

An Evidence-Based Review of the Cardiovascular Risks of Nonsteroidal Anti-Inflammatory Drugs

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Nonsteroidal anti-inflammatory drugs (NSAIDs), both nonselective and cyclooxygenase-2-specific inhibitors, are commonly used medications for the relief of acute and chronic pain associated with a wide range of medical conditions. Because of the extensive use of these agents, adverse events that occur infrequently may still affect the overall risk/benefit ratio of this class of medications. Serious adverse cardiovascular (CV) events have been reported with NSAID use, but unfortunately, definitive evidence regarding the precise CV risk associated with these drugs, as a class and individually, is lacking. Therefore, it is an issue of public health importance that physicians be guided by careful assessment of the existing evidence to make reasonable choices in prescribing these medications. The investigators review the key clinical trials, meta-analyses of clinical trials, and epidemiologic studies on the subject of the CV safety of NSAIDs and identify key variables that define the CV risk of the NSAIDs. In conclusion, it is important that cardiologists, who are not among those physicians frequently prescribing NSAIDs, have a particular responsibility to have up-to-date, thoughtfully synthesized information about the CV risks of these drugs, especially when administered to patients receiving low-dose aspirin for cardioprotection. © 2009 Published by Elsevier Inc. (Am J Cardiol 2009;103:1227–1237)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used medications that reduce inflammation and provide relief of pain for a wide range of medical conditions. However, the risk for serious adverse cardiovascular (CV) effects associated with the use of nonselective and cyclooxygenase (COX)-2-specific NSAIDs is an area of concern. These COX-2-specific inhibitors were developed for their anti-inflammatory properties without the adverse gastrointestinal effects seen with COX-1 inhibition.^{1–3}

Although it is possible to determine the COX selectivity characteristics of individual NSAIDs in vitro (Figure 1),⁴ it is more difficult to determine the CV risk associated with the different chemical subgroups of NSAIDs and of the individual agents within the NSAID class. Recent studies have shed light on the mechanisms by which certain NSAIDs could, in theory, cause myocardial infarction (MI) or thrombotic stroke.

The role of cardiologists is to provide expert consultation and advice to other physicians concerning the balancing of CV risks with the therapeutic benefits of commonly used medications. Cardiologists should advocate the use of low-dose aspirin in patients with CV risk⁵ and advise the most appropriate analgesics to use in patients maintained on low-dose aspirin. A number of guidelines are currently available to assist physicians in the choice of analgesic for the treatment of patients with osteoarthritis, including the recently

published Osteoarthritis Research Society International guidelines,⁶ as well as recommendations from the First International Working Party on GI and CV Effects of NSAIDs and Anti-Platelet Agents.⁷ Although the therapeutic implications of NSAIDs on gastrointestinal safety are acknowledged, they are not a focal point of this review. The purpose of this review is to provide cardiologists with a comprehensive guide to the existing evidence base and expert opinion on the subject of the CV risk of NSAIDs.

Methods

We review the key clinical trials, meta-analyses of clinical trials, and epidemiologic studies on the subject of the CV safety of NSAIDs (nonselective and COX-2-specific inhibitors). Research evidence published from 2000 to June 2008 and pertaining to the topic was systematically reviewed. Key search terms included: “NSAIDs,” “COX-2 inhibitors,” “CV risk,” “studies,” “clinical trials,” and “meta-analyses.” In addition to randomized controlled trials (RCTs), evidence from epidemiologic or observational studies, meta-analyses and systematic reviews, and studies on the effects of concomitant aspirin and NSAID use are also reviewed. A total of 8 RCTs, including active-controlled and placebo-controlled studies, plus 5 epidemiologic studies and 5 meta-analyses were used for the evaluation of the CV risk of nonselective NSAIDs. Some of these trials plus 7 additional studies were used to assess the CV risk of COX-2-specific NSAIDs.

Cardiovascular Risk Profile of Nonselective Nonsteroidal Anti-Inflammatory Drugs

The CV safety of nonselective NSAIDs has not been well studied in long-term controlled trials. This fact came to

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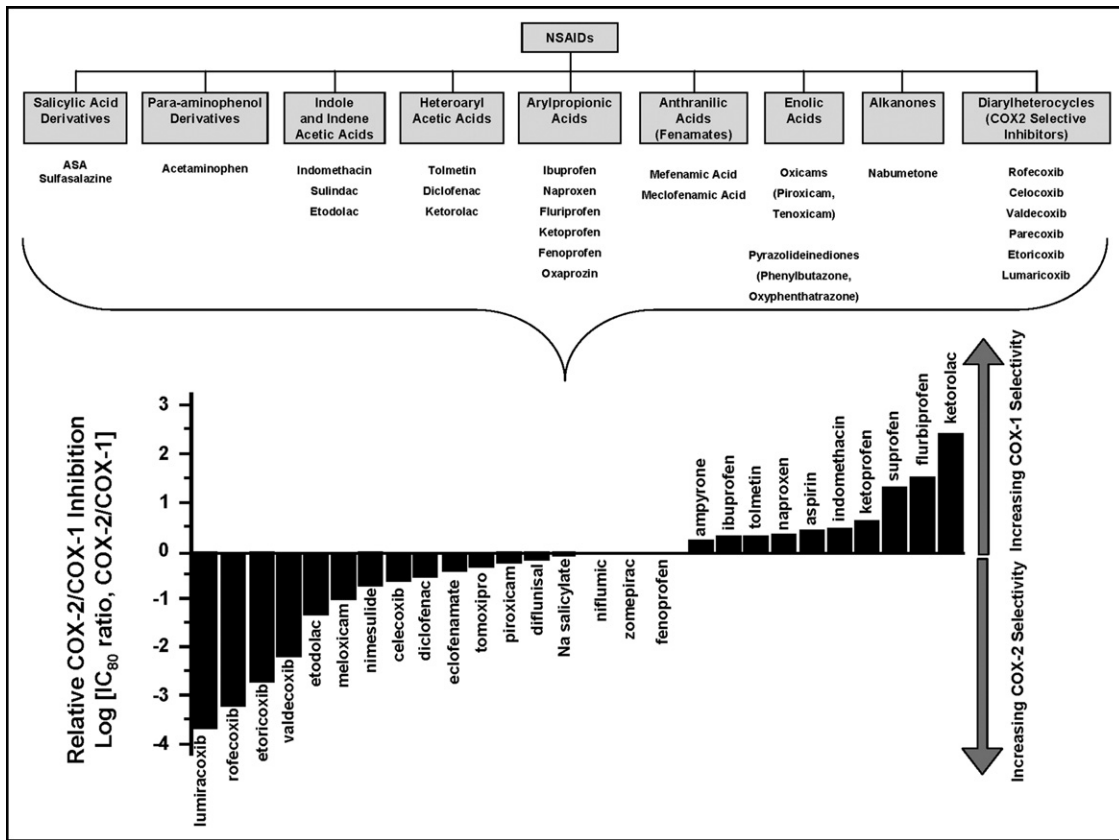


