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FDA Briefing Document

Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee

February 10-11, 2014

Nonsteroidal anti-inflammatory drugs and cardiovascular thrombotic risk

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought nonsteroidal anti-inflammatory drugs and cardiovascular thrombotic risk issue to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Food and Drug Administration
Center for Drug Evaluation and Research

Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee

Nonsteroidal anti-inflammatory drugs and cardiovascular thrombotic risk

February 10-11, 2014

Briefing Materials

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1. Division Director Memo

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

MEMORANDUM

DATE: January 13, 2014

FROM: Sharon Hertz, MD
Deputy Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, CDER, FDA

RE: Overview of the February 10 and 11, 2013 Joint meeting of FDA's Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee

Following emergence of new data about the risk of cardiovascular (CV) thromboembolic events associated with the cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs (NSAIDs), rofecoxib and celecoxib, a joint advisory committee meeting of the Arthritis Advisory Committee (AAC) and the Drug Safety and Risk Management Advisory Committee (DsaRM) was held in February 2005. During the 2005 meeting, data from clinical outcome trials and epidemiology studies of several individual NSAIDs were reviewed, and the committee discussed the risk of CV thromboembolic events associated with the use of both COX-2 selective and nonselective NSAIDs. Based on the data reviewed and the deliberations of the advisory committee members, FDA concluded that the risk for CV thromboembolic events was present for both COX-2 selective NSAIDs and nonselective NSAIDs, and the data available at the time did not permit rank ordering of the drugs with regard to CV risk.[1]

At this joint meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee, we will be discussing recent literature reports and analyses of the risk for cardiovascular (CV) thromboembolic events

[1]http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106201.pdf

associated with the use of NSAIDs published subsequent to the February 2005 joint advisory committee meeting. In particular, a meta-analysis of clinical trial data examined the cardiovascular thromboembolic risk and gastrointestinal risk associated the use of several NSAIDs.[2] This study reinforces the 2005 conclusions by FDA that the risk for CV events is present for both nonselective and COX-2 selective NSAIDs, but also raises the possibility that, in contrast to the 2005 conclusions, there may be a lower risk for one NSAID, naproxen[1]. This study also provides information about the risk for serious gastrointestinal adverse events from the meta-analysis. During this meeting, we will also discuss the results of several epidemiological studies and meta-analyses of observational data as we look at the CV risk associated with individual NSAIDs.

As a result of the conclusions in 2005, a long-term clinical outcome trial, "Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen" (PRECISION) was initiated in response to a request by FDA for additional data describing the CV risk associated with celecoxib. This clinical trial is currently ongoing and is intended to evaluate the relative safety of celecoxib and naproxen and ibuprofen. Based on the available information from the clinical trial data and observational study meta-analyses, the question has been raised as to whether this study should continue; this question is another topic for discussion during this advisory committee.

The Committee will be asked to consider the following discussion topics on February 10 and 11, 2014:

1. Do the accumulated data support naproxen as having a lower risk for CV thrombotic events as compared to the other nonselective NSAIDs, and If so, what are the implications of this finding for prescribers?

2. Do the accumulated data support a differential risk for CV thrombotic events for any of the non-naproxen NSAIDs?

3. Are the data adequate to support the conclusion that there is no latency period for increased CV thrombotic risk with NSAIDs?

4. Based on the available data, is it appropriate to consider any restrictions or specific warnings for those populations who are at higher absolute risk for CV thrombotic events with NSAID use?

5. How do the data related to CV thrombotic risk impact the acceptability of NSAIDs as "over the counter" products at the currently available doses?

[2] Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013; 382: 769-79.

6. Are there are any changes that should be made to the PRECISION trial to respond to the concerns that have been raised?

Tracked Safety Issue (TSI) Integrated Review Memorandum

Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation 2
Center for Drug Evaluation and Research
Food and Drug Administration

Drug class	*Non-steroidal anti-inflammatory drugs*
TSI #	*1230*
Safety Issue Name	*Cardiovascular thrombotic risk*
Author name	*Judith A. Racoosin, MD, MPH*
Date	*January 10, 2014*

Introduction

Over the early part of the 2000s, data began to emerge from large randomized controlled clinical trials demonstrating cardiovascular thromboembolic risk with the COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs), a subgroup of the broader class of NSAIDs. In September of 2004, the voluntary withdrawal of rofecoxib by Merck Pharmaceuticals following identification of an elevated risk for cardiovascular events in a clinical trial of familial adenomatous polyposis (Adenomatous Polyp Prevention on Vioxx [APPROVe]) created an opportunity for a review of the available clinical trial data and epidemiologic studies for all of the COX-2 selective and non-selective NSAIDs. Studies reviewed included efficacy trials in rheumatologic conditions, outcome studies with prespecified gastrointestinal and cardiovascular (CV) safety endpoints, and other trials in conditions where inflammation was postulated to have an etiological effect, including familial polyposis and Alzheimer's disease. On February 16-18, 2005, a joint meeting of FDA's Arthritis Advisory Committee and FDA's Drug Safety and Risk Management Advisory Committee was convened to discuss the risk of cardiovascular thromboembolic events with COX-2 selective NSAIDs and non-selective NSAIDs (e.g., ibuprofen, naproxen, diclofenac, and others).

At the meeting, the advisory committee opined that there appeared to be a class effect for cardiovascular risk associated with the three approved COX-2 selective NSAIDs (i.e., rofecoxib, celecoxib, and parecoxib/valdecoxib); there was less agreement with regard to the non-selective NSAIDs, but the general recommendation was that similar warnings be applied to these drug labels as well.

Following the advisory committee meeting, on April 7, 2005, the FDA made the following conclusions[1]:

[1] http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm103420.htm

- The three approved COX-2 selective NSAIDs (i.e., celecoxib, rofecoxib, and valdecoxib) are associated with an increased risk of serious adverse CV events compared to placebo. The available data do not permit a rank ordering of these drugs with regard to CV risk.

- Data from large long-term controlled clinical trials that have included a comparison of COX-2 selective and non-selective NSAIDs do not clearly demonstrate that the COX-2 selective agents confer a greater risk of serious adverse CV events than non-selective NSAIDs.

- Long-term placebo-controlled clinical trial data are not available to adequately assess the potential for the non-selective NSAIDs to increase the risk of serious adverse CV events.

- Pending the availability of additional long-term controlled clinical trial data, the available data are best interpreted as being consistent with a class effect of an increased risk of serious adverse CV events for COX-2 selective and non-selective NSAIDs.

- Short-term use of NSAIDs to relieve acute pain, particularly at low doses, does not appear to confer an increased risk of serious adverse CV events (with the exception of valdecoxib in hospitalized patients immediately post-operative from coronary artery bypass (CABG) surgery).

- Valdecoxib is associated with an increased rate of serious and potentially life-threatening skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) compared to other COX-2 selective agents and is the only NSAID with a boxed warning for this adverse event in its approved package insert. In the absence of any demonstrated advantage over nonselective NSAIDs, the overall benefit versus risk profile for valdecoxib is unfavorable for marketing.

Based on these conclusions, FDA took the following actions:

- The agency asked Pfizer to voluntarily withdraw Bextra (valdecoxib) from the U.S. market.

- The professional labeling for all prescription NSAIDs was revised to include a boxed warning highlighting the potential increased risk of serious adverse CV events. The boxed warning also includes the well described NSAID class risk of serious, and often life-threatening, GI bleeding, which is currently contained in a bolded warning.

- The labeling for all prescription NSAIDs was revised to include a contraindication for use in patients immediately post-operative from CABG surgery.

- A class NSAID Medication Guide was developed and implemented to inform patients of the potential increased risk of serious adverse CV events and the risk of serious GI bleeding.

- The labeling for non-prescription NSAIDs was revised to include more specific information about potential CV and GI risks and information to assist consumers in the safe use of these drugs.

- The agency requested that all sponsors of non-selective NSAIDs conduct and submit for FDA review a comprehensive review and analysis of available controlled clinical trial databases to further evaluate the potential for increased CV risk.

For additional details of the regulatory history and discussions leading to these conclusions and actions, the reader is referred to the Decisional Memorandum dated April 6, 2005 authored by Dr. John Jenkins of the Office of New Drugs (OND) and Dr. Paul Seligman formerly of the Office of Pharmacoepidemiology and Statistical Science which is included in this background package and also available at this link: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106201.pdf

Around this same time, the European Medicines Agency (EMA) took action on COX-2 selective NSAIDs and non-selective NSAIDs. The EMA came to a different conclusion than FDA and distinguished COX-2 selective NSAIDs as having increased CV thrombotic risk compared to non-selective NSAIDs. EMA made the following recommendations/conclusions:

- COX-2 selective NSAIDs
  - Addition of contraindications stating that COX-2 selective NSAIDs must not be used in patients with established ischemic heart disease and/or cerebrovascular disease (stroke), and also in patients with peripheral arterial disease
  - Reinforced warnings to healthcare professionals to exercise caution when prescribing COX-2 selective NSAIDs to patients with risk factors for heart disease, such as hypertension, hyperlipidemia, diabetes, and smoking
  - Given the association between cardiovascular risk and exposure to COX-2 selective NSAIDs, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment
- Non-selective NSAIDs
  - Non-selective NSAIDs are important treatments for arthritis and other painful conditions.
  - It cannot be excluded that non-selective NSAIDs may be associated with a small increase in the absolute risk for thrombotic events especially when used at high doses for long-term treatment.
  - The overall benefit-risk balance for non-selective NSAIDs remains favorable when used in accordance with the product information, namely on the basis of the overall safety profile of the respective non-selective NSAID, and taking into account the patient's individual risk factors (e.g. gastrointestinal, cardiovascular and renal).

Following announcement of the April 7, 2005 action, a letter was issued on June 14, 2005, to all NSAID sponsors requesting that a boxed warning be added to labeling describing the cardiovascular and gastrointestinal risks along with related changes to other sections of labeling; the letter also requested the addition of a Medication Guide that would be distributed with each dispensed prescription to explain these risks in patient friendly language. The updated labeling was implemented in the next several months following the labeling supplement request. The boxed warning and warning statement is shown below:

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See **WARNINGS** and **CLINICAL TRIALS**).

- TRADENAME is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (See **WARNINGS**).

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see WARNINGS, GI Effects).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see CONTRAINDICATIONS).

The sponsors of the non-selective NSAIDs submitted their reviews of all clinical trial data available to them to evaluate the potential for cardiovascular risk of each of the NSAIDs. The data in these submissions were limited and did not result in new insights about the cardiovascular risks of the non-selective NSAIDs.

In 2006, a large RCT intended to evaluate CV thrombotic risk called "Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen" (PRECISION) was initiated after Pfizer agreed to conduct a postmarketing commitment requested by the Agency. It is a randomized, double-blind, active-controlled, parallel-group study of CV safety in osteoarthritis or rheumatoid arthritis patients with or at high risk for CV disease comparing celecoxib with naproxen and ibuprofen. The trial is currently in progress. It had originally been anticipated to be completed by December 2013; however, event accrual has occurred more slowly than anticipated. The revised date for completion of the trial is July 2016.

In the summer of 2011, a publication by Schjerning-Olsen[2] et al. based on data from the Danish National Registry describing an early risk of CV events in post-MI patients taking NSAIDs led the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) to decide to conduct a review of the substantial literature that had been generated on cardiovascular risk with NSAIDs since the labeling change was made in 2005. The Division of Epidemiology II (DEPI-II) in the Office of Pharmacovigilance and Epidemiology (OPE) in CDER's Office of Surveillance of Epidemiology (OSE) was asked to collaborate on this review. The review was focused on the following questions:

1. Are there data to support differential CV risk (including stroke) across the specific NSAIDs?

2. Are there data to better refine the understanding of time to event for cardiovascular risk (including stroke) with NSAIDs? Is there an early hazard or does risk increase with cumulative use (or both, depending on the population)?

3. Describe any data that suggest specific vulnerable populations (e.g., h/o MI, CV risk factors, post-operative- CABG or others) for NSAID-associated CV risk (including stroke)

4. Does use of NSAIDs in patients with history of MI increase the risk of recurrent MI or death?

Additionally, the Division of Cardiovascular and Renal Products (DCaRP) was consulted regarding the findings of the publication mentioned above. The consult included the following questions:

1. For patients started on chronic NSAID therapy, cardiovascular events are not typically observed within the first few days or weeks of initiating therapy. Based on other clinical studies, are there any physiologic factors in patients post-MI that would make them susceptible to potential prothrombotic effects of NSAIDs, and if so, is a latency of less than one week biologically plausible?

2. Is the potential for inhibition of antiplatelet properties of aspirin by NSAIDs an important etiologic factor for these events?

[2] Schjerning Olsen AM, Fosbol EL, Lindhardsen J, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. *Circulation* 2011; 123:2226-35.

3. Are the findings reported in the attached article, in the context of the existing literature, of clinical relevance?

The DCaRP consult response authored by Dr. Preston Dunnmon is included in this briefing package.

Several reviews were conducted to evaluate the large number of publications identified by the search strategy. This briefing document will review the conclusions drawn from these individual reviews. Included in this background package for your consideration are the following reviews that were drafted in the process of evaluating the relevant published literature:

- Review of epidemiological studies and meta-analyses authored by Dr. Andrew Mosholder of the Division of Epidemiology II (DEPI-II/OPE/OSE);
- Review of individual RCTs authored by Dr. Robert Levin of the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

In the course of reviewing the identified literature, the FDA learned of a large meta-analysis that was being conducted by the Coxib and Traditional NSAID Trialists' (CNT) Collaboration based at Oxford University under the direction of Professor Colin Baigent. A pre-publication version of the meta-analysis was made available to the FDA in February 2013. The meta-analysis[3] was subsequently published in The Lancet in 2013. Reviews of this meta-analysis of vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs authored by Dr. Eugenio Andraca-Carrera of the Division of Biometrics 7 (DB7) and Dr. Andrew Mosholder are also included in the background package.

Based on his review of the epidemiological studies and meta-analysis data informing the cardiovascular risk with the NSAIDs, and his conclusion that naproxen does not have the same increased CV thrombotic risk as celecoxib and ibuprofen, Dr. Mosholder raised the possibility that there is no longer equipoise with regard to conducting the PRECISION trial. Three memos in the briefing package address this possibility. They are authored by Dr. Mosholder, Dr. Judith Racoosin of DAAAP, and Dr. Solomon Iyasu of the Office of Pharmacovigilance and Epidemiology (OPE).

Literature Search

The following literature search was conducted by the FDA library in August 2011 in PubMed:

Database Pubmed (2005-2011, English or Eng. Abstract, human)

Search terms:

NSAIDS [title/abstract] OR NSAID [title/abstract] OR Anti-inflammatory agents, non-steroidal [mesh] OR

[3] Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013; 382: 769-79.

Anti-inflammatory agents, non-steroidal [pharmacological action]

AND

(stroke [mesh] OR heart arrest [mh] OR myocardial ischemia [mh] OR intracranial embolism and thrombosis [mesh] OR brain ischemia [mesh] OR cardiovascular event(s) [ti/ab] OR "cardiovascular thrombotic events" [ti/ab] OR ischemias [ti/ab] OR myocardial infarction(s)" [ti/ab]) OR "heart attack" [ti/ab] OR "myocardial ischemia(s)"[ti/ab] OR "heart arrest [ti/ab] OR "cardiac arrest" [ti/ab] OR "cardiovascular death" [ti/ab] OR "cardiovascular sudden death" [ti/ab] or stroke [ti/ab])

A similar search was conducted in Embase the same month:

Limits 2006-2011, human, English

Search terms: Nonsteroid anti-inflammatory agent (limited as a major point of the article, with subheadings adverse drug reaction or drug toxicity applied to the drug term)

AND

(The following Embase thesaurus terms were used and were limited to the major point of the article with the following subheadings applied of etiology OR side effects:

Stroke, Heart arrest, heart infarction, heart muscle ischemia, brain embolism, thrombosis, brain ischemia)

Dr. Robert Levin of DAAAP reviewed the papers identified as individual randomized controlled trials. Dr. Andrew Mosholder of DEPI2 reviewed the papers identified as epidemiological studies and meta-analyses.

Topics for Consideration

For each of the following topics for consideration, the data informing that topic is summarized for RCT data and epidemiological data based on the reviews enumerated above. Due to the large numbers of studies and trials involved, findings are summarized and some examples are provided.

Product-specific risk

RCT data

Individual studies

The individual RCTs identified by the literature were primarily reanalyses or final analyses of RCTs, the results of which had been previously published (e.g., APPROVE, EDGE II, APC, PreSAP).

The final analysis of the "Adenomatous Polyp Prevention on Vioxx" (APPROVe) trial demonstrated an increased risk of the Antiplatelet Trialists' Collaboration (APTC) composite endpoint (non-fatal MI, non-

fatal stroke, vascular death) with rofecoxib compared to placebo.[4] An analysis of the CV events in the "Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime (VICTOR) Trial" showed a similar increase in the APTC composite endpoint in the rofecoxib arm compared to the placebo arm.[5] In contrast, a study of the CV events that occurred during a study of rofecoxib for prostate cancer prevention showed similar rates of adjudicated CV thrombotic events in the rofecoxib and placebo arms.[6]

In a combined analysis of two studies of celecoxib for the prevention of colorectal adenomas (Adenoma Prevention with Celecoxib [APC] trial and Prevention of Spontaneous Adenomatous Polyps [PreSAP]), there was an increased risk for the composite endpoint of non-fatal MI, non-fatal stroke, vascular death, and heart failure with celecoxib compared to placebo.[7] This increased risk was observed for the 200mg twice daily and 400mg twice daily dose groups, but not for the 400mg daily dose group. A study of etoricoxib vs. diclofenac ("EDGE II") assessing gastrointestinal tolerability demonstrated similar rates of adjudicated cardiovascular events.[8]

CNT Meta-analysis

Before providing the results from the CNT meta-analysis (MA) that inform product-specific risk, we will provide some background information about the MA. The MA was originally conducted using only trial-level data and was published in the British Medical Journal in 2006.[9] It included data from 138 randomized controlled trials of COX-2 selective NSAIDs (coxibs) or nonselective NSAIDs (traditional or tNSAIDs) and demonstrated an increase in cardiovascular events, particularly myocardial infarction (MI), with use of coxibs and of higher dosages of diclofenac and ibuprofen, though not naproxen. To address limitations of the trial-level meta-analysis, the researchers undertook the patient-level meta-analysis.

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[4] Baron JA, Sandler RS, Bresalier RS, et al. Cardiovascular events associated with rofecoxib: final analysis of the APPROVe trial. *Lancet* 2008; 372(9651):1756-64.

[5] Kerr DJ, Dunn JA, Langman MJ, et. al.. Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. *NEJM* 2007; 357(4):360-9.

[6] van Adelsberg J, Gann P, Ko AT, et al. The VIOXX in prostate cancer prevention study: cardiovascular events observed in the rofecoxib 25 mg and placebo treatment groups. *Curr Med Res Opin* 2007; 23(9):2063-70.

[7] Solomon SD, Pfeffer MA, McMurray JJ, et al.. Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. *Circulation* 2006; 114(10):1028-35.

[8] Krueger K, Lino L, Dore R, et al. Gastrointestinal tolerability of etoricoxib in rheumatoid arthritis patients: results of the etoricoxib vs diclofenac sodium gastrointestinal tolerability and effectiveness trial (EDGE-II). *Ann Rheum Dis* 2008; 67(3):315-22.

[9] Kearney PM, Baigent C, Godwin J, et al. Do selective cyclo-oxygenase inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006; 332:1302–1308.

Funding for the project was provided by the UK Medical Research Council and the British Heart Foundation. Pfizer, Merck, Novartis and GSK provided patient-level data for this project, but not funding. The National Cancer Institute and the European Organization for Research and Treatment of Cancer also provided individual patient data from clinical trials they had sponsored.

RCTs of at least four weeks using the following trial designs were eligible for inclusion: coxib vs. tNSAID, coxib vs. placebo, coxib vs. coxib, tNSAID vs. placebo, dose comparisons of a coxib, or dose comparisons of a tNSAID. Exposure was defined by the subject's randomized treatment, and the analysis used an intent-to-treat strategy. The patient's first outcome, if any, was analyzed. Table 1 lists the principal outcomes.

Table 1. Outcomes included in the CNT MA (from Dr. Mosholder's CNT MA review, p. 4).

Outcome (*= primary)	**Definition**
Major vascular event* ^	Nonfatal MI, nonfatal stroke, vascular death
Major coronary event	Nonfatal MI, death from coronary disease
Stroke	Neurological deficit with cerebrovascular cause lasting > 24 hours
Hospitalization for heart failure	Hospitalization for heart failure or pulmonary edema
Upper GI complication*	Bleed, perforation, obstruction
Symptomatic upper GI event	Symptomatic ulcer, upper GI complication
Cause of death	Vascular, non-vascular, unknown

^The "Major Vascular event" outcome is the same as the Antiplatelet Trialists' Collaboration composite outcome of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death.

Table 2 below (Table 1 in Dr. Andraca-Carrera's review) shows the data sources for the 2013 MA compared to the 2006 MA, and indicates what proportion of the data in the 2013 MA was available at the patient level.

