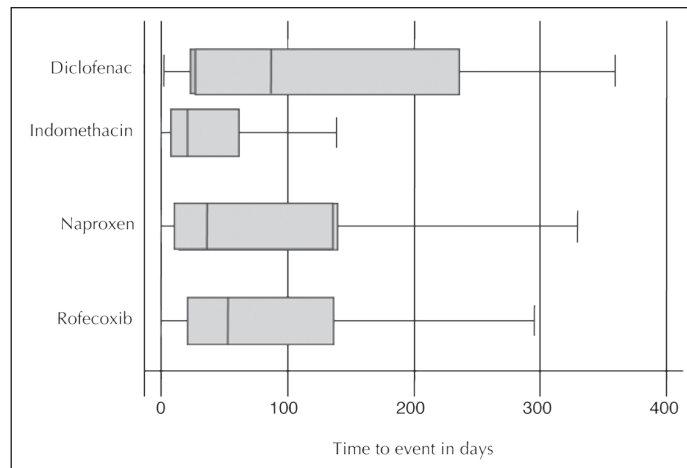


Figure 1. Time to event analysis—box and whisker plot.

more evidence is available, it seems prudent to avoid nonselective NSAIDs found to have an association with adverse CV events. The risk for these adverse effects is likely greatest in patients with a prior history of—or at high risk for—CV disease. ♦

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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