Figure 1. The relative COX-1 and COX-2 inhibition of NSAIDs. Reprinted with permission from *Circulation*.⁴ ASA = acetylsalicylic acid.

light only in the context of the potential CV risk of COX-2-specific agents; the Vioxx Gastrointestinal Outcomes Research (VIGOR) study was the first to seriously raise this concern.⁸ Nonselective NSAIDs have been used in clinical settings for longer than COX-2-specific agents, and much of the available clinical data on their CV risk are based on their use as comparator agents in RCTs for COX-2-specific NSAIDs (Table 1).⁸⁻¹⁵ The largest amounts of data exist on naproxen, ibuprofen, and diclofenac because they have been used as comparator agents in most of the trials for COX-2-specific NSAIDs. In fact, there are no large RCTs evaluating nonspecific NSAIDs for adverse CV events. The ongoing Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen (PRECISION) trial will provide much needed data in this area.

Active comparator trials: Several RCTs have yielded data on the CV effects of NSAIDs. Forest plots showing the rate ratio of CV risk for nonselective NSAIDs, including naproxen, are shown in Figure 2. The VIGOR trial⁸ was a long-term, controlled clinical trial comparing rofecoxib 50 mg/day with naproxen 500 mg twice daily in 8,076 patients with rheumatoid arthritis. An analysis of the data showed a fourfold lower risk for MI in naproxen-treated patients than in rofecoxib-treated patients (0.1% vs 0.4%; relative risk [RR] 0.2, 95% confidence interval [CI] 0.1 to 0.7).⁸

A subset analysis showed that patients at high CV risk (not taking low-dose aspirin, a study exclusion criterion, because of the gastrointestinal end points) accounted for

38% of all MIs. In the other 62% of patients, the difference in MIs between groups was not significant.

The investigators indicated that this difference might have occurred at least in part because high-dose naproxen inhibits platelet aggregation throughout the dosing interval. The investigators noted that these results are in contrast to data obtained from other studies comparing rofecoxib with diclofenac, ibuprofen, or nabumetone in 7,535 patients.⁸ No difference in rates of MI between the groups was observed, presumably because these nonselective NSAIDs do not produce a sustained, maximal inhibition of platelet aggregation.

The Celecoxib Long-Term Arthritis Safety Study (CLASS)¹³ compared the incidence of thromboembolic events in patients treated with celecoxib 400 mg twice daily versus ibuprofen 800 mg three times daily or diclofenac 75 mg twice daily; the CV data were analyzed and published separately.¹⁵ No difference in serious CV adverse events was evident between celecoxib and the 2 NSAIDs, regardless of prophylactic aspirin use. The data suggested no increased CV risk from celecoxib, arguing against a class effect of COX-2-specific inhibitors on the CV system.

The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) compared lumiracoxib 400 mg/day with naproxen 500 mg three times daily and ibuprofen 800 mg three times daily in patients with osteoarthritis.¹² Two separate substudies of identical design were performed, with primary analyses comparing the results of the combined lumiracoxib groups with those of the combined naproxen and ibuprofen groups. At 1-year follow-up, the

Table 1
Randomized controlled trials

Name	Investigators	Year	Purpose	Subjects	Agents	Duration	Cardiovascular Safety
VIGOR	Bombardier et al ⁸	2000	GI safety of rofecoxib	8,056 RA	Rofecoxib 50 mg/day vs naproxen 500 mg bid	9 mos	Naproxen fourfold decrease in MI
CLASS	Silverstein et al ¹³	2000	GI safety of celecoxib	4,573 OA or RA	Celecoxib 400 mg bid with nonselective NSAIDs (ibuprofen and diclofenac)	6 mos	No difference in serious adverse CV events between celecoxib and NSAIDs, regardless of aspirin use
	White et al ¹⁵	2002	Thromboembolic events with celecoxib	7,968	Celecoxib 400 mg bid with nonselective NSAIDs (ibuprofen and diclofenac)		No difference in serious adverse CV events between celecoxib and NSAIDs, regardless of aspirin use
TARGET	Farkouh et al ¹²	2004	CV risk with lumiracoxib in high-risk patients with OA	18,325 OA	Lumiracoxib with naproxen and ibuprofen	1 yr	Ibuprofen increased risk vs lumiracoxib, naproxen decreased risk vs lumiracoxib
MEDAL	Cannon et al ¹¹	2006	CV safety of etoricoxib	34,701	Etoricoxib 60 or 90 mg/day or diclofenac 75 mg bid	18 mos	No difference between the 2 drugs for any CV outcome
	Aisen et al ¹⁰	2003	Alzheimer disease progression with rofecoxib	351	Rofecoxib 25 mg/day vs naproxen 220 mg bid vs placebo	1 yr	8 adverse CV events with rofecoxib vs 4 adverse CV events with naproxen, including 3 MIs with rofecoxib and none with naproxen
ADAPT	ADAPT Research Group ⁹	2006	Alzheimer disease progression with celecoxib	2,528	Naproxen 220 mg bid vs celecoxib 200 mg bid	1–46 mos	Terminated early when a concurrent celecoxib clinical trial showed increased CV events with celecoxib
APC	Solomon et al ¹⁴	2005	Adenoma prevention	2,035	Celecoxib 200 or 400 mg bid vs placebo	2.8–3.1 yrs	Celecoxib 200 and 400 mg hazard risk for CV death 2.3 and 3.4, respectively

bid = twice daily; GI = gastrointestinal; OA = osteoarthritis; RA = rheumatoid arthritis.

incidence of the primary end point (MI, stroke, CV death) was low, with lumiracoxib (59 events [0.65%]) and the NSAIDs (50 events [0.55%]) (hazard ratio [HR] for the lumiracoxib group vs the NSAID group 1.14, 95% CI 0.78 to 1.66, $p = 0.5074$). The incidence of MI (clinical and silent) in the overall population in the individual substudies was 0.38% (18 events) with lumiracoxib, compared with 0.21% (10 events) with naproxen and 0.11% (5 events) with lumiracoxib compared with 0.16% (7 events) with ibuprofen. In the 2 substudies, rates of MI (the primary end point) did not differ between lumiracoxib and naproxen or ibuprofen, irrespective of low-dose aspirin use.