Table 2. Data sources for the 2006 and 2013 meta-analyses

		Trials with available data	Person Years	PY from Individual Patients' Data	Vascular events	
					COX 2	Comparator
2006	coxibs vs. placebo	121	31129	-	216	112
	coxibs vs. tNSAIDs	91	56585	-	340	211
2013	coxibs vs. placebo	184	52628	88%	307	175
	coxibs vs. diclofenac	33*	90644*	99%	386*	378*
	coxibs vs. ibuprofen	22*	11668*	99%	43*	41*
	coxibs vs. naproxen	48*	31633*	95%	167*	88*
	tNSAIDs vs. placebo	158	16305	49%	NA	NA

*Some trials may have included a coxib and more than one tNSAIDs treatment arm and therefore may have been counted in multiple rows on this table.

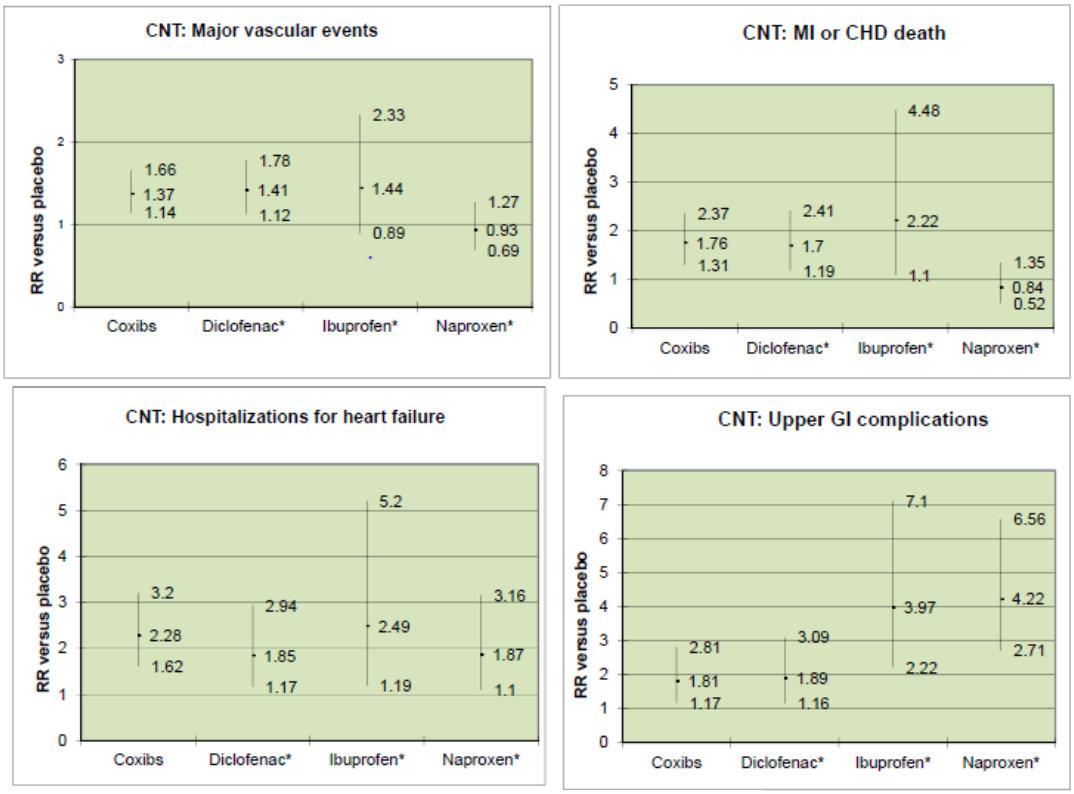
As shown in the table, most of the data from the coxib[10] trials were available at the patient level, whereas only half of the data from trials comparing tNSAIDs to placebo were available at the patient level. The rate ratios comparing coxibs to placebo or tNSAIDs for events of interest were estimated from direct comparisons. However, rate ratios comparing tNSAIDs versus placebo were estimated through a combination of trials with a direct comparison of tNSAIDs versus placebo plus indirect comparisons based on randomized trials of coxibs versus placebo and coxibs versus tNSAIDs. The statistical reviewer, Dr. Andraca-Carrera, judged the methodology used to conduct the indirect comparisons between tNSAIDs and placebo to have reasonably met the necessary conditions to be considered valid.[11] However, he pointed out that this is a subjective assessment and that the indirect comparisons should be considered somewhat less reliable than the direct comparisons.

The key findings of the MA are depicted in the "Forest plots" that follow below in Figure 1. For the outcomes "major vascular events" and "MI or CHD death," diclofenac and ibuprofen had an increased risk similar to that observed with the coxibs. Naproxen did not demonstrate an elevated risk for these outcomes. All the tNSAIDs evaluated had a similarly increased risk of hospitalization for heart failure as the coxibs. With regard to upper GI complications, all products evaluated showed at least some elevation of risk. The coxibs and diclofenac had somewhat lower rate ratio point estimates than ibuprofen and naproxen; however, all the confidence intervals overlapped. Neither the coxibs nor the tNSAIDs demonstrated an increased risk of non-fatal stroke.

[10] The "coxib" group includes celecoxib, etoricoxib, lumiracoxib, rofecoxib, valdecoxib, and GSK's compound GW403681.

[11] See Sections 4-"Statistical Methodology" and 6-"Discussion" of Dr. Andraca-Carrera's review for a more detailed discussion of the potential impact of 25% of the RCTs having studied different indications (familial polyposis, Alzheimer's disease) than the other 75% (osteoarthritis, rheumatoid arthritis) on the interpretability of the indirect comparisons.

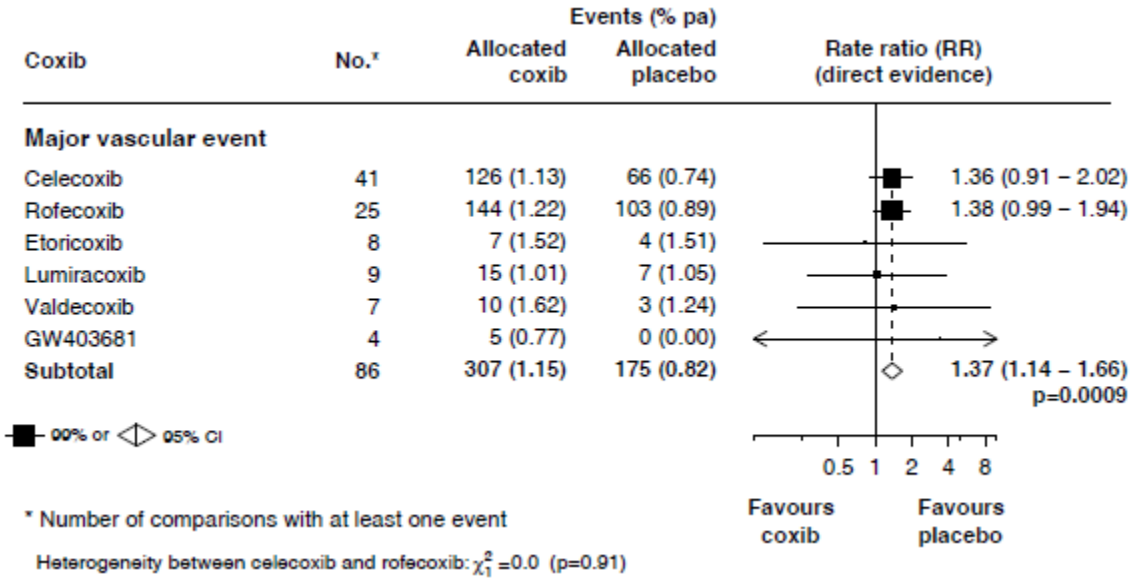
Figure 1. Rate ratios and 95% confidence intervals for main outcomes evaluated in the CNT MA (from Dr. Mosholder's CNT MA review, p. 10). (*Rate ratio calculated using indirect comparison)



*Rate ratio calculated using indirect comparison

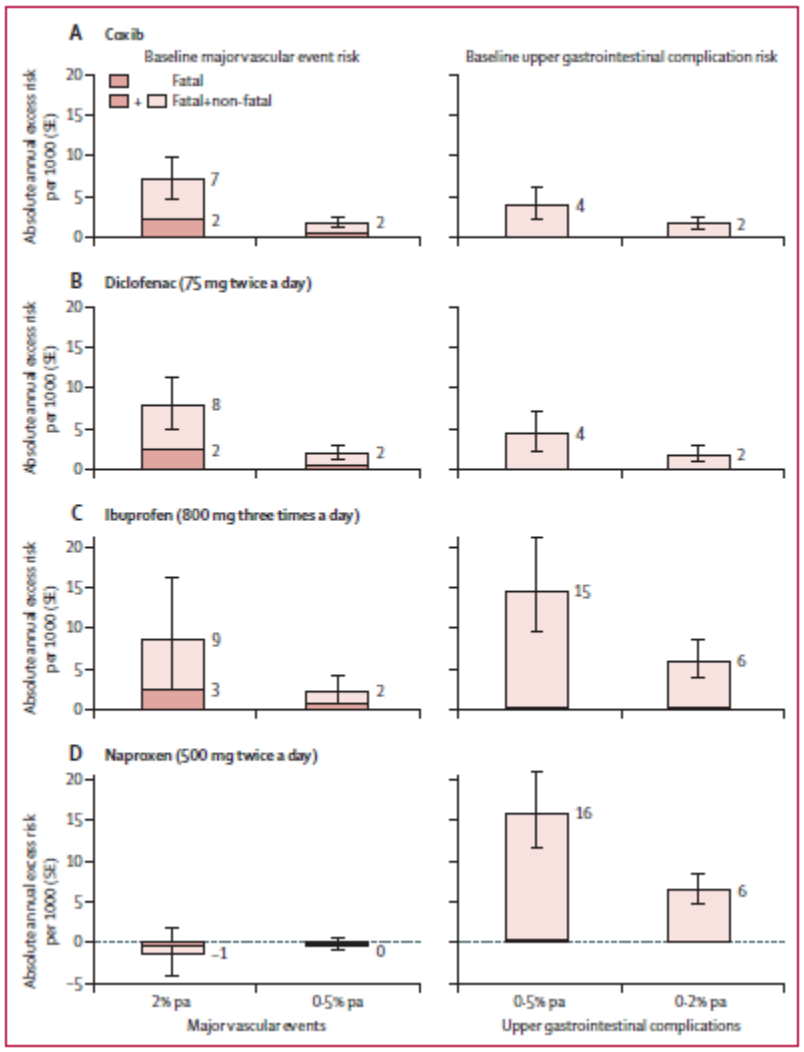
In an analysis of the individual coxibs, celecoxib and rofecoxib accounted for 88% of the major vascular events amongh the six coxibs studied. The following Forest plot demonstrates a similar increase in risk of major vascular events for celecoxib and rofecoxib. The other coxibs had too few events to make a determination about their risk of major vascular events.

Figure 2. Effect of coxib therapy on major vascular events by type of coxib (Webfigure 14 from the CNT Supplementary Appendix)



In addition to rate ratios, the CNT investigators also estimated incidence rate differences (NSAID incidence rate minus placebo incidence rate) for major vascular events and upper GI complications. Excess risks per 1000 person years (pyrs) of treatment were estimated by applying the rate ratios to hypothetical patient populations with high or low baseline rates of the events of interest. Numbers of either type of event expected to be fatal were also estimated. The analysis was predicated on the assumption that rate ratios for the outcomes are consistent across different levels of baseline risk. The results are shown in the Figure 3 below (Figure 5 in the paper). The figure provides another way to visualize the CV and GI risks for the coxibs and tNSAIDs studied.

Figure 3. Annual absolute effects per 1000 of coxibs and tNSAIDs at different baseline risks of major vascular events and upper gastronintestinal complications.



For each category of drug (coxib, diclofenac, ibuprofen, and naproxen), the predicted annual absolute risks of major vascular events (±1 SE) are shown (left) for patients with predicted risk of 2·0% or 0·5% per annum of a major vascular event. For comparison, predicted annual absolute risks of upper gastrointestinal complications (±1 SE) are shown for patients with predicted risks of 0·5% or 0·2% per annum (right). Absolute annual risks for placebo-allocated patients are assumed to be those of a hypothetical patient after all appropriate forms of prophylactic treatment (eg, antihypertensive therapy, statin therapy, proton-pump inhibitors) have been instituted.

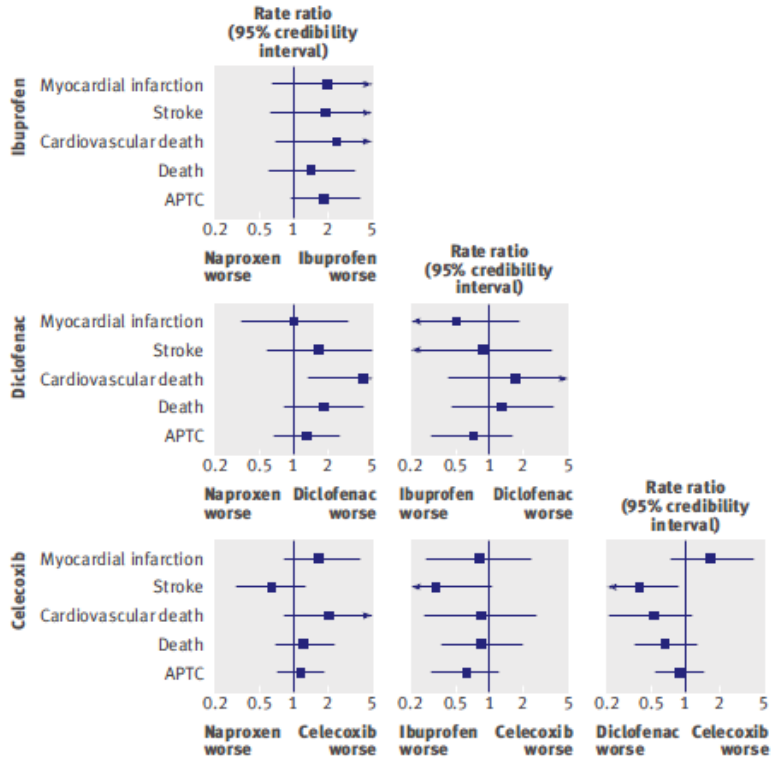
Other meta-analysis

Trelle et al. published a MA that included only large scale RCTs with at least two arms of at least 100 pyrs of follow-up; 31 RCTs studying seven drugs met these criteria and were included in the MA.[12] The

[12] Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011; 342:c7086.

prespecified primary outcome was fatal or non-fatal MI. They also evaluated the APTC composite outcome that was the same as the CNT "major vascular event" outcome. A Bayesian random effects model was used which preserved the randomized treatment comparisons in trials. In Figure 4 below, a portion of Trelle et al.'s Figure 3 that shows the estimates of rate ratios for all possible comparisons for drugs currently marketed in the US is shown below. Consistent with the CNT MA, naproxen appears to have a lower CV thrombotic risk than the other nonselective NSAIDs.

Figure 4. Rate ratios (and 95% credibility intervals) for the endpoints considered for all possible comparisons for drugs currently marketed in the US



Epidemiological data

Since 2005, dozens of epidemiological studies have been conducted in a variety of insurance claims databases, national registries, and integrated healthcare systems to evaluate the CV thrombotic risk of NSAIDs. The reader is referred to Table 4 (p. 13) and the Appendix table (p. 36) of Dr. Mosholder's review of the epidemiological studies for additional detail of the product-specific risk findings.

Several publications have used meta-analytic methods on these observational studies to summarize their findings with regard to product-specific risk. Although meta-analyses of observational studies are fraught with methodological concerns regarding pooling of studies with dissimilar study designs, populations, and approaches to confounder adjustment, the findings below are reported to provide a full picture of the studies that have been conducted to evaluate CV thrombotic risk with the NSAIDs.

In 2011, McGettigan and Henry published the most comprehensive meta-analysis of observational studies of cardiovascular risk with NSAIDs[13] to date (51 studies) that updated an earlier version[14] from 2006 (23 studies). Eligible studies had a case-control or cohort design, reported outcomes of cardiovascular events (predominantly MI) with coxib, tNSAID use, or both, and were compared with nonuse/remote use of the drugs as the reference exposure. The overall results for individual drugs were summarized across studies as pooled RR estimates with 95% confidence intervals (CIs). The summary risk estimate was greatest for etoricoxib and least for valdecoxib; however, the across-drug comparisons were confounded by study type: etoricoxib data were all from case-control studies and valdecoxib data all from cohort studies. Considering only compounds included in at least 10 studies, they found that rofecoxib (summary RR 1.45 [95%CI: 1.33, 1.58]) and diclofenac (summary RR 1.40 [95%CI: 1.27, 1.55]) had the highest pooled relative risk estimates for cardiovascular events, and naproxen the lowest (summary RR 1.09 [95%CI: 1.02, 1.16]).

An earlier meta-analysis of observational data conducted by Hernandez-Diaz et al. included 16 studies and focused on the outcome of MI.[15] To be included in the analysis, studies had to have a case-control or cohort design evaluating the relationship between tNSAID or coxib use and myocardial infarction, and provide either an estimate or enough data to estimate a relative risk comparing NSAID users with nonusers. As seen in Table 3 below, naproxen and celecoxib were not associated with an increased risk of MI, ibuprofen may have been associated with a small increased risk, and rofecoxib and diclofenac were associated with larger increases in risk.

Table 3. Summary RRs (and 95% confidence intervals) for frequently studied COX-2 selective and non-selective NSAIDs

Compound	No. of studies	Summary RR	95% CI
Naproxen	11	0.98	0.92-1.05
Ibuprofen	8	1.07	1.02-1.12
Celecoxib	8	0.96	0.90-1.02
Rofecoxib	8	1.26	1.17-1.36
Diclofenac	4	1.44	1.32-1.56

[13] McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med* 2011; e1001098. Epub 2011 Sep 27.

[14] McGettigan P, Henry D. Cardiovascular risk and inhibition of cylcooxygenase: a systematic review of the observational studies of selective and non-selective inhibitors of cyclooxygenase-2. *JAMA* 2006; 296: 1633–1644.

[15] Hernandez-Diaz S, Varas-Lorenzo C, Garcia Rodriguez LA. Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. *Basic Clin Pharmacol Toxicol* 2006;98(3):266-74.

Time-to-event for cardiovascular thrombotic risk

RCT data

Individual studies

In the individual studies, there were limited data to assess an early hazard. The APPROVe trial findings suggested the hazard ratio for the APTC endpoint was stable over time.[4]

Meta-analysis

The CNT MA looked at time windows of six month periods. Within that framework, the analysis did not detect an early hazard for major vascular events, although it did detect an early hazard for GI events.

Epidemiological data

Dr. Mosholder's review of epidemiological studies described several studies that showed that CV thrombotic risk with NSAIDs occurs without a latency period (p.7). Seven studies found increased CV thrombotic risk with exposures of less than one month. These findings are supported by the early risk of CV thrombotic events observed in the RCT of valdecoxib/parecoxib in the post-CABG period.[16] However, he also identified several studies that did not show an early risk of CV thrombotic events. Dr. Mosholder noted that there were differing contours to the hazard function across studies, so there may be different mechanisms underlying increased CV thrombotic risk operating at different times during the course of NSAID therapy. Some examples from various studies follow below.

Helin-Samivaara et al. published a case-control study on NSAID use and the risk of hospitalization for first MI in the general population of Finland.[17] The increased risk of first MI was present from the earliest time period (1-14 days) and persisted over the subsequent treatment periods out to six months.

Table 4. Risk of first time MI among current users of NSAIDs stratified by the duration of continuous therapy (in days)

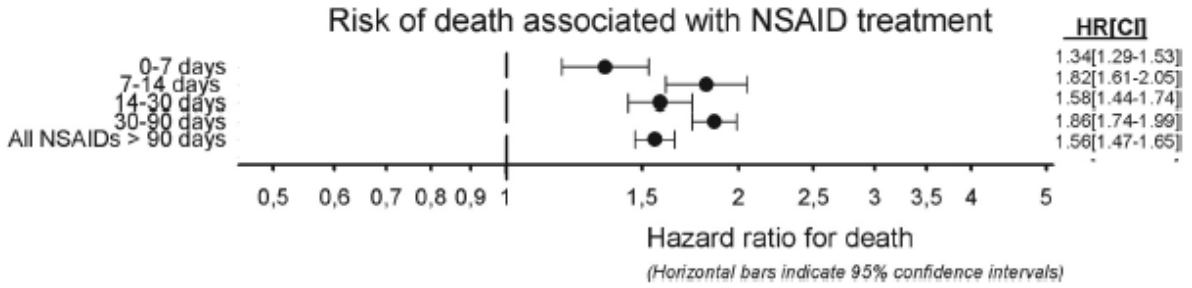
	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Non-users	20 645	92 524	1.00 (Reference)	1.00 (Reference)
Any NSAIDs				
1–14	542	1 509	1.55 (1.39–1.73)	1.39 (1.23–1.58)
15–30	436	1 344	1.37 (1.22–1.54)	1.22 (1.06–1.40)
31–90	670	1 807	1.43 (1.29–1.58)	1.25 (1.11–1.41)
91–180	631	1 551	1.74 (1.57–1.93)	1.54 (1.36–1.74)

[16] Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *NEJM* 2005;352:1081-91

[17] Helin-Salmivaara A, Virtanen A, Vesalainen R, et al. NSAID use and the risk of hospitalization for first myocardial infarction in the general population: A nationwide case-control study from Finland. *Eur Heart J* 2006; 27(14):1657-63.