The Multinational Etoricoxib and Diclofenac Arthritis Long-Term (MEDAL) program analyzed pooled data from 3 trials (the MEDAL study, the Etoricoxib Versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness [EDGE] I trial, and the EDGE II trial) including a total of 34,700 patients.¹¹ Patients with arthritis were randomly assigned to receive etoricoxib 60 or 90 mg/day or diclofenac 75 mg twice daily; no placebo control group was used.

After an average treatment duration of 18 months, an analysis of the data indicated no difference between etoricoxib and diclofenac for any CV outcome, irrespective of aspirin use or dose: the number of thrombotic CV events was 1.24 versus 1.30 per 100 patient-years, respectively (HR 0.95, 95% CI 0.81 to 1.11).

Placebo-controlled trials: Treatment with rofecoxib 25 mg/day was compared with naproxen 220 mg twice daily for the prevention of Alzheimer disease in an RCT of 351 patients.¹⁰ No differences in serious CV events were reported. However, composite serious adverse CV events (MI, stroke, CV death) indicated that there were 8 adverse CV events with rofecoxib compared with 4 adverse CV events with naproxen, including 3 MIs with rofecoxib and none with naproxen.¹⁰

The Alzheimer Disease Anti-Inflammatory Prevention Trial (ADAPT)⁹ was designed to assess the use of naproxen compared with celecoxib for the primary prevention of Alzheimer dementia. However, during the course of the

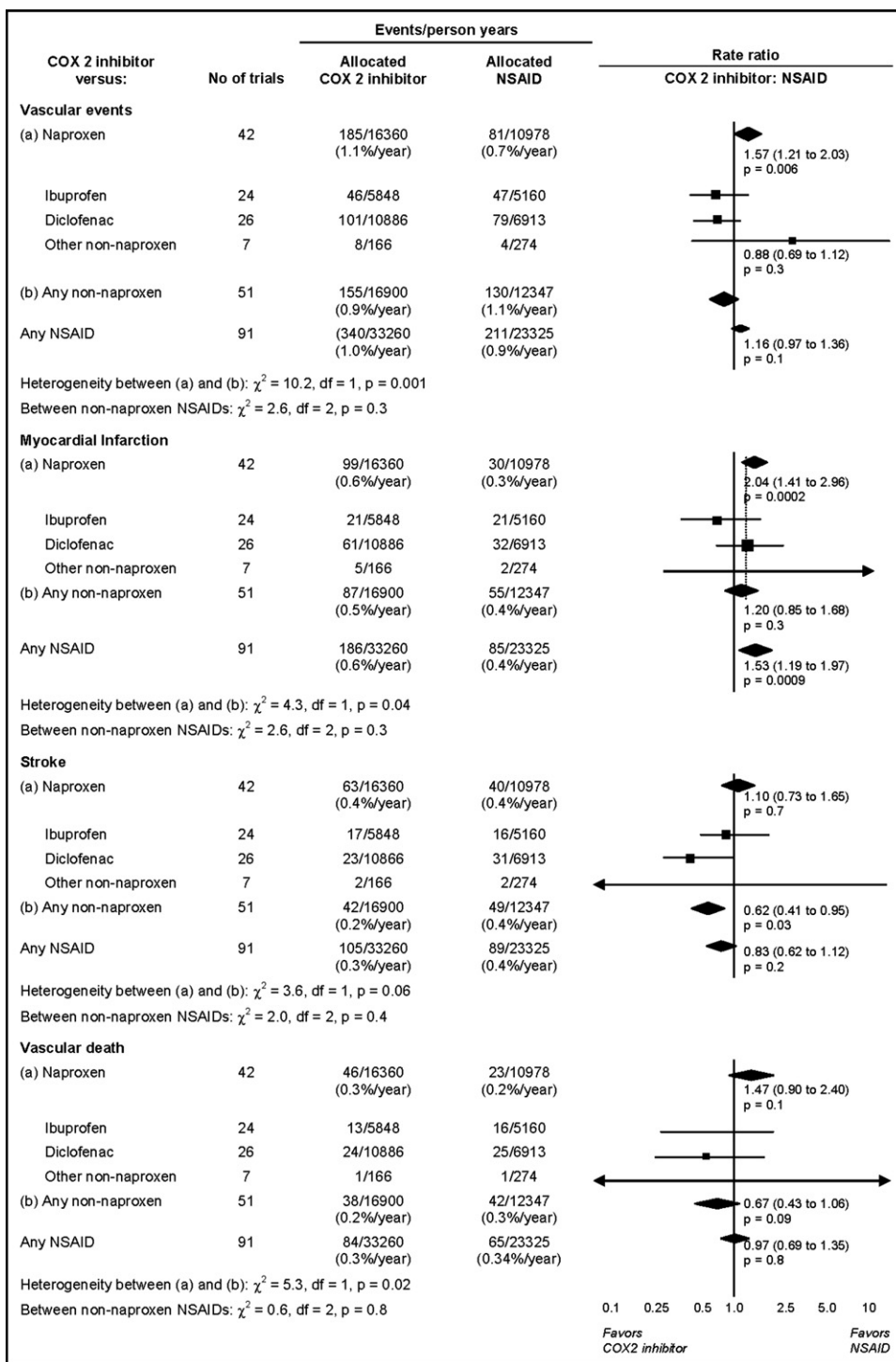


Figure 2. Rate ratio of cardiovascular risk for NSAIDs. Reprinted with permission from *BMJ*.²⁶

study, 2 colon polyp prevention trials, 1 with rofecoxib¹⁶ and 1 with celecoxib,¹⁴ were terminated prematurely because of findings of increased CV event rates. The announcement of the terminations led to safety concerns among officials at the National Institutes of Health. On the basis of these concerns, ADAPT was suspended by the National Institutes of Health.¹⁷ ADAPT randomized 2,528 participants to receive naproxen 220 mg twice daily, celecoxib 200 mg twice daily, or placebo and followed them for

23.5, 23.3, and 22.1 months, respectively.⁹ The number of safety events was small, indicating a smaller CV risk compared with that seen in the Adenoma Prevention With Celecoxib (APC) trial. The composite end point, risk for MI, stroke, or CV death over 3 years, was 3.26% for celecoxib, 4.54% for naproxen, and 3.74% for placebo (naproxen: HR 1.57, 95% CI 0.87 to 2.81, p = 0.13; celecoxib: HR 1.14, 95% CI 0.61 to 2.15, p = 0.68).^{18,19} However, the findings derived from ADAPT have been questioned, with early

Table 2
Epidemiologic studies

Investigators	Year	Subjects	Cardiovascular Safety
Graham et al ²¹	2005	39,639	Naproxen neutral; rofecoxib riskier than celecoxib Naproxen vs remote NSAID use: OR 1.14 Rofecoxib all doses vs celecoxib: OR 1.59
Helin-Salmivaara et al ²²	2006	33,308 first MIs	Nonselective NSAIDs vs COX-2 inhibitors both associated with elevated RR (1.34 and 1.31, respectively)
Garcia-Rodriguez and Gonzalez-Perez ²⁰	2005	4,975 MIs	All NSAIDs >1 yr: RR 1.21 Naproxen: RR 0.87 Diclofenac: RR 1.38
Hippisley-Cox and Coupland ²³	2005	9,218 first MIs	Rofecoxib: OR 1.32 Diclofenac: OR 1.55 Ibuprofen: OR 1.24 Naproxen: OR 1.27
Johnsen et al ²⁴	2005	10,280 first MIs	Rofecoxib: RR 2.52 Celecoxib: RR 2.14 Naproxen: RR 1.65 Nonselective NSAIDs: RR 2.65

termination of the study resulting in data that cannot be interpreted reliably.¹⁷

Epidemiologic and observational studies: Table 2 lists the results of several recent epidemiologic studies.^{20–24}

Data from Kaiser Permanente in California, involving patients treated with NSAIDs and COX-2-specific agents from January 1999 to December 2001, were used for a nested case-control study.²¹ Patients with acute MI and sudden cardiac death were risk-set matched with 4 controls. The data were analyzed to compare current with remote exposure, and rofecoxib was compared with celecoxib. Rofecoxib use was found to increase the risk for serious coronary artery disease (i.e., acute MI or sudden cardiac death) compared with celecoxib (rofecoxib vs celecoxib; odds ratio [OR] 1.59, 95% CI 1.10 to 2.32, $p = 0.015$). Naproxen was found to be neutral regarding the risk for coronary artery disease. For naproxen compared with remote NSAID use, the OR was 1.14 (95% CI 1.00 to 1.30, $p = 0.05$).

The associated risk for hospitalization for first MI with NSAID use in the general population was examined in a population-based, matching case-control study conducted in Finland from 2000 to 2003, which identified 33,309 first MIs. For combined NSAIDs, the adjusted OR for first MI with current use was 1.40 (95% CI 1.33 to 1.48).²² No difference was seen between nonselective NSAIDs (predominantly ibuprofen and diclofenac) and COX-2-specific inhibitors; both were associated with elevated RRs of 1.34 (95% CI 1.26 to 1.43) and 1.31 (95% CI 1.13 to 1.50) in current users. Among individual drugs, the adjusted OR was lowest for naproxen (1.19, 95% CI 1.02 to 1.38) compared with diclofenac (1.35, 95% CI 1.18 to 1.54) and ibuprofen (1.41, 95% CI 1.28 to 1.55); the difference was not statistically significant.²² It was concluded that current use of all NSAIDs carries a modest risk for first MI.

A study by Garcia-Rodriguez and Gonzalez-Perez²⁰ looked specifically at time to onset for RR for MI with the use of naproxen, ibuprofen, and diclofenac. This UK General Practice Database study identified 4,975 patients with MIs and controls in a 1:4 ratio. Current NSAID users (patients who had taken NSAIDs within 1 month) did not have

an increased risk for MI (RR 1.07, 95% CI 0.95 to 1.21). In patients who had used NSAIDs for >1 year, the RR for MI was 1.21 (95% CI 1.00 to 1.48), and for nonfatal MI, it was 1.34 (95% CI 1.06 to 1.70). In patients not receiving low-dose aspirin, the RR was 1.29 (95% CI 1.01 to 1.65). When individual NSAIDs were compared, it was found that the lowest RR was seen with naproxen (0.87, 95% CI 0.47 to 1.62), and the highest was seen with diclofenac (1.38, 95% CI 1.00 to 1.90).

The comparative risk for MI in patients taking nonselective NSAIDs and COX-2-specific inhibitors was analyzed from a UK General Practice Database containing records from 2000 to 2004. This nested case-control study compared 9,218 patients with first MIs with controls in a 1:9 ratio; ORs were adjusted for various CV risk factors.²³ The current use of rofecoxib compared with no use in the previous 3 years was associated with a significantly increased risk for MI (OR 1.32, 95% CI 1.09 to 1.61). Similarly, a significantly increased risk for MI was seen with the current use of diclofenac (OR 1.55, 95% CI 1.39 to 1.72, $p < 0.001$), ibuprofen (OR 1.24, 95% CI 1.11 to 1.39, $p < 0.001$), and naproxen (OR 1.27, 95% CI 1.01 to 1.60, $p = 0.04$). No significant interactions occurred between any of the NSAIDs and either aspirin or coronary artery disease.