Some of the studies that have demonstrated an early CV thrombotic risk for NSAIDs have focused on populations with a history of MI or other serious cardiovascular events (e.g., cardiac revascularization, unstable angina). Observational studies conducted in the Danish National Registry such as the one by Schjerning-Olsen et al. mentioned above have demonstrated that patients prescribed NSAIDs in the post-MI period are at increased risk of reinfarction, cardiovascular-related death, and all-cause mortality beginning in the first week of treatment.[2] Figure 5 below is an excerpt of Figure 6 from that paper that addresses time to event for death or reinfarction by duration of NSAID treatment.

Figure 5. Risk of death/reinfarction by duration of NSAID treatment (all NSAIDs combined)



Ray et al. published a study[18] that evaluated the time to new cardiovascular thrombotic events (MI, coronary death) in a different population with underlying cardiovascular disease. The study included 48,566 patients with recent hospitalization for serious coronary heart disease (MI, revascularization, or unstable angina) from three cohorts (Tennessee Medicaid, Saskatchewan, and the UK General Practice Research Database [GPRD]). An early risk was seen with use of ibuprofen, diclofenac, celecoxib, and rofecoxib for less than 90 days; naproxen use for that period did not demonstrate an increased risk.

[18] Ray WA, Varas-Lorenzo C, Chung CP, et al. Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. *Circ Cardiovasc Qual Outcomes* 2009; 2:155-63.

Figure 6. Time to MI/coronary death in cohort with recent hospitalization for serious CVD

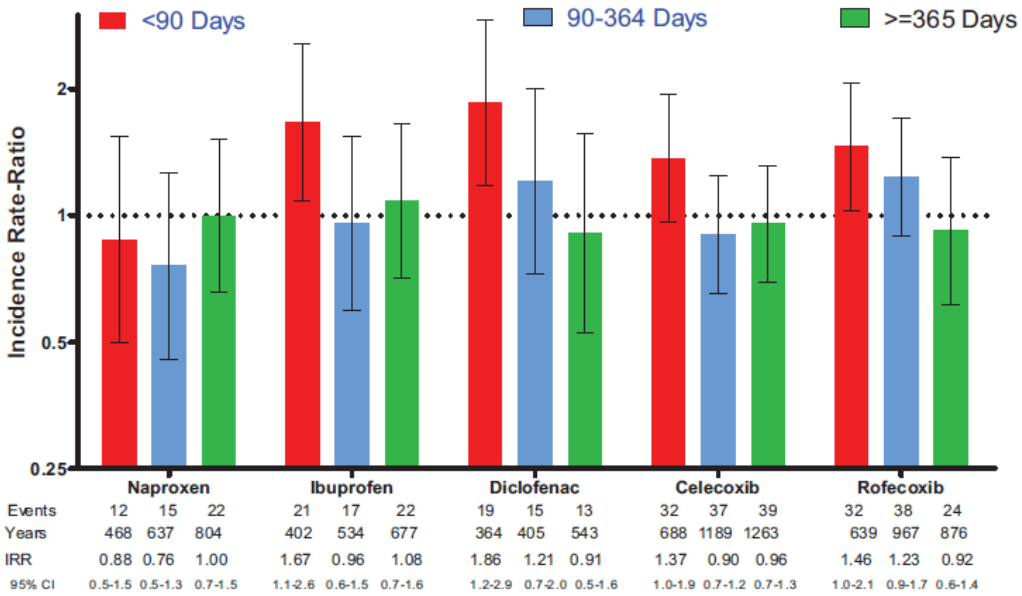


Figure. Occurrence of coronary heart disease by total duration of NSAID current use. Reference category is nonuse of any NSAID.

Vulnerable populations

RCT data

Individual studies

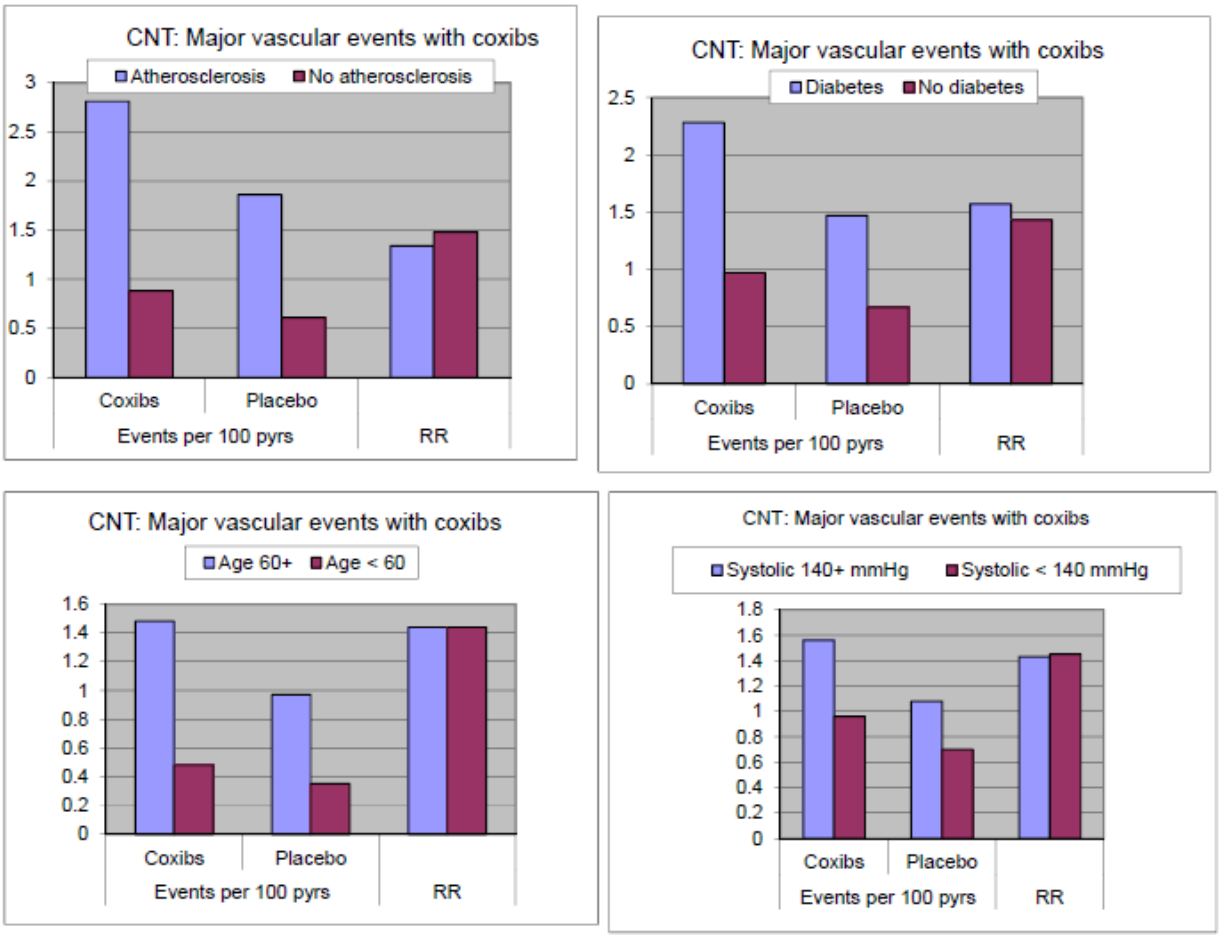
The combined analysis of CV events in the PreSAP and APC trials considered the impact of low dose ASA use and history of CV events. Although the absolute incidences of events were higher in the groups taking low dose ASA or with a history of CV events, the hazard ratio for the composite CV outcome did not differ importantly between the higher and lower risk groups.[7] In the APPROVe trial, there were some high risk groups (e.g., patients with diabetes) that appeared to have a higher risk of the APTC composite outcome with rofecoxib than those without the risk factor, but this pattern was not observed consistently (e.g. those with hypertension, current smokers).[4]

Meta-Analysis

One of the strengths of the CNT MA was that the analysis was able to assess the effect of NSAID therapy on the outcomes stratified by baseline characteristics (see Webfigures 2-11 in the CNT MA Supplementary Appendix). These analyses showed that point estimates for the major vascular event incidence rates were generally higher in subgroups of patients with specific cardiovascular risk factors, for both NSAID-treated and placebo patients, as would be expected; however, the rate ratios for NSAID:placebo were generally similar whether patients had that specific risk factor or not. A few examples of this phenomenon are shown below in Figure 7 (from Dr. Mosholder's review of the

epidemiological studies, p. 11; data for the figure are drawn from Webfigure 2 of the CNT MA Supplementary Appendix).

Figure 7. Comparison of rates of major vascular events between coxib and placebo arms, by selected baseline characteristics

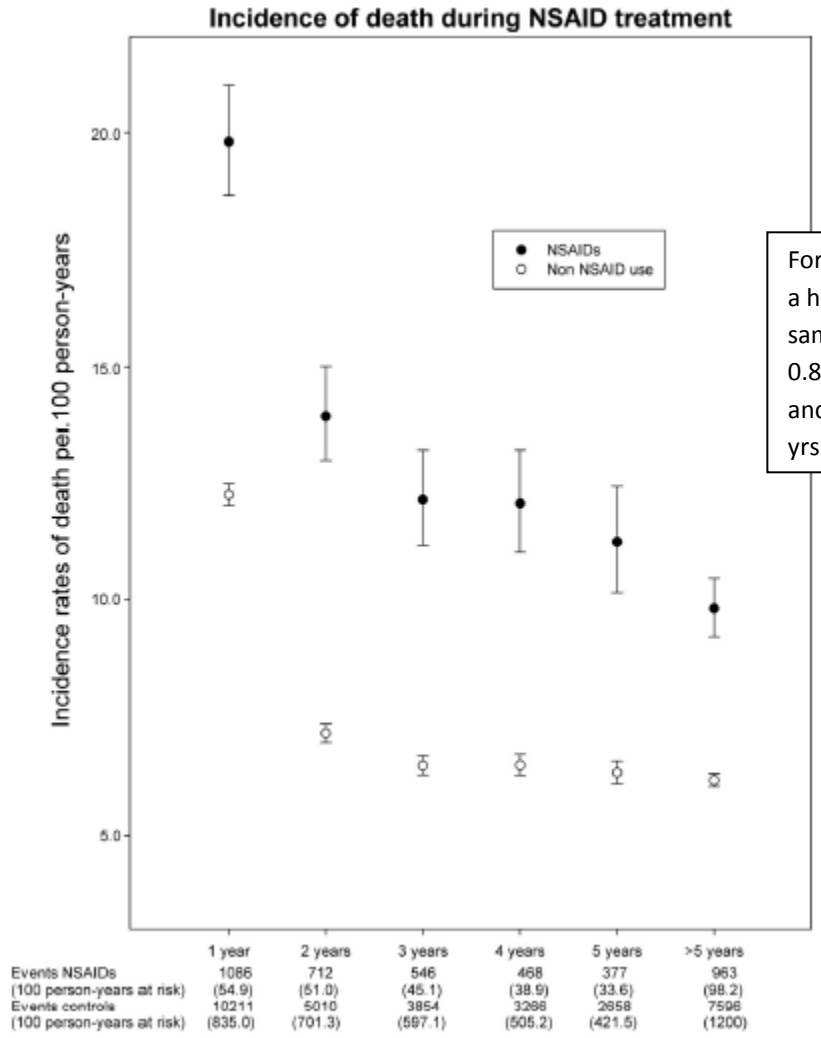


Epidemiological data

Epidemiological studies have sought to better define the populations in which increased CV thrombotic risk with NSAIDs occurs. Table 2 (pp. 9-10) of Dr. Mosholder's review of the epidemiological studies summarizes the findings of 25 studies that included assessment of risk in potentially vulnerable populations (e.g. post-MI patients, patients with CVD risk factors, older age groups). Based on this review, Dr. Mosholder concluded that "vulnerable patient populations often show a higher attributable risk of cardiovascular events with NSAID use compared to the general population, though their relative risk may not differ much from lower risk populations."

Another study from the Danish National Registry conducted by Schjerning-Olsen et al. assessed the risk of death by year following first MI, stratified by NSAID use.[19] The risk of death was highest in the first year post-MI as would be expected, and though it declined subsequently, the risk in NSAID users remained elevated over the subsequent 4 years.

Figure 8. Death rates per 100 person-years during treatment with NSAIDs by year post MI, Danish national health data



For comparison, the death rate in a healthy population from the same Danish national registry was 0.8/ 100 p-yrs in non-NSAID users and ranged from 0.9 – 5.1/ 100 p-yrs in NSAID users (Fosbol 2009)

Subsequent to this study, the investigators who conducted the studies of the Danish national healthcare database added a refinement to previous analyses by specifically examining cardiovascular deaths,

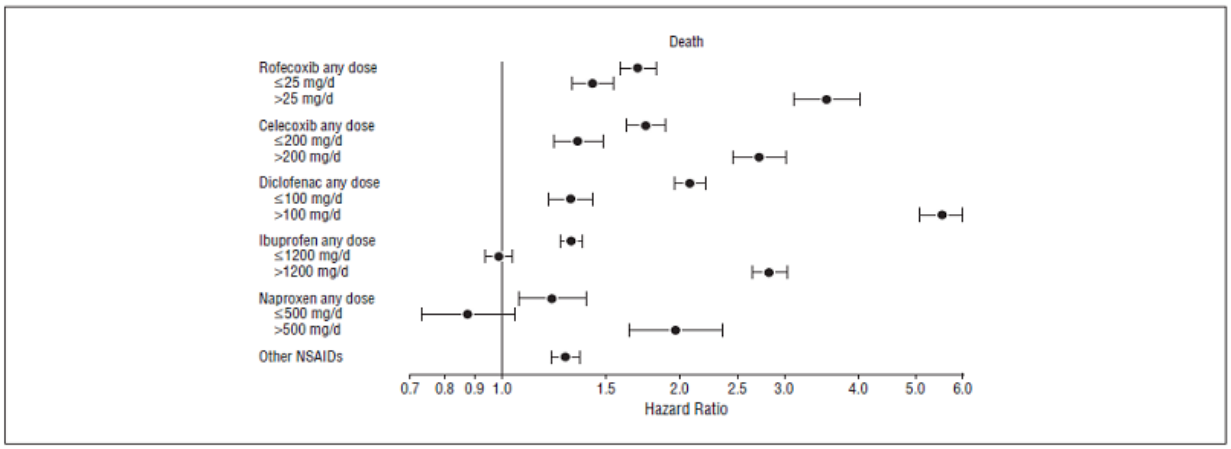
[19] Schjerning Olsen AM, Fosbøl EL, Lindhardsen J, et al. Long-Term Cardiovascular Risk of NSAID Use According to Time Passed After First-Time Myocardial Infarction: A Nationwide Cohort Study. *Circulation* 2012; 126(16):1955-63.

rather than all-cause mortality, among NSAID users with a past MI. In this latest study there was one excess cardiovascular death per 48 person-years of NSAID use.[20]

A study of the impact of NSAID use in a different vulnerable population also measured the excess incidence of cardiovascular death. Bavry et al. assessed the incidence of adjudicated CV events within a cohort of patients with hypertension and clinically stable CVD participating in a controlled trial of antihypertensive drugs.[21] Patients who used NSAIDs chronically had a more than 2-fold increase in cardiovascular mortality (adj. HR 2.26 [95% CI: 1.70-3.01]) compared to patients who used NSAIDs either intermittently or not at all; based on the unadjusted event rates, there was one additional cardiovascular death per 100 person-years of NSAID use.

Another vulnerable population studied in the Danish National Registry was patients who survived their first hospitalization for heart failure.[22] As seen in Figure 9 below, patients with heart failure had an increased risk of death following use of any dose of rofecoxib, celecoxib, or diclofenac; and after high doses of ibuprofen or naproxen.

Figure 9. Hazard ratios for death associated with use of NSAIDs in patients with chronic heart failure



Some epidemiological studies have suggested that risk is not limited to vulnerable patient populations such as those with underlying CVD risk factors or CVD. Risks in absolute terms are considerably higher for vulnerable patients (e.g., post-MI), but NSAID use has also been shown to increase CV events among

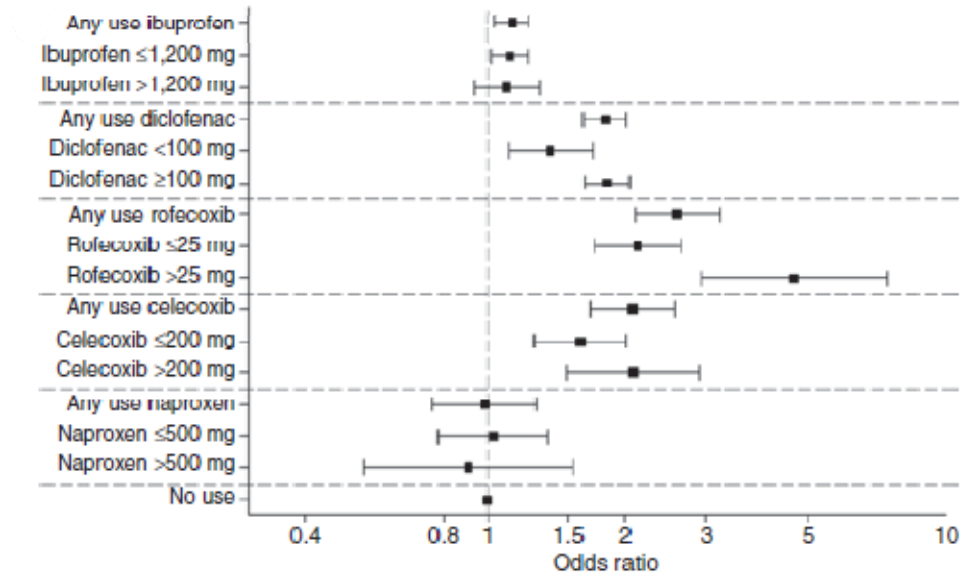
[20] Olsen AM, Fosbøl EL, Lindhardsen J, et al. Cause-specific cardiovascular risk associated with nonsteroidal anti-inflammatory drugs among myocardial infarction patients--a nationwide study. PLoS One. 2013;8(1):e54309.

[21] Bavry AA, Khaliq A, Gong Y, et al. Harmful effects of NSAIDs among patients with hypertension and coronary artery disease. Am J Med. 2011;124:614-20.

[22] Gislason GH, Rasmussen JN, Abildstrom SZ, et al.. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure. *Arch Intern Med* 2009; 169(2):141-9.

apparently healthy patients. Results of a case-crossover analysis[23] of NSAID use and death or MI in apparently healthy patients from the Danish National Registry are depicted in Figure 10 below.

Figure 10. Odds ratios, derived from the case-crossover analysis, for the composite end point of death and myocardial infarction associated with exposure to NSAIDs in a study population of 1,028,437 individuals characterized by no prior concomitant pharmacotherapy and no comorbidity



Dose-response relationship for cardiovascular thrombotic risk

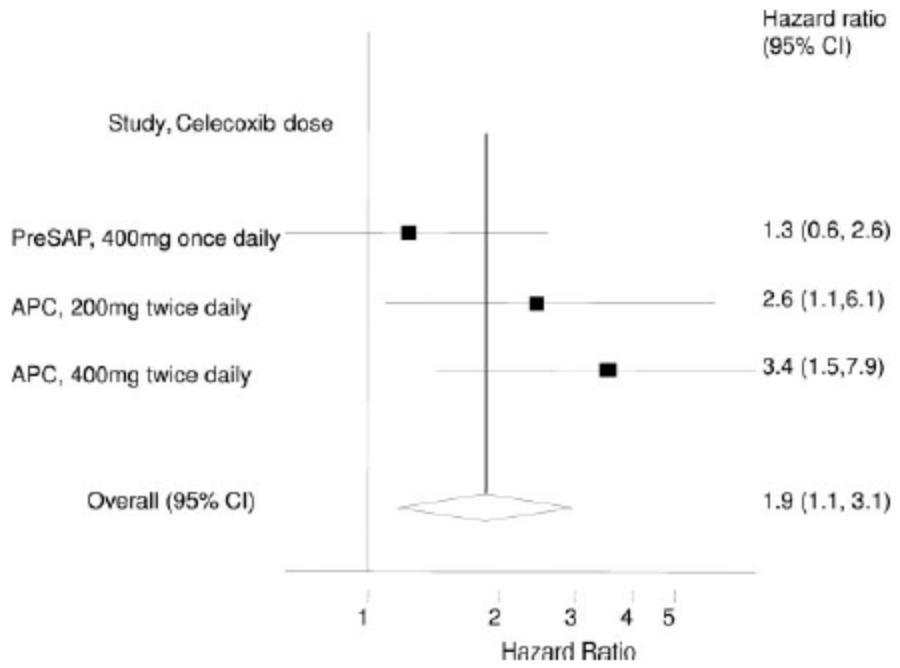
RCT data

Individual RCTs

In the APC trial, the hazard ratios for various combinations of CV outcomes were numerically higher in the celecoxib 400mg twice daily group compared to the 200mg twice daily group and placebo group. The following figure shows the hazard ratios for each of the celecoxib regimens for the primary composite CV outcome (CV death, MI, stroke, and heart failure).[7]

[23] Fosbol EL, Gislason GH, Jacobsen S, et al. Risk of myocardial infarction and death associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) among healthy individuals: a nationwide cohort study. *Clin Pharmacol Ther* 2009; 85:190-7.

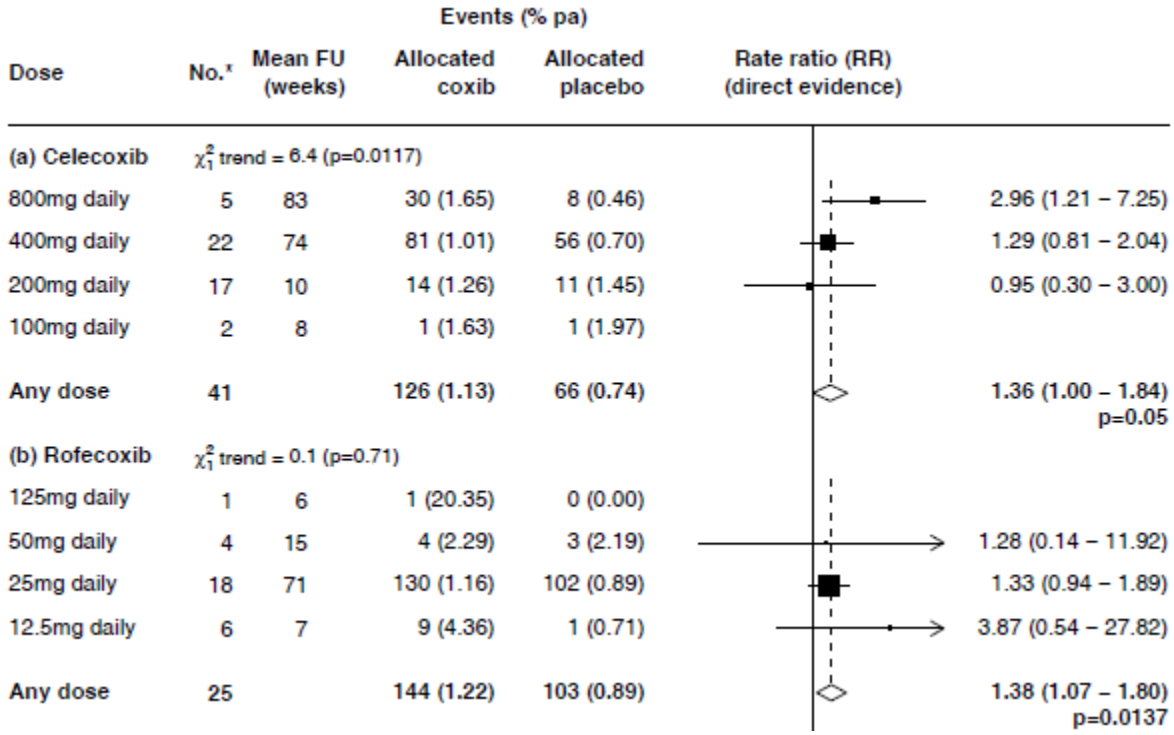
Figure 11. Combined analysis using individual data from each dosing regimen in the PreSAP and APC studies showing HR for the composite outcome of cardiovascular death, myocardial infarction, stroke, or heart failure



Meta-analysis

The CNT MA explored a dose response effect for major vascular events with the coxibs. Figure 12 below depicts a dose-response effect for celecoxib vs. placebo. A dose-response effect for rofecoxib vs. placebo was not observed; however, there were few events and little use at doses other than 25mg daily, so it may not have been possible to discern such an effect in this cohort of studies.

Figure 12. Effect of coxib therapy on major vascular events by type of coxib (CNT MA Supplementary Appendix Webfigure 15)



Epidemiological data

Dr. Mosholder focused part of his evaluation of dose-response relationship with NSAID products and CV thrombotic risk on NSAIDs available "over the counter" (OTC) in the US as the findings of CV thrombotic risk with such products may impact OTC product labeling or availability. No data were available for ketoprofen at OTC doses, and it will not be discussed further here.

Table 9 (p. 17) of Dr. Mosholder's review of the epidemiological studies summarizes the dose-related findings with ibuprofen from ten studies that generally compared risks above and below the threshold of 1200mg/day. Although these studies presented somewhat of a mixed picture, overall Dr. Mosholder concluded that OTC doses of ibuprofen can be associated with an increased risk of CV thrombotic events, and the risk appears dose-related (with higher doses having greater risk). As noted by Dr. Mosholder, because ibuprofen interferes with the beneficial anti-thrombotic effect of low dose aspirin (ASA),[24,25] populations of patients with CVD or risk factors for CVD that have a substantial prevalence of

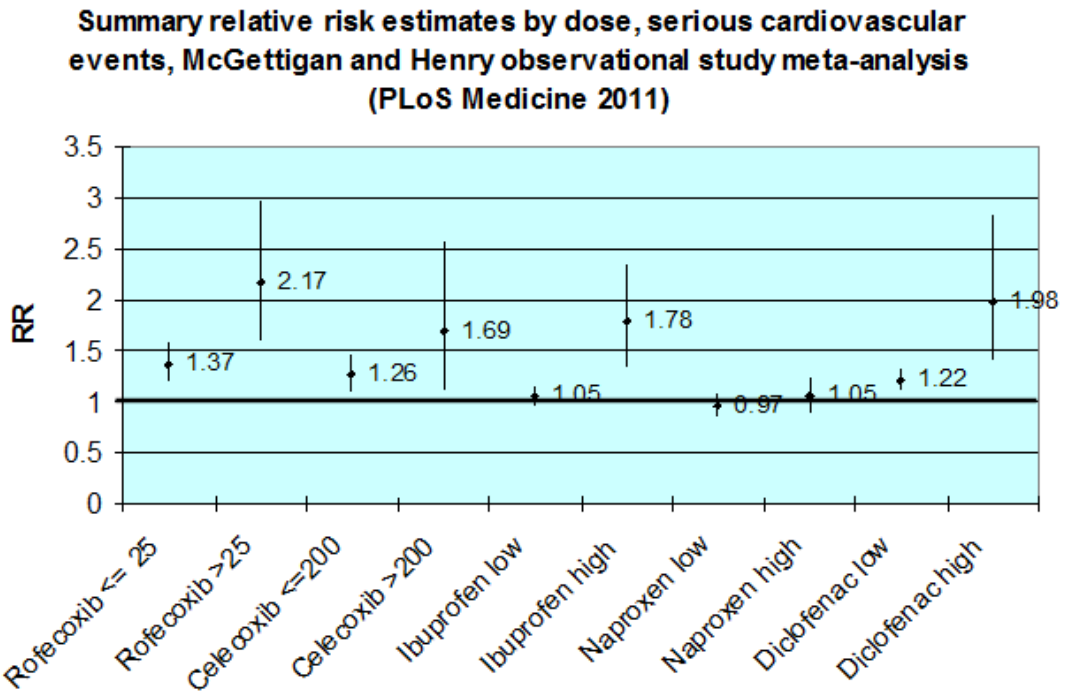
[24] Catella-Lawson F, Reilly MP, Kapoor SC et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. NEJM 2001;345:1809-17.

[25] Food and Drug Administration Science Paper, 9/8/2006. Concomitant Use of Ibuprofen and Aspirin: Potential for Attenuation of the Anti-Platelet Effect of Aspirin. Accessed 10-16-2012 at

low dose ASA use may show an increased risk of CV thrombotic events with concomitant use of ibuprofen.

The large observational study MA[13] by McGettigan and Henry discussed above also evaluated dose response for several NSAIDs. As shown in Figure 13 below, high doses of ibuprofen were associated with an elevated risk of serious cardiovascular events but low doses were not.

Figure 13. Dose-response analysis for NSAIDs from McGettigan and Henry observational study MA



As can be seen in the figure above, neither low dose naproxen nor high dose naproxen was associated with an increased risk of serious cardiovascular events (based on ten studies). Dr. Mosholder's review of the epidemiological studies identified five studies that considered OTC doses of naproxen and found mixed results on the risk of CV thrombotic events.

Table 10 (pp. 20-21) of Dr. Mosholder's review of the epidemiological studies summarizes the subgroup of 18 studies that evaluated the data for a dose-response relationship. The overall conclusion is that the data support a dose-response relationship for CV thrombotic events with the NSAIDs. However, as Dr. Mosholder points out, observational studies are not optimal for examining a dose-response relationship because patients who are sicker may get treated with higher doses of medication (also known as confounding by indication).

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http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM161282.pdf

Stroke

Randomized controlled trials

Individual RCTs

There was limited data from the RCTs identified by the literature review regarding the risk of stroke. The APPROVe trial showed an increased hazard ratio for stroke with rofecoxib of about two-fold compared to placebo.[4]

Meta-analysis

The CNT MA did not show an increased risk of stroke for any of the NSAIDs studied; however, there were relatively few events. The investigators considered that it seemed implausible for there to be no increased risk of stroke when NSAIDs are known to increase blood pressure.

Epidemiological studies

Table 11 (pp. 24-25) of Dr. Mosholder's review of the epidemiological studies summarizes the subgroup of 12 studies that evaluated the data for stroke as an outcome. Based on this summary, it appears that as a group coxib and tNSAIDs are all associated with an increased risk of stroke, including naproxen. One study[26] that evaluated stroke associated with NSAID use in a population of Australian veterans had adequate numbers of hemorrhagic and ischemic strokes to calculate estimates of risk of both. The analysis showed higher point estimates for increased risk of hemorrhagic stroke as compared to ischemic stroke. A study from the Danish National Registry database also examined risk by type of stroke; the population was large cohort of healthy people without hospital admissions for five-years and no important prescription claims for two-years.[27] High dose ibuprofen and diclofenac were significantly associated with about a twofold increased risk of ischemic stroke, and naproxen and high dose diclofenac were significantly associated with a similar degree of increased risk of hemorrhagic stroke.

Concurrent use of aspirin

As described in Dr. Dunnmon's consultation report, the AHA scientific statement regarding use of NSAIDs[28] identified ibuprofen, but not rofecoxib or diclofenac, as capable of interfering with ASA's ability to irreversibly acetylate the platelet COX-1 enzyme, and this would likely reduce ASA's protective

[26] Caughey GE, Roughead EE, Pratt N, et al. Stroke risk and NSAIDs: an Australian population-based study. *Med J Austr* 2011; 195:525-9.

[27] Fosbøl EL, Olsen AM, Olesen JB, et al. Use of nonsteroidal anti-inflammatory drugs among healthy people and specific cerebrovascular safety. *Int J Stroke* 2012; Oct 23 [Epub].

[28] Antman EM, Bennett JS, Daugherty A, et al. Use of Nonsteroidal Antiinflammatory Drugs : An Update for Clinicians: A Scientific Statement From the American Heart Association. *Circulation* 2007; 115:1634-1642.

effect regarding CV thrombotic risk. Additional work reviewed by Dr. Dunnmon and colleagues demonstrates that naproxen in some situations (e.g., lower doses) also has the capability to reduce the protective effect of ASA on the risk of CV thrombotic events (refer to Dr. Dunnmon's consultation report, p. 16).

Randomized controlled trials

Individual RCTs

As mentioned above, use of low dose ASA in the APC and PreSAP trials did not modify the effect of celecoxib on the CV composite outcome.[7] In the APPROVe trial, non-use of low dose ASA was associated with a higher point estimate of the APTC composite outcome associated with rofecoxib use than with use of low dose ASA; however, the confidence intervals overlapped, so it was unclear whether the effects truly differed.[4]

Meta-analysis

In the CNT MA, about 20% of patients reported using ASA at randomization. In the analyses that stratified by baseline characteristics, current ASA users appeared to have a higher risk for any GI event, but ASA use did not appear to affect rate ratios for major vascular events.

Epidemiological studies

The epidemiological studies reviewed by Dr. Mosholder provide a mixed picture with regard to ASA's ability to ameliorate the increased CV thrombotic risk associated with NSAIDs (pp 21-23). As mentioned above, ibuprofen and naproxen have been identified as capable of interfering with ASA's protective effect on CV thrombotic events. The observational-study MA conducted by Hernandez Diaz et al. included a sub-analysis of relative risk for MI stratified by whether or not ASA use was allowed in a study.[15] As seen in Table 5 below, naproxen appeared to have a protective effect in studies in which ASA was not allowed.

Table 5. Summary MI relative risk estimates from observational studies stratified by ASA use.

Compound	No. of studies	Summary RR	95% CI
Naproxen—ASA allowed	9	1.03	0.96-1.10
Naproxen—no ASA use	4	0.83	0.72-0.90
Ibuprofen—ASA allowed	9	1.10	1.04-1.16
Ibuprofen—no ASA use	4	0.88	0.78-1.01

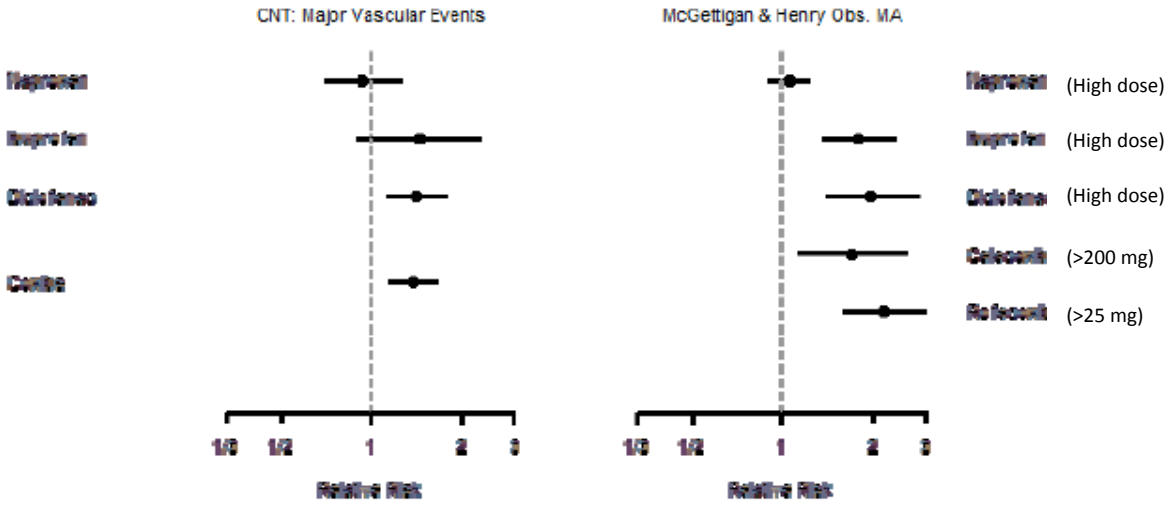
Discussion

A substantial amount of data has been published on various aspects of the relationship between NSAID use and CV thrombotic risk since the boxed warning was added to the NSAID class labeling in 2005. The data presented above assess product-specific risk, time to event, CV thrombotic risk in vulnerable populations, CV thrombotic risk at OTC doses, and the effect of concurrent ASA on CV thrombotic risk with NSAIDs.

Product-specific risk: Naproxen

Currently, the warning statement in NSAID class labeling does not distinguish differential risk across the class. However, data from the CNT MA, as well as other RCT MAs, suggest that naproxen is not associated with an increased risk of CV thrombotic events. This finding is further supported by the McGettigan and Henry observational study MA.[13]

Figure 14. Product-specific CV thrombotic risks observed in the CNT MA and in the McGettigan and Henry observational study MA



The CNT MA investigators refrained from endorsing naproxen as less risky than the other nonselective NSAIDs because they were uncertain how an interaction with ASA might manifest both at high dose (no additional benefit from ASA) and at low dose (may interfere with ASA benefit); they were uncertain whether the the apparent advantage of naproxen would hold up over time; and they noted the substantial risk of upper GI complications observed with naproxen.[3]

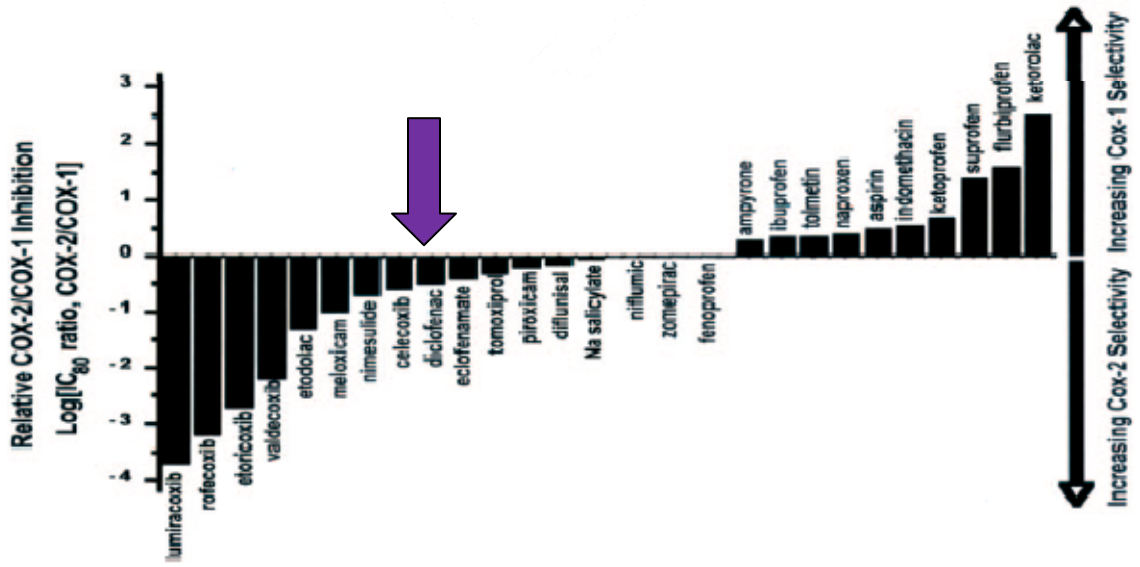
On October 18, 2012, the EMA published their assessment report on NSAIDs and CV risk[29]. With regard to naproxen they noted that it "…may be associated with a lower risk for arterial thrombotic events than Cox-2 inhibitors and other NSAIDs, but a small risk cannot be excluded."

FDA seeks the committee's opinion on whether the accumulated data support naproxen as having a lower risk for CV thrombotic events as compared to the other nonselective NSAIDs.

Product-specific risk: Commonly studied non-naproxen NSAIDs

Celecoxib, a COX-2 selective inhibitor, and ibuprofen and diclofenac, non-selective NSAIDs, are the other NSAIDs marketed in the US that have been widely studied both in RCTs and observational studies. As depicted in the figure below from Antman et al. 2005, diclofenac has COX-2 selectivity similar to celecoxib (see purple arrow).[30]

Figure 15. Relative degree of COX-1 vs COX-2 selectivity for commonly used COX-2 selective and non-selective NSAIDs



As described in the introduction, back in 2005 the EMA made the decision that COX-2 selective NSAIDs conferred increased CV thrombotic risk compared to non-selective NSAIDs, and contraindicated them in patients with ischemic heart disease and/or cerebrovascular disease (stroke), and also in patients with peripheral arterial disease. Recently, the EMA completed a reassessment of the CV thrombotic risk with

[29] Assessment report for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and cardiovascular risk (accessed December 30, 2013)
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/11/WC500134717.pdf

[30] Antman EM, DeMets D, Loscalzo J. Cyclooxygenase inhibition and cardiovascular risk. *Circulation* 2005; 112: 759-770.

diclofenac and determined that it should have the same restrictions on use as the COX-2 selective NSAIDs.[31]

At the time the boxed warning was added in 2005, FDA concluded that the increased CV thrombotic risk with the COX-2 selective NSAIDs was present with the non-selective NSAIDs as well, and the data did not allow a distinction to be made between the two groups of products. In light of the more recently available data, FDA has again assessed the evidence regarding the CV thrombotic risk associated with the non-naproxen NSAIDs from the available RCT MAs, observational study MAs, and individual epidemiological studies.

In his review of the epidemiological studies, Dr. Mosholder concluded that "To the extent that the cardiovascular risk with diclofenac is similar to that with rofecoxib, which was removed from the market [by the sponsor] for its cardiovascular risks, the risk-benefit balance for diclofenac should be re-evaluated." Subsequent to his review of the CNT MA, Dr. Mosholder modified his recommendation stating, "…the conclusion that diclofenac has a particularly unfavorable cardiovascular risk profile is now tempered by the finding that ibuprofen at a dose of 2400mg/day had a comparable risk."