A Danish registry study identified 10,280 patients with first hospitalizations for MI, with matched controls at a ratio of 1:10, along with all prescriptions for NSAIDs before hospitalization.²⁴ Current users of rofecoxib had the greatest elevated risk estimate for hospitalization for MI (RR 1.80, 95% CI 1.47 to 2.21). An elevated risk was also found for current users of celecoxib (RR 1.25, 95% CI 0.97 to 1.62), naproxen (RR 1.50, 95% CI 0.99 to 2.29), other nonselective NSAIDs (RR 1.68, 95% CI 1.52 to 1.85), and other COX-2-specific inhibitors besides rofecoxib and celecoxib (RR 1.45, 95% CI 1.09 to 1.93). Additionally, the risk for new users was markedly greater than that for current users of rofecoxib (RR 2.52, 95% CI 1.74 to 3.64), celecoxib (RR 2.13, 95% CI 1.45 to 3.13), naproxen (RR 1.65, 95% CI 0.57 to 4.83), and other nonselective NSAIDs (RR 2.65, 95% CI 2.00 to 3.50).²⁴

Table 3
Meta-analyses

Investigators	Year	No. of Studies	Cardiovascular Safety
Chou et al ¹⁸	2006	351 of 2,800	Naproxen moderately superior to any COX-2-specific NSAID
McGettigan and Henry ²⁷	2006	17 case-control, 6 cohort	Rofecoxib ≤ 25 mg/day: RR 1.33 Rofecoxib > 25 mg/day: RR 2.19 Celecoxib: RR 1.06 Diclofenac: RR 1.40 Naproxen: RR 0.97 Ibuprofen: RR 1.07
Kearney et al ²⁶	2006	138	COX-2-specific NSAIDs: moderate increase of CV risk High-dose ibuprofen and diclofenac: moderate risk for CV events Naproxen not associated with increase in CV events
Salpeter et al ²⁸	2006	13	Nonselective NSAIDs had no effect on CV events
Juni et al ²⁵	2004	18 RCTs, 11 observational studies	Rofecoxib should probably have been withdrawn several years earlier

Systematic reviews and meta-analyses of clinical trial data: Table 3 lists the results of several recent meta-analyses of clinical trial data.^{18,25–28}

The Agency for Healthcare Research and Quality screened approximately 2,800 studies, including RCTs, observational studies, meta-analyses, and systematic reviews, and found 351 studies that met the predetermined inclusion criteria. Data were assessed by examining a number of parameters, including the number and quality of studies and the consistency of results among studies. The CV safety of naproxen was determined to be moderately superior to that of any COX-2-specific NSAID.¹⁸ There were 3.3 additional MIs for every 1,000 patients treated with any COX-2-specific inhibitor instead of naproxen for 1 year. The CV safety of nonselective NSAIDs other than naproxen was similar to that of COX-2-specific NSAIDs. In an indirect analysis, naproxen was the only nonselective NSAID associated with neutral CV risk relative to placebo.

A recently conducted systematic review of 17 case-control studies and 6 cohort studies of nonselective NSAIDs and COX-2-specific inhibitors suggested a possible CV risk for some nonselective NSAIDs, particularly diclofenac.²⁷ Data were combined using a random-effects model. Naproxen neither increased nor decreased the RR of CV events, with an RR of 0.97 (95% CI 0.897 to 1.07) compared with other nonselective NSAIDs including ibuprofen (RR 1.07, 95% CI 0.97 to 1.18), piroxicam (RR 1.06, 95% CI 0.70 to 1.59), and diclofenac (RR 1.40, 95% CI 1.16 to 1.70). The other agent with a summary RR close to 1.00 was celecoxib, at 1.06 (95% CI 0.91 to 1.23). A dose-related risk was evident with rofecoxib, with an RR of 1.33 for ≤ 25 mg/day, which increased to an RR of 2.19 (95% CI 1.64 to 2.91) at doses of > 25 mg/day. The risk was also found to be elevated during the first month of treatment.

A meta-analysis by Kearney et al²⁶ assessed the risk for vascular events with COX-2-specific inhibitors compared with NSAIDs or placebo. This analysis used data from all RCTs conducted to date, including unpublished data from NSAID manufacturers, for a total of 138 trials. Compared with placebo, COX-2-specific inhibitors were associated with an increased RR, corresponding to a 42% proportional increase in the incidence of a first serious vascular event (0.9%/year vs 1.2%/year; RR 1.42, 95% CI 1.13 to 1.78, $p = 0.003$; no difference among individual COX-2-specific

drugs). This difference was largely attributable to a twofold increased risk for MI (RR 1.86, 95% CI 1.33 to 2.59, $p = 0.0003$). In trials > 1 year in duration (mean 2.7 years), the rate ratio for vascular events was 1.45 (95% CI 1.12 to 1.89, $p = 0.005$). Overall, there was no difference between COX-2-specific inhibitors and nonselective NSAIDs in serious vascular events (RR 1.16, 95% CI 0.97 to 1.38, $p = 0.10$). There was a difference between COX-2-specific inhibitors and naproxen (RR 1.57, 95% CI 1.21 to 2.03, $p = 0.0006$). High-dose regimens of ibuprofen (RR 1.51, 95% CI 0.96 to 2.37) and diclofenac (RR 1.63, 95% CI 1.12 to 2.37), but not naproxen (RR 0.92, 95% CI 0.67 to 1.26), were associated with an increased risk for vascular events compared with placebo.

A meta-analysis of RCTs of nonselective NSAIDs was conducted from 1996 to 2005 to ascertain the effect of NSAIDs on CV risk. The 13 trials included 7,718 patients with Alzheimer disease or joint disease, reported ≥ 1 CV event or death, and lasted for ≥ 6 weeks.²⁸ The outcome measure was the composite rate of death, MI, and stroke. Nonselective NSAIDs had no significant effect on the incidence of CV events (OR 1.3), and there was no difference between naproxen and the other nonselective NSAIDs. In these studies, almost no patients received diclofenac ($n = 69$), and only a very small number of patients received NSAIDs other than naproxen.

After the withdrawal of rofecoxib and the outcome of the VIGOR trial, a cumulative meta-analysis was performed by Juni et al²⁵ to ascertain whether evidence in the published research existed before the market withdrawal of rofecoxib in 2004. A total of 18 RCTs and 11 observational studies involving 25,273 patients were used to determine the risk for CV events (MI) with rofecoxib, nonselective NSAIDs, and placebo. By the end of 2000, the RR for MI from RCTs was 2.30 (95% CI 1.22 to 4.33, $p = 0.01$); there was no evidence that the RR was influenced by the control group or trial duration. The observational studies included 8 case-control studies and 3 retrospective cohort studies that were analyzed to determine the RR of MI for naproxen. Here, the RR for MI in naproxen-treated patients was 0.86 (95% CI 0.75 to 0.99) compared with controls. Non-naproxen NSAIDs and COX-2-specific agents had the same RR for MI. The investigators concluded that if there is any benefit to naproxen in reducing MI risk, it is very small and not

close to that required to explain the VIGOR results. They concluded that rofecoxib should have been withdrawn from the market earlier.

Cardiovascular Risks of Cyclooxygenase-2-Specific Nonsteroidal Anti-Inflammatory Drugs

Placebo-controlled trials: Many of the studies relevant to an assessment of the CV risk for COX-2-specific agents have been presented and discussed previously. In this section, additional placebo-controlled trial data are introduced.

The Adenomatous Polyp Prevention on Vioxx (APPROVe) trial was the first relatively large trial ($n = 2,600$) comparing rofecoxib with placebo in patients with histories of colorectal adenocarcinoma.¹⁶ Patients taking $\geq 80\%$ of their doses during the placebo run-in period were randomized to receive rofecoxib 25 mg/day (the maximum recommended long-term daily dose) or placebo for 3 years. The results showed a greater number of MIs and ischemic cerebrovascular events with rofecoxib (RR 1.92, 95% CI 1.19 to 3.11, $p = 0.008$). The original study suggested no difference in vascular events until 18 months; however, on careful analysis, the increased risk for congestive heart failure, pulmonary edema, and heart failure actually became apparent by 5 months.¹⁶ On the basis of these data, physicians may consider switching patients from COX-2-specific NSAIDs to nonspecific agents. However, physicians need to be cognizant of the underlying CV and gastrointestinal risks of these agents. Although the 2 classes of NSAIDs have CV risks, the use of a nonspecific NSAID could result in a two- to threefold increase in the risk for serious upper gastrointestinal complications.²⁹

Soon afterward, the APC trial, which compared celecoxib 200 and 400 mg twice daily with placebo in 2,035 patients at risk for recurrent colon polyps, reported a similar result.¹⁴ Although the results showed similar trends to CLASS, there was an increased RR for serious adverse CV events (two- to threefold) compared with placebo after a mean duration of 33 months in APC. On the basis of these results, the data and safety monitoring board recommended the early discontinuation of celecoxib.

The Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial was an international, multicenter, placebo-controlled study of 1,561 patients with histories of adenomatous polypectomy.³⁰ Patients were randomized to receive celecoxib 400 mg/day or placebo and were followed for up to 3 years. Serious adverse CV events were greater in the celecoxib group than in the placebo group (2.5% vs 1.9%, RR 1.30, 95% CI 0.65 to 2.62). However, the number of events was small in the 2 groups, with no statistically significant differences.

The safety of celecoxib was studied in a combined analysis of the data from the APC and PreSAP trials.³¹ This analysis confirmed significant elevated CV risk (CV death, nonfatal MI, nonfatal stroke, congestive heart failure) with celecoxib 200 mg twice daily (RR 2.6, 95% CI 1.1 to 6.1) and 400 mg twice daily (RR 3.4, 95% CI 1.5 to 7.9). This study also confirmed the lower CV risk in patients who were receiving celecoxib 400 mg/day (RR 1.3, 95% CI 0.6 to 2.6). Significant dose-related elevations in blood pressure were also noted in the 2 twice-daily dosing groups but not in the once-daily dosing group ($p < 0.0001$ for the differ-

ence between studies). A composite comparison with placebo showed an overall increased RR for serious adverse CV events of 1.9 (95% CI 1.1 to 3.1).

The safety of the COX-2-specific inhibitor valdecoxib was assessed in 1,671 patients who had undergone coronary artery bypass grafting. The patients were randomly assigned to receive intravenous parecoxib for ≥ 3 days followed by oral valdecoxib through day 10, intravenous placebo followed by oral valdecoxib, or oral placebo.³² Patients were followed for 30 days after treatment. Serious adverse CV events (MI, cardiac arrest, stroke, pulmonary embolism) occurred in 2.0% of the combined drug-treated groups, compared with 0.5% of the placebo group (RR 3.7, 95% CI 1.0 to 13.5, $p = 0.03$). These results raised concern about the use of valdecoxib not only in this setting but also in general, especially given the short follow-up of only 30 days.

Additional studies: A meta-analysis of CV safety data from all celecoxib RCTs in osteoarthritis, rheumatoid arthritis, and other painful conditions was recently reported by White et al.³³ Thirty-seven trials, ranging from 4 weeks to 1 year in duration (median 12 weeks), were included in the analysis (not including the PreSAP or APC trials). A total of 7,462 patients were exposed to celecoxib 200 to 800 mg/day for 1,268 patient-years, compared with 4,057 patients treated with placebo for 585 patient-years. Additionally, a total of 19,773 patients were treated with celecoxib 200 to 800 mg/day for 5,651 patient-years, compared with 13,990 patients treated with nonselective NSAIDs for 4,386 patient-years. Diclofenac was the predominant nonselective NSAID, and just 2 smaller placebo-controlled trials used celecoxib doses of 800 mg/day. No difference was found between celecoxib and placebo or the nonselective NSAIDs on the Antiplatelet Trialists' Collaboration (ATC) composite end points of nonfatal MI, nonfatal stroke, and CV death, regardless of dose or aspirin use.

Aspirin Interaction Studies

Ibuprofen and aspirin: Ibuprofen may interfere with the antithrombotic effects of aspirin through competitive inhibition at the receptor binding site of the COX-1 enzyme.^{33–36} Renda et al³⁶ compared celecoxib 200 mg twice daily with ibuprofen 600 mg three times daily and placebo administered for 7 days to 24 patients receiving long-term, low-dose aspirin for cardioprotection. A significant increase in serum thromboxane B₂ levels (an index of COX-1 activity in platelets) was found with the coadministration of aspirin and ibuprofen ($p < 0.001$); no effect was seen with the coadministration of celecoxib. Arachidonic acid-induced platelet aggregation was increased ($p < 0.05$), and occlusive thrombus formation occurred faster ($p < 0.01$) with ibuprofen, but not with celecoxib. Therefore, ibuprofen, but not celecoxib, was found to interfere with the irreversible inhibition of platelet COX-1 by aspirin.