FDA seeks the committee's opinion on whether the accumulated data support any of the non-naproxen NSAIDs as having a differential risk for CV thrombotic events as compared to the others.

Time to event for CV thrombotic risk

Currently the warning statement in NSAID class labeling includes the following statement: "To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible." This statement could be interpreted as short term use is without risk. Although the RCT data reviewed were not enlightening on this topic, several epidemiological studies pointed to the absence of a latency period for CV thrombotic risk.

Additionally, Dr. Dunnmon's consultation on this topic concluded thus, "Though a double-blind trial randomizing immediately post-MI patients to escalating doses of NSAIDs has not been reported in the literature that this reviewer is aware of, the results of the post-CABG NSAID-treatment study by Nussmeier et. al.[16] suggests a biologically plausible mechanism whereby the latency period for the onset of CV events could indeed be shown to be less than one week, if this phenomenon were looked for in an appropriately sized and powered clinical trial."

FDA seeks the committee's opinion on whether the accumulated data supports the conclusion that there is no latency period for increased CV thrombotic risk with NSAIDs.

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[31] New safety advice for diclofenac – CMDh endorses PRAC recommendation (28 June 2013). Accessed December 30, 2013.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001830.jsp&mid=WC0b01ac058004d5c1

Vulnerable populations

Based on the CNT MA and data from individual RCTs and observational studies, the relative increase in CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CVD or risk factors for CVD. However, patients with known CVD or risk factors had a higher absolute incidence of excess CV thrombotic events, due to their increased baseline rate.

Data from the Danish National Registry demonstrated the elevated absolute rates of CV thrombotic events and death due to such events in the post-MI and heart failure populations.

In his consultation, Dr. Dunnmon points out that patients with acute coronary syndrome may have a similar pathophysiological state to post-CABG patients because of platelet activation, and thus may experience a similar increase in risk of CV thrombotic events with NSAIDS as was observed in the post-CABG study with parecoxib and valdecoxib.[16] He points out that this risk would be moot if post-MI patients were never exposed to NSAIDs; however, NSAIDs are part of standard post-MI pericarditis pain management.

FDA seeks the committee's opinion on whether the accumulated data support any restrictions or specific warnings for those populations who are at higher absolute risk for CV thrombotic events with NSAID use (e.g., something akin to the contraindication in post-CABG patients that was based on the findings of the Nussmeier et. al.[16] study mentioned above).

Safety at "over the counter" (OTC) doses

Dr. Mosholder's review of the epidemiological studies showed that a subset of studies demonstrated some evidence of an association of ibuprofen and naproxen at OTC doses with an increase in CV thrombotic risk. However, the McGettigan and Henry observational study MA did not identify either low dose ibuprofen or naproxen as having an increased risk.[13] Observational studies may not be the most reliable setting for assessing a dose-response relationship because patients are titrated to various doses for a variety of reasons that may be related to outcome (i.e., confounding by indication).

FDA seeks the committee's opinion on whether the accumulated data related to CV thrombotic risk support any changes in the acceptability of NSAIDs as over the counter products at the currently available doses.

PRECISION trial[32]

Based on his reviews of the epidemiological studies and the CNT MA, Dr. Mosholder raised three concerns in his memorandum dated October 17, 2013 regarding whether the PRECISION trial should be continued: 1) Is the trial still capable of meeting its objective because of specific study design features? 2) Is the trial still necessary to answer the research question? 3) Is the trial still considered reasonably

[32] For additional detail, the reader is referred to the three memoranda in the briefing package that address the PRECISION trial as described in the introduction to this briefing document.

safe for the participants? Dr. Mosholder enumerated concerns regarding the study design that called into question the ability of the trial to meet its stated objectives. Dr. Mosholder also explicated results from the CNT MA and observational studies to support his conclusion that naproxen had a better safety profile for CV thrombotic events than the comparator drugs celecoxib and ibuprofen. Finally, Dr. Mosholder described results from some epidemiological studies that he concluded raise the concern that patients are being exposed to an undue risk by remaining in the PRECISION trial, and he identified regulations that would support putting the trial on "clinical hold," (i.e., requiring that the study be discontinued). Dr. Mosholder concluded with the following recommendations:

> "Sufficient grounds for a clinical hold exist for the reasons stated above. Randomization of subjects is no longer reasonable because of the recently delineated difference in CV risk among the treatments, and significant difficulties with interpretation of the results will compromise the trial's ability to meet its scientific objective.
>
> If a clinical hold is not imposed, subjects should be reconsented so that they can be informed of the findings of the Oxford CNT meta-analysis regarding the PRECISION study drugs, and can have the option of withdrawing. Subjects and investigators should also be reminded of the instructions for taking low dose ASA."

As per the DAAAP memorandum dated November 4, 2013, which has been included in this background package, we note that research and experience have demonstrated that the results of large meta-analyses of clinical trials do not always produce an answer that ultimately can be considered to be accurate. The DAAAP memorandum considers two recent examples (among others) involving tiotropium and rosiglitazone. With tiotropium, the results of a large MA were not borne out by a large RCT addressing cardiovascular safety. In the case of rosiglitazone, a large open-label RCT ("Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes [RECORD])" did not show the CV risk that was observed in the RCT MAs that had been conducted. Because of ongoing concerns about CV risk with rosiglitazone, a subsequent large RCT (Thiazolidinedione Intervention with Vitamin D Evaluation [TIDE]) was stopped in 2010. Recently a readjudication of the RECORD trial outcomes discussed at an FDA Advisory Committee meeting lessened concern about rosiglitazone CV risk. Based on this recent experience, DAAAP believes that there is reason to continue with the PRECISION trial. Regarding the trial conduct issues, DAAAP is always concerned whether a trial has been conducted properly, but this cannot be determined until after the trial has been submitted and the study conduct has been reviewed. Finally, the PRECISION trial has a data safety monitoring board that is regularly evaluating the pattern of occurrence of study endpoints to determine if the stopping rules have been met. DAAAP has not received any communications from Pfizer that such a point has been reached.

FDA seeks the committee's opinion on whether there are any changes that need to be made to the PRECISION trial to respond to the concerns that have been raised.

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/s/

JUDITH A RACOOSIN
01/10/2014

BOB A RAPPAPORT
01/10/2014

MEMORANDUM

DATE: April 6, 2005

FROM: John K. Jenkins, M.D.
Director, Office of New Drugs (OND)

and

Paul J. Seligman, M.D., M.P.H
Director, Office of Pharmacoepidemiology and Statistical Science (OPaSS)

THROUGH: Steven Galson, M.D., M.P.H.
Acting Director, Center for Drug Evaluation and Research

TO: NDA files 20-998, 21-156, 21-341, 21-042

SUBJECT: Analysis and recommendations for Agency action regarding non-steroidal anti-inflammatory drugs and cardiovascular risk

Executive Summary

Following a thorough review of the available data we have reached the following conclusions regarding currently approved COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs)[1] and the risk of adverse cardiovascular (CV) events:[2]

- The three approved COX-2 selective NSAIDs (i.e., celecoxib, rofecoxib, and valdecoxib) are associated with an increased risk of serious adverse CV events compared to placebo. The available data do not permit a rank ordering of these drugs with regard to CV risk.
- Data from large long-term controlled clinical trials that have included a comparison of COX-2 selective and non-selective NSAIDs do not clearly demonstrate that the COX-2 selective agents confer a greater risk of serious adverse CV events than non-selective NSAIDs.

[1] A list of the non-selective NSAIDs is available on http://www.fda.gov/cder/drug/infopage/cox2/default.htm.
[2] The degree of COX-2 selectivity for any given drug has not been definitively established, and there is considerable overlap in *in-vitro* COX-2 selectivity between agents that have been generally considered to be COX-2 selective (e.g., celecoxib, rofecoxib, valdecoxib, parecoxib, lumiracoxib, etoricoxib) and older NSAIDs that have been considered to be non-selective (e.g., diclofenac, ibuprofen, naproxen). For purposes of simplicity of discussion and comparisons, this document maintains the traditional separation between COX-2 selective and non-selective agents, but our use of this nomenclature should not be considered as FDA endorsement of such designations.

- Long-term placebo-controlled clinical trial data are not available to adequately assess the potential for the non-selective NSAIDs to increase the risk of serious adverse CV events.
- Pending the availability of additional long-term controlled clinical trial data, the available data are best interpreted as being consistent with a class effect of an increased risk of serious adverse CV events for COX-2 selective and non-selective NSAIDs.
- Short-term use of NSAIDs to relieve acute pain, particularly at low doses, does not appear to confer an increased risk of serious adverse CV events (with the exception of valdecoxib in hospitalized patients immediately post-operative from coronary artery bypass (CABG) surgery).
- Controlled clinical trial data are not available to rigorously evaluate whether certain patients derive greater relief of pain and inflammation from specific NSAIDs compared to others or after failing to respond to other NSAIDs.
- The three approved COX-2 selective drugs reduce the incidence of GI ulcers visualized at endoscopy compared to certain non-selective NSAIDs. Only rofecoxib has been shown to reduce the risk of serious GI bleeding compared to a non-selective NSAID (naproxen) following chronic use. The overall benefit of COX-2 selective drugs in reducing the risk of serious GI bleeding remains uncertain, as does the comparative effectiveness of COX-2 selective NSAIDs and other strategies for reducing the risk of GI bleeding following chronic NSAID use (e.g., concomitant use of a non-selective NSAID and a proton pump inhibitor).
- Valdecoxib is associated with an increased rate of serious and potentially life-threatening skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) compared to other COX-2 selective agents and is the only NSAID with a boxed warning for this adverse event in its approved package insert. In the absence of any demonstrated advantage over other NSAIDs, the overall benefit versus risk profile for valdecoxib is unfavorable for marketing.

Based on these conclusions, we recommend the following regulatory actions to further improve the safe and effective use of these drugs by prescribers, patients, and consumers:

- The agency should ask Pfizer to voluntarily withdraw Bextra (valdecoxib) from the U.S. market. In the event Pfizer does not agree to a voluntary withdrawal, the agency should initiate the formal withdrawal procedures; i.e., issuance of a Notice of Opportunity for Hearing (NOOH).
- The professional labeling for all prescription NSAIDs should be revised to include a boxed warning highlighting the potential increased risk of serious adverse CV events. The boxed warning should also include the well described NSAID class risk of serious, and often life-threatening, GI bleeding, which is currently contained in a bolded warning.
- Pending the availability of additional data, the labeling for all prescription NSAIDs should include a contraindication for use in patients immediately post-operative from CABG surgery.

- A class NSAID Medication Guide should be developed to inform patients of the potential increased risk of serious adverse CV events and the risk of serious GI bleeding.
- The labeling for non-prescription NSAIDs should be revised to include more specific information about potential CV and GI risks and information to assist consumers in the safe use of these drugs.
- The boxed warning for Celebrex (celecoxib) should specifically reference the available data that demonstrate an increased risk of serious adverse CV events and other sections of the labeling should be revised to clearly reflect these data.
- The agency should carefully review any proposal from Merck for resumption of marketing of Vioxx (rofecoxib). We recommend that such a proposal be reviewed by the FDA Drug Safety Oversight Board and an advisory committee before a final decision is reached.
- The agency should request that all sponsors of non-selective NSAIDs conduct and submit for FDA review a comprehensive review and analysis of available controlled clinical trial databases to further evaluate the potential for increased CV risk.
- The agency should work closely with sponsors and other interested stakeholders (e.g., NIH) to encourage additional long-term controlled clinical trials of non-selective NSAIDs to further evaluate the potential for increased CV risk.

Background

Vioxx (rofecoxib) was voluntarily withdrawn from the market by Merck in September 2004 following the observation of an increased risk of serious adverse CV events compared to placebo in a long-term controlled clinical trial. Subsequent to that action, reports of additional data from controlled clinical trials became available for other COX-2 selective NSAIDs that also demonstrated an increased risk of serious adverse CV events compared to placebo. These new data prompted the agency to conduct a comprehensive review of the available data and to present the issue for review at a joint meeting of FDA's Arthritis and Drug Safety and Risk Management Advisory Committees on February 16-18, 2005.

Following the joint meeting, CDER conducted a thorough internal review of the available data regarding cardiovascular (CV) safety issues for COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This memorandum summarizes the major issues considered in that review, our conclusions regarding the interpretation of the available data, and our recommendations for regulatory actions necessary to further improve the safe and effective use of these drugs by prescribers, patients, and consumers.

Participants in the CDER review included staff from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products, the Division of Over-the-Counter Drug Products, the Offices of Drug Evaluation II and V, the Office of New Drugs, the Office of Drug Safety, the Office of Biostatistics, the Office of Pharmacoepidemiology and Statistical Science, the Office of Medical Policy, the Office of Regulatory Policy, and the Office of the Center Director. Materials reviewed included the regulatory histories and the NDA and postmarketing databases of the various NSAIDs, FDA and sponsor background documents prepared for the Advisory Committee meeting, all materials and data submitted by other

stakeholders to the Advisory Committee meeting, presentations made at the Advisory Committee meeting, the discussions held by the Committee members during the meeting, and the specific votes and recommendations made by the joint Committee.

Summary of available data

The most persuasive evidence in support of an increased risk of serious adverse CV effects of the COX-2 selective NSAIDs is derived from a small number of long-term placebo- and active-controlled clinical trials in patients with arthritis or in the disease prevention setting. We will briefly summarize the available data from the long-term controlled clinical trials for the three approved and two investigational COX-2 selective agents. We will also briefly summarize the available data from long-term controlled clinical trials to assess the potential for increased CV risk for the non-selective NSAIDs. Finally, we will briefly summarize the available data from observational studies that have sought to assess the potential for increased CV risk for NSAIDs. We will focus our discussion on the combined endpoint of death from CV causes, myocardial infarction (MI), and stroke, as that is a widely accepted endpoint in assessing the benefits and risks of a drug for CV outcomes. It should be noted that the exact definitions and adjudication procedures for this combined endpoint vary to some degree across the trials discussed below.

Celecoxib

The strongest data in support of an increased risk of serious adverse CV events for celecoxib comes from the National Cancer Institute's Adenoma Prevention with Celecoxib (APC) trial in patients at risk for recurrent colon polyps. In the APC trial a 2-3 fold increased risk of adverse CV events was seen for celecoxib compared to placebo after a mean duration of treatment of 33 months. There was evidence of a dose response relationship, with a hazard ratio[3] of 2.5 for celecoxib 200 mg twice daily and 3.4 for celecoxib 400 mg twice daily compared to placebo for the composite endpoint of death from CV causes, myocardial infarction (MI), or stroke.

The results from the APC trial were not replicated, however, in the nearly identical Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial. Based on preliminary, unpublished data presented by the PreSAP investigators at the AC meeting, the hazard ratio was 1.1 for celecoxib 400 mg once daily compared to placebo for the composite endpoint of death from CV causes, MI, or stroke. It is worth noting that the dosing interval differed between the APC trial (twice daily) and the PreSAP trial (once daily), although both trials included a total daily dose of celecoxib of 400 mg. It remains unclear what, if any, role this difference in dosing interval may have played in the disparate findings between the two trials.

Another long-term controlled clinical trial of celecoxib versus placebo, the National Institute of Aging's Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) in patients at

[3] The hazard rate is a measure of risk per unit of time in an exposed cohort (e.g., the event rate per month). The hazard ratio is the ratio of the hazard rates from the treatment group relative to the control group, and is often used to represent the relative risk when the relative risk is constant over time.

risk for Alzheimer's disease, also does not appear to have shown an increased risk for celecoxib 200 mg twice daily compared to placebo for the composite endpoint of death, MI, or stroke. Preliminary, unpublished data shared with FDA by the ADAPT investigators showed no increased relative risk for celecoxib compared to placebo.[4] Finally, there was a small one-year trial comparing celecoxib 200 mg twice daily to placebo in patients with Alzheimer's disease that did not demonstrate a significantly increased risk of serious adverse CV events, but did show a trend toward more CV events in the celecoxib treatment arm.

The only available data from a long-term comparison of celecoxib to non-selective NSAIDs come from the Celebrex Long-Term Arthritis Safety Study (CLASS) in which celecoxib 400 mg twice daily was compared to diclofenac and ibuprofen in approximately 8000 patients with osteoarthritis or rheumatoid arthritis. No differences were observed for serious adverse CV events between celecoxib and the two non-selective NSAID comparators in this trial.

The ADAPT trial also included naproxen as an active control and will provide an additional comparison of celecoxib to a non-selective NSAID when the final study results become available. Preliminary, unpublished data shared with FDA by the ADAPT investigators showed that celecoxib was intermediate between placebo (lowest incidence) and naproxen (highest incidence) for the composite endpoint of death, MI, or stroke.

Rofecoxib

The strongest data from a long-term placebo-controlled trial for an increased risk of serious adverse CV events with rofecoxib come from the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial in which rofecoxib 25 mg once daily was compared to placebo for up to three years. A relative risk of approximately two was seen for rofecoxib compared to placebo for serious adverse CV events. It is noteworthy that the rofecoxib and placebo CV event curves in a Kaplan-Meier plot did not appear to begin to separate until after approximately 18 months of treatment. In contrast to the results seen in APPROVe, two long-term placebo-controlled trials in patients with early Alzheimer's disease, including up to four years of treatment in a small number of patients, did not show a significant difference in CV events between rofecoxib 25 mg once daily and placebo.

The only long-term controlled clinical trial comparison of rofecoxib to a non-selective NSAID comes from the Vioxx GI Outcomes Research (VIGOR) trial in which rofecoxib 50 mg once daily was compared to naproxen for up to 12 months. In VIGOR, rofecoxib was associated with a hazard ratio of approximately two compared to naproxen based on the composite endpoint of death, MI, or stroke. In contrast to the findings in APPROVe, in VIGOR the Kaplan-Meier CV event curves for rofecoxib and naproxen began to separate after approximately two months of treatment.

Valdecoxib

[4] Relative risk is defined as the cumulative risk in the treatment group (e.g., number of events per the number of individuals in this group) divided by the cumulative risk in the control group. The term relative risk is often used interchangeably with the hazard ratio.

No long-term controlled clinical trials have been conducted comparing valdecoxib to either placebo or non-selective NSAIDs. Data are available from two short-term placebo-controlled trials of early dosing with intravenous parecoxib (a pro-drug for valdecoxib) followed by oral valdecoxib in patients immediately post-operative from coronary artery bypass graft (CABG) surgery. In both studies, valdecoxib was associated with an approximately two-fold increased risk of serious adverse CV events compared to placebo. In contrast, a short-term placebo-controlled trial of intravenous parecoxib followed by oral valdecoxib in patients undergoing various types of non-vascular general surgical procedures showed no differences for serious adverse CV events.

Investigational COX-2 Selective Agents

Data from long-term controlled clinical trials are also available for two investigational COX-2 selective agents (lumiracoxib and etoricoxib), and were presented at the AC meeting. These data are summarized here as they provide further insights regarding the issue of CV risk for COX-2 selective agents and the comparison of CV risks between COX-2 selective drugs and non-selective NSAIDs.

The Therapeutic COX-189 Arthritis Research and Gastrointestinal Event Trial (TARGET) compared lumiracoxib 400 mg once daily to naproxen and ibuprofen for one year in approximately 18,000 patients with osteoarthritis. TARGET was designed as two sub-studies and the planned primary analysis was to be the combined lumiracoxib groups compared to the combined naproxen and ibuprofen groups. The study design, however, did not clearly reflect this intent since randomization occurred at the sub-study level rather than across the entire study. For reasons that are not entirely clear, but possibly related in part to the randomization schema, the event rates for serious adverse CV events in the lumiracoxib groups in the two sub-studies were very different, i.e., 1.1 events per 100 patient years in the naproxen sub-study versus 0.58 events per 100 patient years in the ibuprofen sub-study. The event rates for serious adverse CV events for naproxen and ibuprofen were very similar in the two sub-studies; i.e., 0.76 events per 100 patient years for naproxen and 0.74 events per 100 patient years for ibuprofen.

The pre-specified primary analysis of TARGET found no difference in serious adverse CV events between the combined lumiracoxib groups and the combined naproxen and ibuprofen groups. The validity of combining the two lumiracoxib groups for purposes of the primary analysis is debatable, however, given the study design and the very different lumiracoxib event rates in the two sub-studies. It is unfortunate that the study design did not call for randomization of treatment assignment across the entire study, which would have allowed for a much more powerful comparison of lumiracoxib to the two non-selective NSAIDs.

Given the study design, the data from TARGET have also been analyzed by sub-study. In the naproxen sub-study, a hazard ratio of 1.44 was observed for the comparison of lumiracoxib and naproxen for serious adverse CV events. In the ibuprofen sub-study, a hazard ratio of 0.79 was observed for the comparison of lumiracoxib and ibuprofen for

serious adverse CV events. The observed differences between lumiracoxib and the NSAID comparators were not statistically significantly different in either sub-study.