Catella-Lawson et al³⁴ compared ibuprofen 400 mg, acetaminophen 1,000 mg, and rofecoxib 25 mg administered 2 hours before or after aspirin 81 mg for a total of 6 days. Ibuprofen, even at this dosage, blocked the inhibition of serum thromboxane B₂ and arachidonic acid-induced platelet aggregation at 24 hours when taken before aspirin. No other drugs had any effect, regardless of dosing order.

Multiple doses of ibuprofen also had this effect at day 6 when given at 10 AM, 3 PM, and 8 PM and when aspirin was given at 8 AM. Thus, the concomitant administration of ibuprofen antagonizes the irreversible platelet inhibition induced by aspirin.

MacDonald and Wei³⁵ studied 7,107 patients discharged from the hospital with diagnoses of CV disease; they were receiving low-dose aspirin and had survived ≥ 1 month. Compared with patients receiving aspirin alone, patients receiving concomitant ibuprofen had an increased risk for CV mortality (RR 1.73, 95% CI 1.05 to 2.84, $p = 0.0305$) and all-cause mortality (RR 1.93, 95% CI 1.30 to 2.87). This increased mortality was not found with diclofenac or any other NSAID. Of note, there were several limitations to this study, including the number of patients and the fact that no adjustments were made for the severity of CV disease, doses of individual NSAIDs, smoking, or body mass index.³⁵

A recent study by Gengo et al³⁷ assessed the magnitude and duration of platelet aggregation inhibition using ibuprofen, and aspirin alone and in combination. This study in healthy volunteers was followed by a confirmatory study in patients receiving NSAID therapy who received concomitant aspirin for secondary stroke prevention. The findings suggested that ibuprofen prevents the irreversible inhibition of platelet aggregation elicited by aspirin required for secondary stroke prophylaxis.

Naproxen and aspirin: The interaction between naproxen and aspirin is complex. A pharmacodynamic interaction was demonstrated when a single dose of aspirin 100 mg and naproxen 500 mg were coadministered in 4 healthy subjects, with no detectable antiplatelet activity at 1 hour after dosing. However, multiple-dose administration of naproxen 500 mg twice daily 2 hours before or after the administration of aspirin 100 mg/day for 6 consecutive days failed to interfere with the antiplatelet effect of the aspirin.³⁸ According to the investigators, the likely reason for the lack of effect with naproxen given before or after aspirin is that naproxen has an aspirin-like effect, which compensates for the inhibition of its cardioprotective effect. Similar results to those obtained by Capone et al³⁸ have since been reported in a study of similar design, using an over-the-counter dosage of naproxen (220 mg three times daily).³⁹

A post hoc analysis of TARGET by baseline CV risk, treatment assignment, and low-dose aspirin use was also performed.⁴⁰ In high-risk patients who were aspirin users, those in the ibuprofen substudy experienced more primary events with ibuprofen than with lumiracoxib (2.14% vs 0.25%, $p = 0.038$), whereas rates in the naproxen substudy were similar between naproxen and lumiracoxib users (1.58% vs 1.48%, $p = 0.899$). High-risk patients not taking aspirin had fewer primary events with naproxen than with lumiracoxib (0% vs 1.57%, $p = 0.027$) but not with ibuprofen (0.92% vs 0.80%, $p = 0.920$). In patients at high CV risk, congestive heart failure developed more often with ibuprofen than with lumiracoxib (1.28% vs 0.41%, $p = 0.031$), whereas no difference in incidence was seen between naproxen and lumiracoxib users (0.83% vs 0.81%, $p = 0.95$). It was concluded that ibuprofen may confer an increased risk for thrombotic and congestive heart failure

events compared with lumiracoxib in aspirin users at high CV risk, while naproxen may be associated with lower risk than lumiracoxib in aspirin nonusers. These results are consistent with the ability of ibuprofen to interfere with the antiplatelet effects of aspirin.

Antiplatelet effects of naproxen and aspirin: Data support an apparent antiplatelet effect for naproxen, similar to that of aspirin.^{41,42} The antiplatelet activity of naproxen and low-dose aspirin were compared in healthy subjects in a study by Capone et al.⁴¹ Naproxen at a prescription dose of 500 mg twice daily or aspirin 100 mg/day was administered to 9 subjects for 6 days in this crossover, open-label study. The effects on thromboxane B₂ were assessed up to 24 hours after oral dosing. The administration of naproxen or aspirin caused a similar suppression of whole-blood thromboxane B₂ production, an index of platelet COX-1 activity *ex vivo*, by $94 \pm 3\%$ and $99 \pm 0.3\%$, respectively. Urinary excretion of 11-dehydro-thromboxane B₂, an index of the systemic biosynthesis of thromboxane A₂ *in vivo*, was similarly suppressed by naproxen and aspirin ($85 \pm 8\%$ and $78 \pm 7\%$, respectively). This study provides the evidence from a mechanistic point of view that the neutral CV risk for naproxen observed in epidemiologic studies might be explained by this similar antiplatelet activity to aspirin.

Lower over-the-counter doses of naproxen (220 mg twice daily and three times daily) were compared with low-dose aspirin (81 mg/day) and prescription-dose naproxen (550 mg twice daily) to assess antiplatelet activity in a single-center, randomized, open-label, placebo-controlled, 2-period crossover trial in healthy volunteers.⁴² Patients were administered 1 of 3 naproxen regimens or placebo for 7 days; after a washout period of ≥ 6 days, they were crossed over to receive aspirin for 7 days. The primary end point was serum thromboxane B₂ level. The results showed that the antiplatelet effect of naproxen at the 2 over-the-counter doses was similar to that seen with aspirin 81 mg/day and naproxen 550 mg twice daily in the evaluable population and the intent-to-treat population. Although the full clinical relevance of these data is unknown, this study adds to the body of evidence about the CV safety of naproxen.