Depending on which analysis of the TARGET study one considers, the conclusions may be very different. The pre-specified primary analysis would suggest that lumiracoxib, a highly COX-2 selective agent, is indistinguishable from two non-selective agents with regard to the risk of serious adverse CV effects. The sub-study results, however, would suggest that lumiracoxib may be associated with a slightly increased CV risk compared to naproxen and a slightly decreased CV risk compared to ibuprofen. The cross sub-study comparison of naproxen and ibuprofen, however, would suggest no difference in CV risk for these non-selective NSAIDs. Overall, this study does not support a clear distinction between lumiracoxib and the non-selective NSAIDs.

The Etoricoxib versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness Trial (EDGE) compared etoricoxib 90 mg once daily versus diclofenac for up to 16 months in approximately 7100 patients with osteoarthritis. The relative risk for serious adverse CV events was 1.07 for the comparison of etoricoxib to diclofenac (not significantly different). EDGE, therefore, is another large controlled clinical trial that did not distinguish COX-2 selective and non-selective NSAIDs with regard to CV risk.

Non-selective NSAIDs

Long-term placebo- and active-controlled trials are generally not available for the non-selective NSAIDs, with the exception of the studies noted above where certain non-selective NSAIDs were used as active controls in studies of COX-2 selective drugs.

Observational studies

Data are available from a number of published and unpublished observational studies to address the issue of increased risk of serious adverse CV events for COX-2 selective and non-selective NSAIDs. These studies have utilized a variety of designs, methods, source databases, and comparison groups, and each study has been characterized by strengths and weaknesses. In most of the observational studies, the estimated relative risks of the COX-2 selective NSAIDs have ranged from 0.8 to 1.5, with many point estimates not achieving statistical significance. These data were presented and discussed in detail at the AC meeting and the committee members generally agreed that the observational data could not definitively address the question of a modestly increased CV risk for the COX-2 selective compared to the non-selective NSAIDs, with the possible exception of data on rofecoxib 50 mg.

Overall, the most consistent finding for increased CV risk was observed for rofecoxib 50 mg, where statistically significant relative risks of approximately 2 and 3 were seen in two studies. The signal for increased CV risk for the 25 mg rofecoxib dose, however, was smaller and did not consistently achieve statistical significance. The relative risks in the seven observational studies for celecoxib ranged from 0.4 to 1.2, with statistical significance observed once for a lowered risk and once for a higher relative risk. The available data for

the non-selective NSAIDs from the observational studies are limited, and no consistent signals were observed.

Analysis and Conclusions

As noted above, the most persuasive evidence in support of an increased risk of serious adverse CV effects of the COX-2 selective NSAIDs is derived from a small number of long-term placebo- and active-controlled clinical trials in patients with arthritis or in the disease prevention setting. The data from these trials, however, are not consistent in demonstrating an increased risk of serious adverse CV effects for COX-2 selective drugs. Perfect replication of study results cannot be expected, and is not required to reach a valid scientific conclusion. However, the degree of inconsistency observed in the data from long-term controlled clinical trials has a considerable impact on our ability to reach valid conclusions about the absolute magnitude of increased risk and to make risk versus benefit determinations for particular doses of specific drugs.

The data from controlled clinical trial comparisons of COX-2 selective and non-selective NSAIDs do not clearly demonstrate an increased relative risk for the COX-2 selective drugs, despite the substantial size of these studies. Only VIGOR clearly indicates such a difference with CLASS and EDGE giving no suggestion of a difference and TARGET giving analysis-dependent results. These findings, and the absence of any long-term placebo- or active-controlled clinical trials for most of the non-selective NSAIDs, make it difficult to conclude that the COX-2 selective drugs as a class have greater CV risks than non-selective NSAIDs. The data from the well-controlled observational trials also have not provided consistent assessments of risk when comparing COX-2 selective and non-selective NSAIDs. The point estimates of the relative risk comparisons from these data are mostly in a range where interpretation may be difficult and influenced by uncontrolled residual confounding or biases often inherent in the design and data limitations of these studies

Despite the limitations of the available data, overall, there is evidence, principally from a small number of placebo-controlled trials, that the approved COX-2 selective NSAIDs (i.e., celecoxib, rofecoxib, valdecoxib) are associated with an increased risk of serious adverse CV events (e.g., MI, stroke, and death). It remains unclear, however, that it is the presence of, or the degree of, COX-2 selectivity that accounts for these observations, as some have hypothesized. As noted above, in various controlled clinical trials, COX-2 selective drugs have been indistinguishable from non-selective NSAIDs (i.e., ibuprofen, diclofenac) in studies of substantial size and duration. Further, although on theoretical grounds the addition of low-dose aspirin (a COX-1 inhibitor) to a COX-2 selective drug should resolve any increased CV risk caused by COX-2 selectivity, this effect has not in fact been observed in several studies in which such comparisons are possible. Taken together, these observations raise serious questions about the so called “COX-2 hypothesis,” which suggests that COX-2 selectivity contributes to increased CV risk. It, therefore, remains unclear to what extent the COX-2 selectivity of an individual drug predicts the drug’s potential for an increased risk of adverse CV events compared to drugs that are less COX-2 selective.

After carefully reviewing all the available data, we believe that the data are sufficient to support a conclusion that celecoxib, rofecoxib, and valdecoxib are associated with an increased risk of serious adverse CV events when compared to placebo. For celecoxib and rofecoxib these conclusions are primarily supported by the data from the APC and APPROVe trials, respectively. However, for celecoxib a nearly identical long-term placebo-controlled trial (the PreSAP trial) and a similarly sized placebo-controlled trial in patients at increased risk for Alzheimer's disease did not replicate these findings. For rofecoxib, other long-term placebo-controlled trials of equal or greater duration (the Alzheimer's treatment trials) did not replicate the APPROVe findings. There are no long-term placebo-controlled trial data for valdecoxib. It is difficult to know how to extrapolate the findings from the parecoxib/valdecoxib CABG trials to the chronic use situation given the significant physiologic and traumatic impact on the coronary vasculature during and following CABG surgery, and the systemic pro-inflammatory response resulting from heart-lung bypass. We believe, however, that it is reasonable from a public health perspective to assume that valdecoxib does not differ from the other COX-2 selective agents with regard to increased CV risk with chronic use pending the availability of data from long-term controlled clinical trials that would indicate otherwise.

The long-term controlled clinical trial data comparing COX-2 selective agents (i.e., celecoxib, rofecoxib, lumiracoxib, etoricoxib) to non-selective NSAIDs are limited in number, but include several trials of very substantial size. They raise significant unresolved questions. First, rofecoxib 50 mg clearly appears to have an increased risk of serious adverse CV events compared to naproxen based on the data from the VIGOR trial.[5] The absence of a placebo arm in the VIGOR trial, however, precludes a determination of whether chronic use of naproxen might also confer an increased risk of serious adverse CV events, albeit at a lower rate than rofecoxib. The VIGOR trial also does not provide a comparison between lower doses of rofecoxib and naproxen. Other controlled clinical trial data have also suggested some increased risk of serious adverse CV events for COX-2 selective agents versus naproxen (i.e., lumiracoxib in the naproxen sub-study in TARGET and etoricoxib in the NDA database); however, these studies also leave unresolved the question of whether naproxen is itself associated with an increased CV risk. The ADAPT trial is the only long-term controlled clinical trial in which a COX-2 selective agent and naproxen have been compared to placebo. The preliminary data from the ADAPT trial, however, do not appear to follow the pattern of the other COX-2 selective versus naproxen trials, showing a trend toward a higher event rate on naproxen compared to celecoxib and placebo (see above). Further, the cross sub-study comparison of naproxen and ibuprofen in TARGET suggests no difference in CV risk between these two non-selective NSAIDs. Taken together these data provide some support for the conclusion that a difference exits in the risk of serious adverse CV events between COX-2 selective agents and naproxen, but they do not provide any assurance that naproxen itself confers no increased CV risk; i.e., we cannot consider naproxen to be equal to or better than placebo.

[5] Rofecoxib 50 mg is not recommended for chronic use in the approved labeling for Vioxx. The higher dose of rofecoxib was used in the VIGOR trial to provide a "worst case" estimate of the risk of serious GI bleeding for rofecoxib in comparison to naproxen.

The comparisons of COX-2 selective agents to certain other non-selective NSAIDs also raise interesting, and in the end unresolved, questions regarding the relative risk of COX-2 selective drugs compared to non-selective NSAIDs, despite the very large size of some of the trials. Several long-term controlled clinical trial comparisons of COX-2 selective agents to diclofenac have failed to provide evidence that diclofenac has a lower risk of serious adverse CV events than COX-2 selective agents (e.g., versus celecoxib in CLASS, versus etoricoxib in the NDA database, versus etoricoxib in EDGE). Large, long-term controlled clinical trial comparisons of COX-2 selective agents to ibuprofen, an unequivocally non-selective agent, also have failed to suggest a clear separation with regard to the risk of serious adverse CV events (e.g., versus celecoxib in CLASS, versus lumiracoxib in the ibuprofen sub-study in TARGET). While even these large studies cannot rule out a small true difference in CV risk between COX-2 selective agents and diclofenac and ibuprofen, they show no clear trend and are best interpreted as showing that the risk of serious adverse CV events between COX-2 selective agents and either diclofenac and ibuprofen are in fact very similar. The latter interpretation, taken together with the findings of an increased risk of serious adverse CV events from the long-term placebo-controlled clinical trials of COX-2 selective agents, would support a conclusion that at least some of the non-selective NSAIDs are also associated with an increased risk of serious adverse CV events.

The inability to reliably estimate the absolute magnitude of the increased risk of serious adverse CV events for individual COX-2 agents, combined with the inability to reliably draw conclusions about the risk of COX-2 agents compared to one another or to other NSAIDs, highlights the conundrum the Agency faces in making decisions on appropriate regulatory actions. There is an urgent public health need to make appropriate regulatory decisions because the adverse events at issue are serious and a very large number of patients use selective and non-selective NSAIDs to treat chronic pain and inflammation. At the same time, erroneous conclusions and inappropriate actions are themselves potentially harmful to the public health. Although the currently available data are not definitive, the Agency cannot await more definitive data, which may take years to accumulate from studies that have not even begun, before taking action.

In summary, we conclude that the three approved COX-2 selective drugs are associated with an increased risk of serious adverse CV events, at least at some dose, with reasonably prolonged use. We do not believe, however, that the currently available data allow for a rank ordering of the approved COX-2 selective drugs with regard to CV risk. We also believe that it is not possible to conclude at this point that the COX-2 selective drugs confer an increased risk over non-selective NSAIDs in chronic use. Naproxen may be an exception, but the comparative data to COX-2 selective agents are not entirely consistent, we do not have adequate long-term placebo-controlled data to fully assess its potential CV risks, and the cross sub-study comparison to ibuprofen in TARGET does not suggest a lesser CV risk. For the vast majority of non-selective NSAIDs we do not have any data that allow comparisons with COX-2 selective agents for CV risk, and where data exist, primarily from very large studies, they do not consistently demonstrate that the COX-2 agents confer a greater risk. Finally, there are no data from long-term placebo-controlled trials for the non-selective NSAIDs (other than the preliminary data for naproxen from ADAPT) that are analogous to the data available for the COX-2 selective agents.

The absence of long-term controlled clinical trial data for the non-selective NSAIDs significantly limits our ability to assess whether these drugs may also increase the risk of serious adverse CV events. The long marketing history of many of these drugs cannot be taken as evidence that they are not associated with an increased risk of serious adverse CV events since CV events occur fairly commonly in the general population and small increases in common adverse events are impossible to detect from spontaneous reporting systems. The adverse CV risk signal for the COX-2 selective drugs became apparent only from large, long-term controlled clinical trials and large retrospective cohort studies. Similar clinical trials are needed to assess the potential risks of the non-selective NSAIDs.

Given our inability to conclude, based on the available data, that the COX-2 selective agents confer an increased risk of serious adverse CV events compared to non-selective NSAIDs, we believe that it is reasonable to conclude that there is a "class effect" for increased CV risk for all NSAIDs pending the availability of data from long-term controlled clinical trials that more clearly delineate the true relationships. This interpretation of the available data will serve to promote public health by alerting physicians and patients to this class concern and will make it clear that simply switching from a COX-2 selective agent to a non-selective NSAID does not mean that the potential for increased risk of serious adverse CV events has been fully, or even partially, mitigated.

With a "class effect" of NSAIDs on CV risk as a baseline, other factors must be considered in determining the overall risk versus benefit profile for individual drugs within the class and what, if any, regulatory actions are appropriate. Some of the factors that must be considered include any demonstrated benefit of a given drug over other drugs in the class (e.g., superiority claims, effectiveness in patients who have failed on other drugs) and any unique toxicities (or absence of a toxicity) of a given drug over other drugs in the class.

With regard to greater or special effectiveness, while it is widely believed that patients differ in their response to NSAIDs, there are no controlled clinical trial data (e.g., studies in non-responders to a particular NSAID) to support such conclusions. Nonetheless, despite the lack of rigorous evidence, this widely accepted belief is at least in part a valid rationale for maintaining a range of options in the NSAID class from which physicians and patients may choose. In addition, as noted above, there is no basis for concluding that the risk of serious adverse CV events for some NSAIDs is worse than the risk for the others, which supports maintaining a range of options.

With regard to toxicities, the primary goal in developing COX-2 selective agents was to reduce the serious, and often life-threatening, risk of gastrointestinal (GI) bleeding associated with chronic use of all NSAIDs. To date, the only COX-2 selective agent that has demonstrated a reduced risk for serious GI bleeding is rofecoxib, but only in comparison to naproxen. All of the approved COX-2 selective agents have been shown to reduce the incidence of GI ulcers visualized at endoscopy compared to certain non-selective NSAIDs, but the clinical relevance of this finding as a predictor of serious GI bleeding has not been confirmed (e.g., no difference in serious GI bleeding was observed in CLASS). Improved GI tolerability of NSAIDs is an important issue from an individual patient and public health

perspective and is, at least in part, a valid rationale for maintaining a range of options in the NSAID class from which physicians and patients may choose. Besides the COX-2 selective NSAIDs, other strategies are available that may reduce the risk of GI bleeding with NSAIDs (e.g., combined use of a non-selective NSAID with misoprostol or a proton pump inhibitor), but data are currently lacking on how these strategies compare to the use of COX-2 selective drugs. With the exception of the comparison of rofecoxib to naproxen, data are not available to confirm a reduced risk of serious GI bleeding for the COX-2 selective agents, though it is widely believed that these agents are better tolerated by many patients.

In addition to the risk of serious and potentially life-threatening GI bleeding, NSAIDs are also associated with other potentially serious adverse effects, including, but not limited to, fluid retention, edema, renal toxicity, hepatic enzyme elevation, and bronchospasm in patients with aspirin-sensitive asthma. Comparative data to differentiate NSAIDs from one another with regard to these adverse effects are generally not available or are inconclusive.

Boxed warnings are currently included in the approved labeling for two single ingredient NSAID products.[6] Bextra (valdecoxib) has a boxed warning for serious and potentially life-threatening skin reactions (i.e., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme). Toradol (ketorolac) has a boxed warning emphasizing that it is approved only for short-term (≤5 days) use in patients with moderately severe acute pain that requires analgesia at the opioid level, usually in a post-operative setting. Toradol is the only NSAID indicated for treatment of pain available for parenteral use (i.e., IV or IM injection); it therefore provides an important therapeutic option for physicians and patients in settings where the patient cannot take analgesics by mouth.[7] This therapeutic advantage favors continued availability of Toradol, despite the need for a boxed warning about the potential for increased frequency of serious adverse reactions with long-term (≥5 days) use. In contrast, there are no data to support a unique therapeutic benefit for Bextra over other available NSAIDs, which might offset the increased risk of serious and potentially life-threatening skin reactions. While other COX-2 selective and non-selective NSAIDs also have a risk for these rare, serious skin reactions, the reported rate for these serious side effects appears to be greater for Bextra than for other COX-2 agents.[8] To date, the agency has received 7 reports of deaths from serious skin reactions in patients following treatment with Bextra. The occurrence of these serious skin reactions in individual patients is unpredictable, occurring with and without a history of sulfa allergy (valdecoxib is a

[6] The package insert for Arthrotec, a combination of diclofenac and misoprostol, includes a boxed warning, but the warning relates to potential toxicities of misoprostol, not diclofenac.

[7] Indomethacin is also available as a parenteral formulation, but is only indicated for parenteral use for treatment of patent ductus arteriosus.

[8] The agency has recently received a Citizens Petition regarding the risk of Stevens-Johnson syndrome with ibuprofen (February 15, 2005). Although the petition is currently under review, and the agency has not reached a decision on the requested actions, based on analyses of data obtained before the petition was submitted, the agency has determined that the labeling for non-prescription NSAIDs should be updated to warn of the potential for skin reactions. Accordingly, along with the changes to the label to address CV risks, the agency will ask manufacturers of non-prescription NSAIDs to make these changes. After we have completed our review of the petition, we may determine that additional labeling changes with regard to potential skin reactions are warranted. The risk for serious skin reactions is already included in the labeling for most prescription NSAIDs.

sulfonamide) and after both short- and long-term use, which makes attempts to manage this increased risk difficult.

Several non-selective NSAIDs are currently available to consumers without a prescription (e.g., ibuprofen, naproxen, ketoprofen). The non-prescription doses of these products are generally well below the maximum daily prescription doses for the same active ingredient and the duration of treatment without specific alternate instructions from a physician is limited to 10 to 14 days. The applicability of the increased risk of serious adverse CV events as described above from controlled clinical trials to low-dose, short-term use of these non-prescription products for the relief of acute pain is unclear, although any such risk is expected to be minimal. No signal for increased risk of serious adverse CV events has been detected in the short-term controlled clinical trials that supported the approval of these agents for treatment of acute pain. While these studies were primarily designed to evaluate effectiveness, the absence of a signal of increased CV risk provides some reassurance of the safety of short-term use. Further, with the exception of the parecoxib/valdecoxib CABG studies, the increased risk of serious adverse CV events in the controlled clinical trials described above have only become apparent after months to years of treatment. The parecoxib/valdecoxib data also provide support for the safety of short-term use. The two short-term placebo-controlled CABG studies showed an increased risk of serious CV events, but, a short-term placebo-controlled trial in general surgery patients did not show an increased risk. These data may suggest that in the absence of a predisposing condition, such as recent CABG surgery, the CV risk of short-term use of NSAIDs is very small, if any, particularly at low doses and given the typically intermittent nature of use of non-prescription NSAIDs for relief of acute pain.

Aspirin is also an NSAID that is available and widely used without a prescription. However, aspirin has other unique pharmacologic properties, including irreversible inhibition of platelet function, that distinguish it from the rest of the NSAID class. Further, data from long-term controlled clinical trials have clearly demonstrated that aspirin significantly reduces the risk of serious adverse CV events in certain patient populations (e.g., patients with a history of a MI). Aspirin, therefore, is an exception to the apparent "class effect" of increased risk for serious adverse CV events for NSAIDs described above. Data from large, long-term controlled clinical trials clearly showing no increased CV risk or a reduction in CV risk would be necessary before concluding that other NSAIDs are also exceptions to the class risk.

Recommendations

We summarize below our recommendations for appropriate regulatory actions for the NSAID class and select individual agents.

<u>NSAIDs as a class</u>

Boxed Warning and Contraindication

We recommend that the professional labeling (package insert) for all prescription NSAIDs, including both COX-2 selective and non-selective drugs, be revised to include a boxed warning highlighting the potential increased risk of CV events. The boxed warning should also include the well described risks of serious, and often life-threatening GI bleeding. We believe that a boxed warning with regard to potential increased CV risk is an appropriate response to the currently available data and will serve to highlight to physicians and patients that they must carefully consider the risks and benefits of all NSAIDs, as well as other available options, before deciding on a treatment plan for relief of chronic pain and inflammation. If it is determined that chronic use of an NSAID is warranted for an individual patient, the boxed warning will help to emphasize the importance of using the lowest effective dose for the shortest duration possible along with appropriate attention to reduction of other risk factors for cardiovascular disease. The language of the boxed warning should be standardized across the class, with the exception of those situations where specific data or other information is available for an individual drug. In those cases, the standardized class wording should be maintained and the drug specific information added, including the results of any large controlled clinical trials.

The recommendation for a boxed warning for potential increased risk of CV events is supported by the unanimous vote of the Advisory Committees (28 yes) on the question of whether the labeling for the non-selective NSAIDs should be modified to include the absence of long-term controlled clinical trial data to assess the potential CV effects of these drugs.[9] While the AC did not specifically vote on a boxed warning, many of the committee members commented that such a warning would be an appropriate response given the current data. The Advisory Committees also strongly supported boxed warnings for the individual COX-2 selective drugs for increased CV risk.

The recommendation that the boxed warning also include the well recognized serious, and often life-threatening, risk of GI bleeding associated with chronic use of NSAIDs is intended to further reinforce the existing bolded warning. The GI bleeding risk with NSAIDs is clearly consistent with our current approach to the use of boxed warnings, and placing this information in a boxed warning will serve to further emphasize this serious risk and ensure that physicians and patients keep this risk in mind as they are considering options for chronic therapy of pain and inflammation.

We also recommend that the labeling for all NSAIDs include a contraindication for use in patients in the immediate post-operative setting following CABG surgery. Data are only available in this setting from valdecoxib, but we have concluded that this short-term increased CV risk should be extrapolated to long-term use of valdecoxib. It is logical to also extrapolate this finding to other NSAIDs, pending the availability of other data that would suggest otherwise given the serious nature of the adverse events noted in the valdecoxib CABG study and the high-risk nature of the patients undergoing CABG surgery. The contraindication for NSAID use in this setting would NOT apply, however, to aspirin for the reasons noted above.

[9] There were 32 voting members of the Advisory Committees, but 4 members had left the meeting by the time this question was discussed.

Medication Guide

We recommend that the patient labeling for all prescription NSAIDs, including both COX-2 selective and non-selective drugs, include a Medication Guide. The Medication Guide should focus on the potential increased risk of serious adverse CV events and the risks of serious GI bleeding. The Medication Guide will also inform patients of the need to discuss with their doctor the risks and benefits of using NSAIDs and the importance of using the lowest effective dose for the shortest duration possible if treatment with an NSAID is warranted. To avoid confusion and to allow for more rapid implementation, we recommend that the text of the Medication Guide be standardized across the class, following the model that was recently successfully implemented for anti-depressants.

Comprehensive Data Review and New Studies

We recommend that the agency request that the sponsors of all non-selective NSAIDs conduct and submit for FDA review a comprehensive review and analysis of all available data from controlled clinical trials to further evaluate the potential risk of serious adverse CV events. The search and analysis strategy should be similar across sponsors and drugs. The agency should carefully review the data as they become available and take any appropriate regulatory actions based on the findings.

The agency should also work closely with sponsors of non-selective NSAIDs and other stakeholders (e.g., NIH, professional associations, patient groups) to encourage the conduct of additional long-term controlled clinical trials of the non-selective NSAIDs to better evaluate the potential for increased risk of serious adverse CV events.

Non-prescription NSAIDs

We recommend that the NSAIDs that are currently available without a prescription for the short-term treatment of acute pain continue to be available to consumers. While this would apparently represent the first time that products that have a boxed warning in the prescription package insert would also be available for non-prescription use, we believe the available data support a conclusion that short-term use of low doses of the available non-prescription NSAIDs is not associated with an increased risk of serious adverse CV events. The overall benefit versus risk profile for the non-prescription NSAIDs remains very favorable when they are used according to the labeled instructions, and we believe that it is important to maintain a range of therapeutic options for the short-term relief of pain in the OTC market. Further, the other available non-prescription drugs for short-term relief of pain and fever can also be associated with serious, and potentially life-threatening, adverse events in certain settings and patient populations.

To further encourage the safe use of the non-prescription NSAIDs, we believe that the labeling for these products should be revised to include more specific information about the potential CV and GI risks, instructions about which patients should seek the advice of a physician before using these drugs, and stronger reminders about limiting the dose and duration of treatment in accordance with the package instructions unless otherwise advised

by a physician. In addition, as noted earlier, the agency has determined that the labeling for non-prescription NSAIDs should be revised to warn of the potential for skin reactions. We also recommend that the Agency continue its current consumer education efforts regarding the safe and effective use of non-prescription pain relievers and that this new information be highlighted in those campaigns.

CELEBREX ®, NDA 20-998/NDA 21-156 (celecoxib capsules)

After carefully reviewing all the available data, we conclude that the benefits of celecoxib outweigh the potential risks in properly selected and informed patients. Therefore, we recommend that celecoxib remain available as a prescription drug with the revised labeling described below in addition to the NSAID class boxed warning, contraindication, and Medication Guide described above.

Boxed warning and other labeling changes

We recommend that the boxed warning for Celebrex include specific reference to the controlled clinical trial data that demonstrate an increased risk of serious adverse CV events (e.g., the APC trial). The text in the box may be brief and include a reference to the CLINICAL PHARMACOLOGY, Clinical Studies section of the labeling where the available long-term controlled clinical trial data should be described in greater detail. Finally, we recommend that the INDICATIONS section of the labeling be revised to clearly encourage physicians to carefully weigh the potential benefits and risks of celecoxib and other treatment options for the condition to be treated before a decision is made to use Celebrex, and to use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

Postmarketing study commitment

We strongly recommend that CDER request a written commitment from the sponsor to conduct an additional long-term study (or studies) to address the safety of celecoxib compared to naproxen and other appropriate active controls (e.g., other non-selective NSAIDs, appropriate non-NSAID active comparators). CDER should be actively involved in the design of the trial(s) and insist on aggressive timelines for initiation and completion of the study(ies).

The above recommendations are consistent with the votes and recommendations made by the Advisory Committees for Celebrex. The Advisory Committees were unanimous in their conclusion that an increased risk of cardiovascular adverse events has been demonstrated for celecoxib. After carefully considering all the available data, the Advisory Committees voted 31 yes to 1 no in response to the question: "Does the overall risk versus benefit profile of celecoxib support marketing in the US?" While specific votes were not taken on the issue of what labeling changes and other risk management options would be appropriate, the overwhelming majority of the Advisory Committee member voiced their support for a boxed warning, a Medication Guide, and postmarketing study commitments to further explore the long-term safety of Celebrex in comparison to other appropriate comparators.

After carefully considering all the available data and risk management options, we have concluded that the overall risk versus benefit profile for Bextra is unfavorable at this time. We therefore recommend that Bextra be withdrawn from the U.S. market. We have concluded, as noted above, that Bextra has been demonstrated to be associated with an increased risk of serious adverse CV events in short-term CABG trials and that it is reasonable from a public heath perspective to extrapolate these findings to chronic use. The increased risk of serious adverse CV events alone, however, would not be sufficient to warrant withdrawal of Bextra since we have no data showing that Bextra is worse than other NSAIDs with regard to CV risk. Our recommendation for withdrawal is based on the fact that, in addition to this CV risk, valdecoxib already carries a boxed warning in the package insert for serious, and potentially life-threatening, skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) and FDA has received 7 spontaneous reports of deaths from these reactions. The reporting rate for these serious skin reactions appears to be greater for Bextra than other COX-2 selective agents. Further, the risk of these serious skin reactions in individual patients is unpredictable, occurring in patients with and without a prior history of sulfa allergy, and after both short- and long-term use, which makes risk management efforts difficult. To date, there have been no studies that demonstrate an advantage of valdecoxib over other NSAIDs that might offset the concern about these serious skin risks, such as studies that show a GI safety benefit, better efficacy compared to other products, or efficacy in a setting of patients who are refractory to treatment with other products.

The recommendation that Bextra be withdrawn is supported, at least in part, by the specific votes and recommendations of the Advisory Committees. The Advisory Committees were unanimous in their conclusion that an increased risk of cardiovascular adverse events has been demonstrated for valdecoxib. In response to the question "Does the overall risk versus benefit profile of valdecoxib support marketing in the US?" the Advisory Committees voted 17 yes and 13 no with 2 abstentions. Several of the advisory committee members who voted no expressed concerns about the strong signal of CV risk from the CABG trials, the absence of long-term controlled trial data to more clearly define the potential CV risks of Bextra, the fact that Bextra already carried a boxed warning for serious skin reactions, and the fact that there were no data to support a conclusion that Bextra offered a therapeutic advantage over NSAIDs.

One potential argument in favor of continued marketing of valdecoxib is that it provides an additional therapeutic option for management of arthritis and that prescribers and patients could be informed of the potential increased risk of CV events and serious GI bleeding, in addition to the potential for serious and possibly life-threatening skin reactions, and be allowed to make individualized treatment decisions. This approach, in fact, was strongly favored by practicing rheumatologists on the Advisory Committee. It is important to note, however, that there are more than 20 other NSAIDs on the market. This range of options diminishes the value of continued marketing of valdecoxib, particularly in the face of an already existing boxed warning regarding serious, and potentially life-threatening, skin

reactions and the fact that there are no data that demonstrate that valdecoxib offers any therapeutic advantage over other NSAIDs.

We recommend that FDA request that Pfizer voluntarily withdraw Bextra from the U.S. market. If Pfizer does not agree to that request, we recommend that FDA initiate the formal withdrawal process by preparing and publishing a Notice of Opportunity for Hearing.

We recommend that FDA remain open to allowing limited access to valdecoxib under an IND to those patients who believe that it is their best option, if the sponsor proposes such an IND. If additional clinical trials subsequently demonstrate that valdecoxib does not have an increased CV risk (or if its risk is significantly less than other available agents) or a therapeutic advantage for valdecoxib over other NSAIDs, FDA should carefully consider those data and reassess the current conclusions regarding the overall risks and benefits for valdecoxib.

VIOXX ®, NDA 21-042 (rofecoxib tablets and oral suspension)

VIOXX was voluntarily withdrawn from the U.S. market by the sponsor on September 30, 2004, following the announcement of the results from the APPROVe trial. Therefore, no regulatory action is warranted at this time. Should the sponsor seek to resume marketing for rofecoxib, a supplemental NDA with revised labeling will be required. The supplemental NDA would require FDA review and approval prior to implementation of the new labeling since the changes would not be of the type allowed under FDA regulations for a "Changes Being Effected (CBE)" labeling supplement The supplemental application should specifically outline the sponsor's proposal for revised labeling designed to provide for safe and effective use of the drug in populations where the potential benefits of the drug may outweigh potential risks, and all data and arguments that support resumption of marketing.

We believe that FDA should carefully review any such proposal submitted by the sponsor. We would also recommend that the FDA Drug Safety Oversight Board (DSB) and an advisory committee be consulted before a final decision is taken. Our rationale for recommending review by the DSB and an advisory committee includes the following factors. First, there is limited precedent for a drug that has been withdrawn from the U.S. market for safety reasons to be returned to marketing. The only recent example that we can recall was Lotronex, and that application was reviewed by an advisory committee before FDA reached a final decision on the sponsor's request.[10] Second, concerns were expressed at the recent advisory committee meeting that Vioxx may be associated with a higher risk of increased blood pressure, fluid retention, and congestive heart failure than other COX-2 selective NSAIDs. We believe that these additional potential serious risks of Vioxx need to be fully explored through a public process before a decision is made regarding resumed marketing. Third, the recent advisory committee meeting was a general issues meeting, not one specifically devoted to the issue of resumption of marketing of Vioxx. While the committees narrowly voted in the affirmative that the overall risk versus benefit profile of rofecoxib supported marketing in the U.S., the committee members expressed a wide variety

[10] The FDA Drug Safety Oversight Board had not been established at the time of the review of the Lotronex resubmission.

of often contradictory opinions on what regulatory actions (e.g., labeling changes, risk management efforts) would be appropriate to allow resumed marketing. Specific votes were not taken on these important issues, and we believe the agency would benefit from the advice of an advisory committee meeting specifically devoted to the resumption of marketing of Vioxx before the FDA reaches a decision on final action. Finally, the withdrawal of Vioxx has been the subject of intense public interest and debate, and we believe that a transparent process for reaching an agency decision on resumption of marketing is needed to ensure public confidence in the agency's decision-making process.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: NSAID Clinical Trial Meta-analysis for Vascular and Gastrointestinal Effects by the CNT Collaboration

Date:	November 7, 2013
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Drug Name(s):	Nonsteroidal anti-inflammatory drugs (NSAIDs)
Subject:	Review of NSAID Clinical Trial Meta-analysis for Vascular and Gastrointestinal Effects by the CNT Collaboration
OSE RCM #:	2011-45

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EXECUTIVE SUMMARY

The Coxib and traditional NSAID Trialists' Collaboration (CNT) of the Clinical Trial Service and Epidemiological Studies Units at Oxford University conducted a randomized clinical trial meta-analysis of cardiovascular and upper gastrointestinal (GI) events with non-steroidal anti-inflammatory drugs (NSAIDs). Data from 280 placebo-controlled and 474 active-controlled NSAID trials were analyzed, using individual patient level data when available. Risk estimates for vascular events with coxibs, ibuprofen 2400 mg/day and diclofenac 150 mg/day were comparable, while no vascular risk was observed with naproxen (excepting heart failure, which was increased by all treatment categories). Coxibs and diclofenac were associated with lower risks for upper GI complications compared to naproxen 1000 mg/day or ibuprofen 2400 mg/day. Vascular risks of celecoxib were dose related, with the risk at doses above 200 mg/day appearing similar to that for rofecoxib. A higher proportion of vascular adverse events than upper GI adverse events were fatal, so that in this sample of older adults treated with NSAIDs the absolute risk increase for a fatal event was lowest with naproxen 1000 mg/day.

To reduce the population burden of drug-related deaths from NSAID toxicity, naproxen should be considered first line treatment in patients for whom the risk of cardiovascular adverse events is relevant. Accordingly, the class NSAID labeling should be amended to reflect the more favorable cardiovascular risk profile of naproxen. The NSAID labeling should also be updated with respect to the association with heart failure.

Other recommendations from the 12-4-2012 DEPI II review should still be considered valid in the light of this new analysis, though the conclusion that diclofenac has a particularly unfavorable cardiovascular risk profile may be tempered by the finding that ibuprofen at a dose of 2400 mg/day had a comparable risk.

1 INTRODUCTION

This document will review a new randomized clinical trial meta-analysis of cardiovascular and upper gastrointestinal (GI) events with non-steroidal anti-inflammatory drugs (NSAIDs). The Coxib and traditional NSAID Trialists' Collaboration (CNT), of the Clinical Trial Service and Epidemiological Studies Units at Oxford University,[1] performed the analysis. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) obtained a pre-publication report of the analysis from the CNT, and requested reviews from the Division of Epidemiology II and the Division of Biometrics 7.

1.1 BACKGROUND

A trial-level meta-analysis, published in 2006,[2] included data from 138 randomized controlled trials of selective COX-2 inhibitors (coxibs) or traditional NSAIDs (tNSAIDs). It showed an increase in cardiovascular events, particularly myocardial infarction (MI), with use of coxibs and of higher dosages of diclofenac and ibuprofen, though not naproxen. To address limitations of the trial-level meta-analysis, the researchers undertook the patient-level meta-analysis described herein.

For a review of the recent pharmacoepidemiology literature on NSAIDs and ischemic cardiovascular events, please refer to the DEPI II review dated 12-4-2012.

Funding for the project was provided by the UK Medical Research Council and the British Heart Foundation. Pfizer, Merck, Novartis and GSK provided patient-level data for this project, but not funding. The National Cancer Institute and the European Organisation for Research and Treatment of Cancer also provided individual patient data, from clinical trials they had sponsored.

1.2 REGULATORY HISTORY

In September 2004, the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial was halted early because of an excess of adverse cardiovascular events in the rofecoxib arm, and Vioxx was withdrawn from the market worldwide. In April 2005, FDA announced that it was requesting class labeling for both prescription and over-the-counter NSAIDs regarding the risks of thrombotic cardiovascular events.[3]

1.3 PRODUCT LABELING

The class labeling is shown here (source: Clinoril (sulindac) label).

> WARNINGS
>
> CARDIOVASCULAR EFFECTS--Cardiovascular Thrombotic Events
>
> Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.
>
> There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see GI WARNINGS).
>
> Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see CONTRAINDICATIONS).

2 REVIEW METHODS AND MATERIALS

The materials available for review included the CNT manuscript and supporting information, which FDA received confidentially on 2-7-2013, and the protocol for the CNT project.[4] Also available was the draft review of these materials (Dr. Eugenio Andraca-Carrera, reviewer) from the Division of Biostatistics 7 (DB7). Lancet e-published the manuscript 5-30-2013,[5] and the data as published were considered final if they differed from the 2-7-2013 manuscript.

3 REVIEW RESULTS

3.1 STUDY OVERVIEW

This study was a meta-analysis of randomized clinical trial data of coxibs and tNSAIDs for outcomes of vascular events, heart failure, and upper GI events. Data from a total of 280 placebo-controlled and 474 active-controlled trials of NSAIDs were analyzed, using individual patient level data when available, and otherwise trial level summary data.

3.2 STUDY OBJECTIVES/SPECIFIC AIMS/SCOPE

The protocol describes the aim of the study as follows:

The chief aim of this Collaboration will be to conduct analyses of the effects of coxibs and tNSAIDs on the most common adverse effects of coxibs and tNSAIDs, namely "major vascular events" and "upper gastrointestinal (GI) complications".

3.3 STUDY METHODS

3.3.1 Design & Setting

3.3.1.1 Study Type

This was a retrospective meta-analysis of randomized clinical trial data for safety outcomes.

3.3.1.2 Population & Time Period

Trials had to be completed by January 2011 for inclusion. The population of these trials was primarily arthritis patients, with a minority of trials involving dementia or cancer prevention or treatment.

3.3.1.3 Selection, Inclusion and Exclusion Criteria

Randomized controlled trials at least 4 weeks in duration were eligible for the analysis. According to the protocol, eligible trial designs included coxib vs. tNSAID, coxib vs. placebo, coxib vs. coxib, tNSAID vs. placebo, dose comparisons of a coxib, or dose comparisons of a tNSAID. In addition, the protocol stated that shorter trials conducted in patient populations with cardiovascular disease were to be included, but no such studies were analyzed.

Trials were identified by searches of on-line databases, clinical trial registers, literature references, and consultation with experts and manufacturers. The investigators identified 24,278 references to be considered for inclusion; most were excluded based on review of the title and abstract alone, leaving 1598 references that were reviewed in full. Of these, 891 references were excluded after review because they did not meet the eligibility criteria, and another 101 were excluded because of missing data on patients or events. This left 639 trials to be included in the analysis.

3.3.2 Outcome & Exposure

Exposure was defined by the subject's randomized treatment, and the analysis used an intent-to-treat strategy.

The patient's first outcome, if any, was analyzed. The following table lists the principal outcomes.

Outcome (*= primary)	Definition
Major vascular event*	Nonfatal MI, nonfatal stroke, vascular death
Major coronary event	Nonfatal MI, death from coronary disease
Stroke	Neurological deficit with cerebrovascular cause lasting > 24 hours
Hospitalization for heart failure	Hospitalization for heart failure or pulmonary edema
Upper GI complication*	Bleed, perforation, obstruction
Symptomatic upper GI event	Symptomatic ulcer, upper GI complication
Cause of death	Vascular, non-vascular, unknown

Analyses of some additional secondary outcomes specified in the protocol (such as pulmonary embolus, coronary revascularization, etc.) were not presented in the current report.

Outcomes were to be reported if they were the first event in each category and occurred prior to the cutoff date for that trial (which could have been post-treatment). Definite or probable outcomes were to be reported. Adjudicated outcomes were to be used when available; otherwise, the protocol provided a list of MedDRA terms that could be used to define outcomes.

3.3.3 Covariates

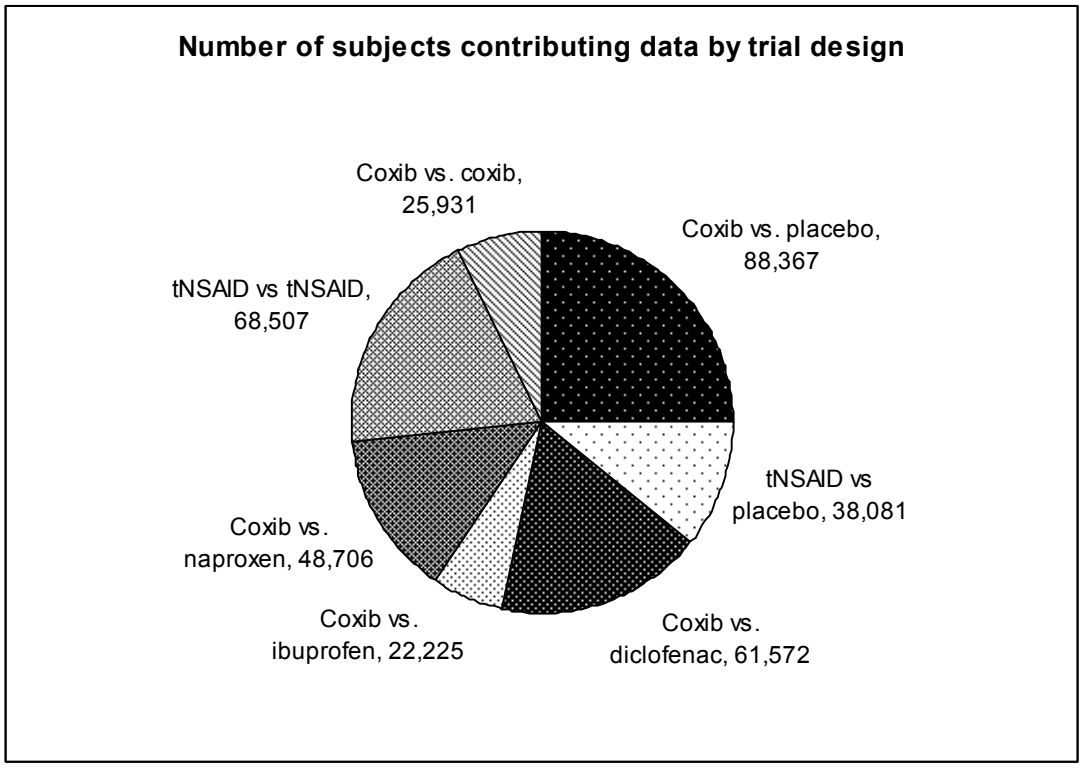
Though covariates were not used per se in the analysis, the following subgroups were analyzed: Age < 60 years versus 60+ years, sex, indication (arthritis, cancer, other, unknown), history of atherosclerosis (yes/no), diabetes (yes/no), upper GI ulcer (yes/no), current smoker (yes/no), current drinker (yes/no).