Current Synthesis of the Evidence

Clearly, the association of CV risk with the use of NSAIDs is related to a number of factors. Our synthesis of the evidence suggests that there are 5 key variables that determine the extent of CV toxicity (Table 4): (1) COX-2 selectivity, (2) dose responsiveness, (3) plasma half-life, (4) blood pressure, and (5) interaction with aspirin.

Nonselective NSAIDs: NAPROXEN. Of all of the nonselective NSAIDs, naproxen has shown a lower CV risk than rofecoxib and lumiracoxib in large RCTs. Most observational studies have indicated neutral risk relative to placebo and lower risk than other nonselective NSAIDs. Meta-analyses and systematic reviews have consistently demonstrated lower risk with naproxen than with other nonselective NSAIDs and COX-2-specific agents. However, along with this propensity for low CV risk is the potential for increased gastrointestinal risk relative to other agents.² Studies on platelet effects (over-the-counter and

Table 4
Cardiovascular safety profile on the basis of 5 key variables

Agent	High COX-2 Selectivity	Dose Responsivity to CV Effects	Long Plasma Half-Life	Increase in Blood Pressure	Interaction With Aspirin
Nonselective NSAIDs					
Naproxen	–	–	++	–	+–
Ibuprofen	–	++	–	+++	+++
Diclofenac	+	++	–	+++	–
Others	–	–	–	–	–
COX-2 inhibitors					
Rofecoxib	+++	+++	+++	+++	–
Celecoxib	+	+++	++	–	–
Lumiracoxib	+++	++	–	–	–
Valdecoxib	++	++	++	–	–
Etoricoxib	+++	+++	++	+++	–

– = nonsignificant; + = mildly significant; ++ = moderately significant; +++ = highly significant; +– = unknown.

prescription doses) and aspirin interaction studies suggest no diminution of the cardioprotective effect of aspirin when used concomitantly.

IBUPROFEN. The data on ibuprofen derived from RCTs have indicated a risk comparable to that of celecoxib. Most observational studies have shown a slight elevation of risk relative to placebo and comparable to COX-2-specific and nonselective NSAIDs. In meta-analyses and systematic reviews, ibuprofen tended to rank just above naproxen in CV risk (slightly more risk). Aspirin interaction studies and the TARGET post hoc analysis have suggested that the concomitant use of ibuprofen interferes with the cardioprotective effects of aspirin. Recently, the United States Food and Drug Administration proposed 3 new label warnings for ibuprofen in the over-the-counter monograph (<http://www.fda.gov/ohrms/dockets/dailys/03/sept03/090803/77n-0094I-c000004-06-Conclustions-vol7.pdf>): 1 related to gastrointestinal effects (including, heartburn, upset stomach, and pain), 1 related to renal effects (e.g., in patients who are taking diuretics or are >65 years of age), and 1 related to use with anticoagulant agents.

DICLOFENAC. The data on diclofenac indicated a comparable risk with etoricoxib and celecoxib, as determined through RCTs. Diclofenac has also been associated with the greatest elevation of risk relative to placebo in most observational studies. In most meta-analyses and systematic reviews, diclofenac has been found to have the highest CV risk among nonselective NSAIDs. No interaction with aspirin has been documented.

OTHER NONSELECTIVE NSAIDS. Unfortunately, no RCTs are available to assess the CV safety of other nonselective NSAIDs. Most observational studies assess their risk as comparable with that of the COX-2-specific agents. In meta-analyses and systematic reviews, this group tended to rank between naproxen at the low-risk end and diclofenac at the high-risk end. Limited data are available on aspirin interactions.

COX-2-specific NSAIDs: CELECOXIB. Celecoxib is currently the only drug in its class available in the United States. Clinical trial evidence suggests an elevated risk for thromboembolic CV events, especially at higher doses (400 mg twice daily), but also at 200 mg twice daily.³¹ On the basis of the available data, no CV interaction with aspirin has

been noted. Celecoxib may pose less risk than other COX-2-specific NSAIDs when used once daily or at low doses.

ROFECOXIB. The RCT evidence is definitive, indicating an increased CV risk for rofecoxib. This increase in CV risk led to the withdrawal of rofecoxib from the United States market.⁴³ It was these data regarding rofecoxib that awakened the medical community to the CV risk of NSAIDs in general. On the basis of the CV risk in the context of multiple alternatives and an insufficient efficacy advantage, the market withdrawal of this agent was justified.

LUMIRACOXIB. The RCT evidence to date suggests the possibility of limited or no increased CV risk with lumiracoxib (not currently approved for use in the United States) compared with the nonselective NSAIDs. This is curious in light of the high degree of COX-2 selectivity but further argues against a simple relation between enzyme selectivity and CV risk. The results of a recent 4-week, double-blind, parallel-group study showed that lumiracoxib 100 mg/day produced clinically significant lower blood pressure in patients with osteoarthritis and well-controlled hypertension than ibuprofen 600 mg three times daily.⁴⁴ This may help account for the more favorable CV profile of lumiracoxib compared with ibuprofen.

VALDECOXIB. RCT evidence exists for a marked increase in risk after coronary artery bypass grafting for valdecoxib in a short-term, 5-day study in high-risk patients. In contrast to rofecoxib and celecoxib, valdecoxib has not been evaluated in any long-term studies. Clinical studies have shown increased risk for serious CV events with valdecoxib. On the basis of the increased CV risk and associated hypersensitivity skin reactions and in the context of multiple alternatives and insufficient efficacy advantage, the regulatory action was justified.

ETORICOXIB. RCTs have indicated a lack of difference from nonselective NSAIDs, but the NSAIDs used as controls in these trials were diclofenac and ibuprofen, both of which have been associated with increased risk.¹¹ Only a comparison with placebo would establish the true CV risk of this agent. Until true CV safety can be established, and in view of the multiple alternative agents and lack of evidence for an efficacy advantage, the Food and Drug Administration decided to reject the new drug application for etoricoxib.

Conclusion

The use of an NSAID involves weighing the benefits and risks from a CV and gastrointestinal perspective. This review provides a synthesis of the evidence for CV safety and should be used to form decisions for individual patients.

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