3.3.4 Sample Size/Power

The table below, derived from the table in the paper, displays the numbers of trials and subjects contributing data by trial design category. Also shown is the proportion of data that was available at the patient level. As shown, individual patient data was available for the majority of subjects in trials involving a coxib.

Trial design	No. of trials contributing data	No. of subjects	% of subjects with individual patient data	Person-yrs
Coxib vs. placebo	184	88,367	83.3%	52,466
tNSAID vs placebo	158	38,081	47.3%	16,217
Coxib vs. diclofenac	33	61,572	95.6%	90,644
Coxib vs. ibuprofen	22	22,225	96.3%	11,668
Coxib vs. naproxen	48	48,706	86.7%	31,631
tNSAID vs tNSAID	335	68,507	1.1%	22,418
Coxib vs. coxib	35	25,931	98.1%	9,093

The following figure displays the sample sizes graphically.



3.3.5 Statistical Analyses

The following is an overview of the statistical methodology; in addition, please refer to the statistical review by Dr. Eugenio Andraca-Carrera of DB7. Combined rate ratios were estimated from the individual trial data using the logrank observed minus expected statistic and its corresponding variance for each trial, calculated from either trial-level or patient-level data, whichever was available. For comparisons of tNSAIDs (ibuprofen, naproxen, and diclofenac) to placebo, an indirect method had to be used to supplement the smaller sample of trials involving both a placebo and a tNSAID. The indirect method derived rate ratios for tNSAIDs versus placebo using rate ratios from trials of coxibs versus placebo and trials of coxibs versus tNSAIDs. Subgroup analyses assessed risks according to demographic and clinical characteristics. Absolute risks of major vascular events and upper GI events were projected for coxibs, naproxen, and non-naproxen tNSAIDs.

3.4 STUDY RESULTS

Please see above for the sample sizes. The following table lists the modal daily doses among the patients contributing data, by compound.

Compound	Modal dose (mg/day) (from paper Webtable 1)
Diclofenac	150
Ibuprofen	2400
Naproxen	1000
Celecoxib	400
Rofecoxib	25
Lumiracoxib	200
Etoricoxib	60/90
Valdecoxib	20

The following table is reproduced from the CNT publication and displays the characteristics of the subjects with individual data.

	Overall	Coxib vs placebo	tNSAID vs placebo	Coxib vs naproxen	Coxib vs other tNSAID
No. randomised	192981	73635	18018	42222	84680
No. trials	157	113	47	34	54
Age, years	61.2 (11.3)	60.1 (12.4)	59.7 (13.6)	60.6 (11.3)	61.6 (10.6)
Female, %	68	59	67	73	73
Caucasian, %	79	82	72	76	77
Indication for treatment, %					
Rheumatoid arthritis	20	20	28	36	17
Osteoarthritis	63	44	52	57	77
Cancer prevention/treatment	7	19	0	0	0
Alzheimers	3	7	11	4	0
Other known indication	5	10	9	2	4
Unknown	1	0	0	1	2
Prior disease, %					
Diabetes	9	8	6	9	8
Atherosclerotic disease	9	10	9	8	9
Upper GI ulcer	7	7	9	7	7
Medication, %					
Aspirin	20	14	15	14	27
Proton pump inhibitor	17	5	3	2	33
Other/multiple gastroprotectants	3	5	5	6	1
Current smoker, %	13	14	13	15	12
Physical measurements					
BMI, kg/m^2	29.3 (6.2)	29.2 (6.3)	28.9 (6.5)	29.1 (6.4)	29.3 (6.1)
Systolic blood pressure, mmHg	132 (16)	131 (16)	131 (17)	132 (17)	132 (16)
Diastolic blood pressure, mmHg	79 (9)	79 (9)	79 (9)	79 (9)	79 (9)
Laboratory measurements					
Total cholesterol, mmol/L	5.3 (1.0)	5.3 (1.0)	5.2 (0.8)	5.2 (0.8)	5.4 (1.0)
Creatinine, umol/L	79 (21)	81 (19)	80 (19)	76 (20)	79 (23)
Haemoglobin, g/dL	13.7 (1.3)	13.9 (1.4)	13.7 (1.3)	13.6 (1.3)	13.6 (1.3)

Mean (SD) or % shown

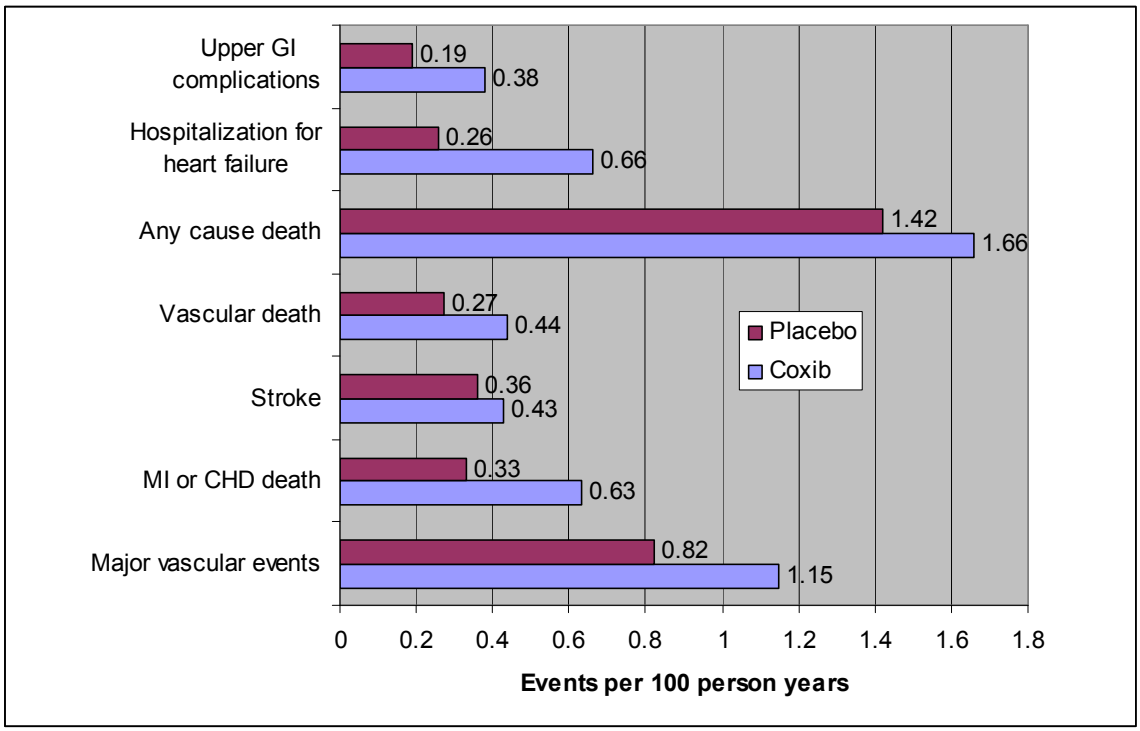
Overall, a total of 192,981 patients contributed data. They were 68% female, with a mean age of 61 years, and 79% Caucasian. The predominant indication studied was osteoarthritis (63%), followed by rheumatoid arthritis (20%). Atherosclerotic disease was present in 9%, and 7% had a

history of upper GI ulcer disease. Twenty percent of the sample used aspirin, and 20% used gastroprotectant medication.

The following table lists the numbers of outcomes, and the graph displays the unadjusted event rates, for trials comparing a coxib to placebo. Event counts and rates for other trial designs were not presented. The authors reported in the text that 2% of all upper GI complications were fatal. A corresponding case fatality percentage was not reported in the paper, though the data below suggest approximately 30% of major vascular events were fatal in coxib trials.

Table. Numbers of outcomes for trials comparing coxib to placebo (coxib/placebo)

Major vascular events	MI or CHD death	Stroke	Upper GI complications
307/175	142/62	94/67	68/29
Vascular death	**Any cause death**	**Hospitalization for heart failure**	
95/49	365/265	118/39	



The following tables, from Dr. Andraca-Carrera's statistical review, and used here with his kind permission, provide a concise overview of the main results. Rate ratios with confidence intervals excluding unity are highlighted.

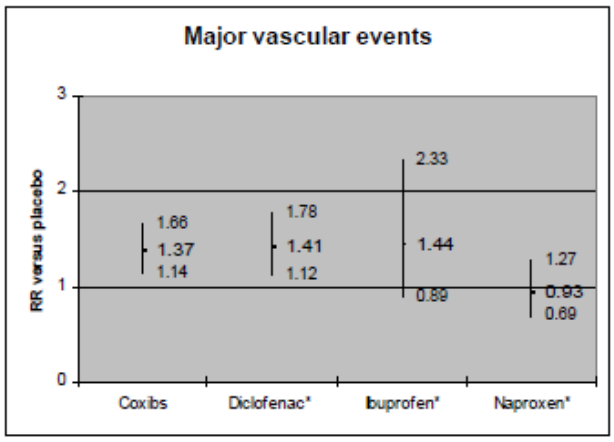
Table. Main outcome results from the CNT NSAID clinical trial meta-analysis (Rate Ratios and 95% CI)

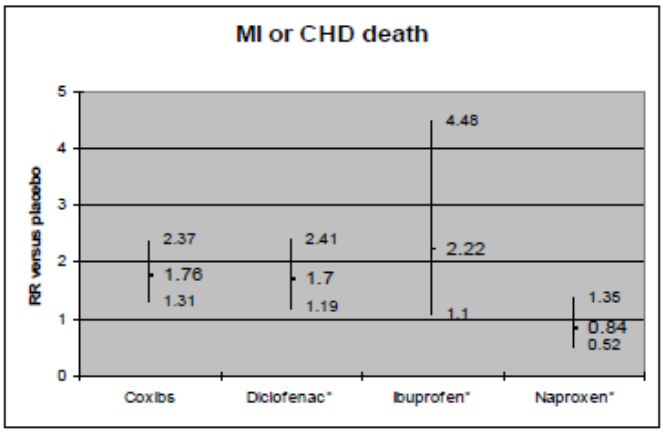
Comparison	Major vascular events	MI or CHD death	Stroke
coxibs vs. placebo	1.37 (1.14, 1.66)	1.76 (1.31, 2.37)	1.09 (0.78, 1.52)
coxibs vs. naproxen	1.49 (1.16, 1.92)	2.11 (1.44, 3.09)	1.14 (0.74, 1.73)
coxibs vs. ibuprofen	0.92 (0.58, 1.46)	0.81 (0.41, 1.61)	1.00 (0.44, 2.25)
coxibs vs. diclofenac	0.97 (0.84, 1.12)	1.04 (0.84, 1.28)	0.92 (0.71, 1.20)
diclofenac vs. placebo*	1.41 (1.12, 1.78)	1.70 (1.19, 2.41)	1.18 (0.79, 1.78)
ibuprofen vs. placebo*	1.44 (0.89, 2.33)	2.22 (1.10, 4.48)	0.97 (0.42, 2.24)
naproxen vs. placebo*	0.93 (0.69, 1.27)	0.84 (0.52, 1.35)	0.97 (0.59, 1.60)

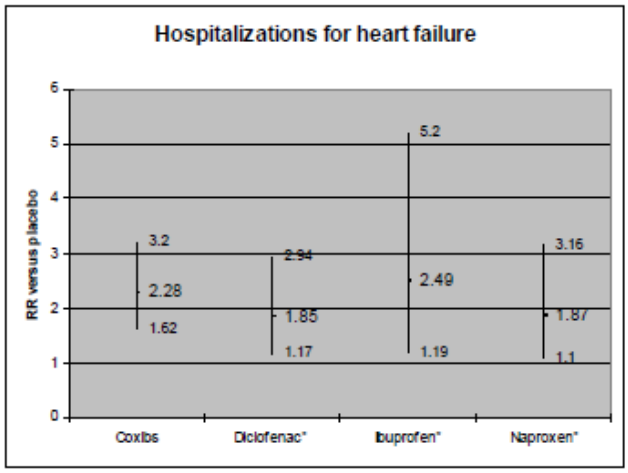
	Vascular death	Any cause death	Hospitalization for heart failure	Upper GI complications
coxibs vs. placebo	1.58 (1.11, 2.24)	1.22 (1.04, 1.44)	2.28 (1.62, 3.20)	1.81 (1.17, 2.81)
coxibs vs. naproxen	1.53 (0.89, 2.62)	1.23 (0.86, 1.75)	1.17 (0.76, 1.79)	0.37 (0.28, 0.49)
coxibs vs. ibuprofen	0.83 (0.32, 2.16)	0.78 (0.43, 1.42)	0.83 (0.42, 1.64)	0.40 (0.25, 0.64)
coxibs vs. diclofenac	0.96 (0.74, 1.23)	1.02 (0.84, 1.24)	1.23 (0.87, 1.73)	0.94 (0.72, 1.24)
diclofenac vs. placebo*	1.65 (0.95, 2.85)	1.20 (0.94, 1.54)	1.85 (1.17, 2.94)	1.89 (1.16, 3.09)
ibuprofen vs. placebo*	1.90 (0.56, 6.41)	1.61 (0.90, 2.88)	2.49 (1.19, 5.20)	3.97 (2.22, 7.10)
naproxen vs. placebo*	1.08 (0.48, 2.47)	1.03 (0.71, 1.49)	1.87 (1.10, 3.16)	4.22 (2.71, 6.56)

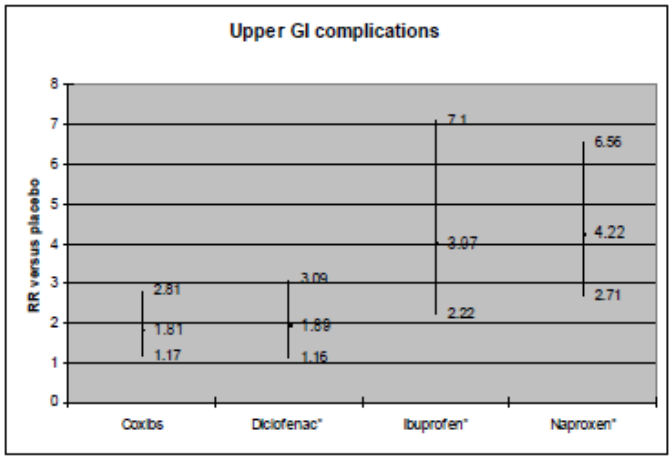
*Rate ratio calculated using indirect comparison

The following graphs depict the rate ratios (RR) and 90% confidence intervals associating coxibs and tNSAIDS with selected outcomes.









*Rate ratio calculated using indirect comparison

Relative to placebo, coxibs were associated with all outcomes except stroke. Although coxibs were associated with upper GI complications, rate ratios for upper GI complications with naproxen and ibuprofen were higher than with coxibs. Naproxen was not associated with any cardiovascular outcomes except hospitalization for heart failure (which was increased with all treatments). There were no associations with stroke, though the smaller numbers of strokes may have limited statistical power.

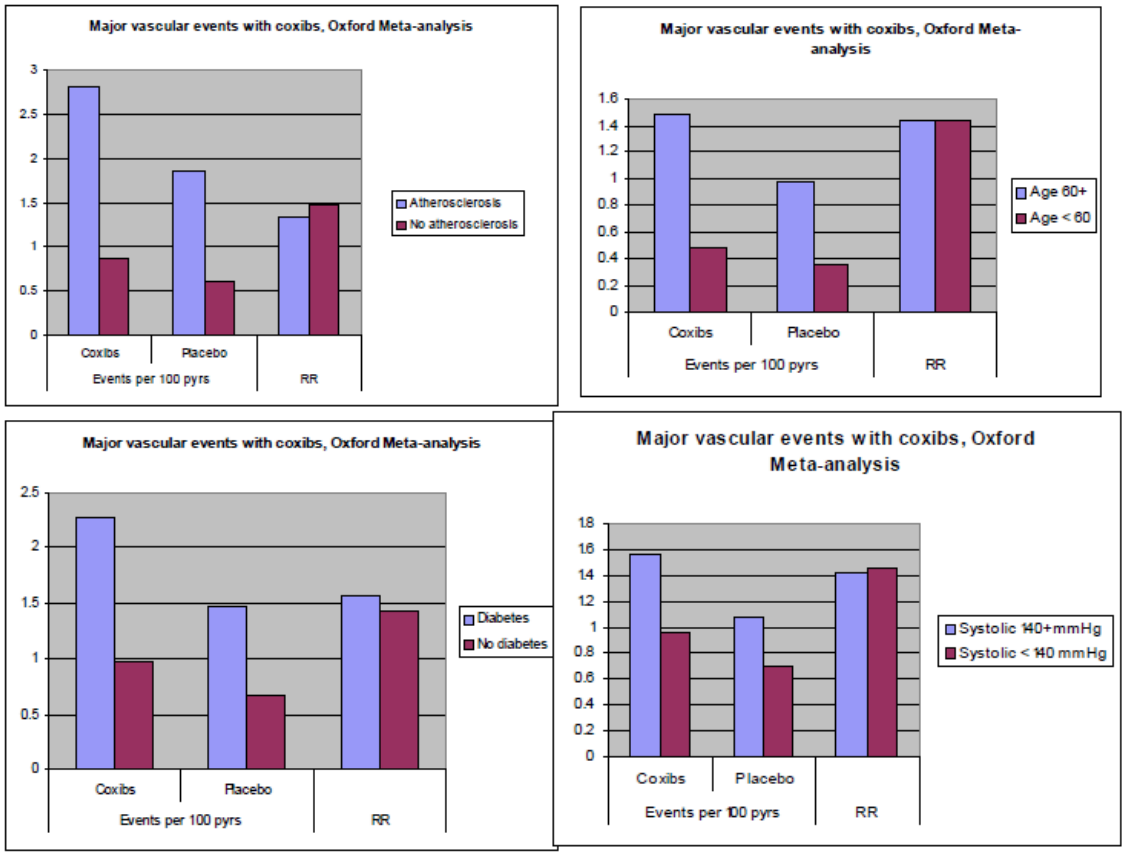
Comparisons of active treatments to each other were notable for the following findings. Coxibs had a significantly increased rate ratio for major vascular events compared to naproxen (rate ratio and 95% CI 1.49, 1.16-1.92 overall, and 1.65, 1.21-2.24 in patients with a history of atherosclerosis), while coxibs had significantly decreased risk of upper GI complications relative to either naproxen (0.37, 0.28-0.49) or ibuprofen (0.40, 0.25-0.64).

Subgroup analyses in general detected no important differences in risk; however, statistical power was limited. A history of atherosclerosis did not appear to impact point estimates for cardiovascular rate ratios. For any GI event, current smokers appeared to have a lower risk, and current aspirin (ASA) users a higher risk, with non-naproxen NSAIDs. Naproxen also appeared to convey a higher risk of any symptomatic GI event among ASA users.

Notably, ASA use did not have a discernable influence on rate ratios for major vascular events; ASA users were only 1/5 of the total sample, so the statistical power for comparison was limited.

Similarly, gastroprotectant medication did not appear to change the risk for a GI event, but gastroprotection users were only 1/5 of the total sample, so the same statistical limitations apply.

Point estimates for the vascular event incidence rates were generally higher in subgroups of patients with specific cardiovascular risk factors, for both NSAID-treated and placebo patients, as would be expected; however, the rate ratios for NSAID:placebo were generally similar whether patients had that specific risk factor or not. Some examples are shown in the figure below for coxibs (the incidence rates by subgroup were only provided for coxibs). In other words, the increase in the absolute incidence of vascular events resulting from NSAID exposure is greater among patients with cardiovascular risk factors, but the proportionate increase over a patient's baseline vascular event rate appears similar, whether the patient has or does not have that CV risk factor.



With respect to duration of treatment, subgrouping by 6 month intervals did not reveal any clear trends in rate ratios versus placebo for major vascular events, though the highest point estimates were after 18 months for coxibs and diclofenac. For GI events, risks relative to placebo were highest in the first 6 months for all treatments.

Regarding individual coxib compounds, for major vascular events, the rate ratio versus placebo was almost identical for celecoxib and rofecoxib (1.36, CI 0.91-2.02 for celecoxib and 1.38, CI 0.99-1.94 for rofecoxib). Other coxib compounds had very sparse data on major vascular events. With respect to dose, there was a statistically significant trend for higher risk by dose of celecoxib, across doses of 200, 400 and 800 mg/day. The rate ratio for celecoxib 200 mg/day was 0.95, but with a wide confidence interval of 0.30-3.00. For the small number of trials comparing coxibs to diclofenac directly, the rate ratio for major vascular events for celecoxib versus diclofenac was 0.94 (0.54-1.63) and for rofecoxib versus diclofenac 0.45 (0.16-1.22).

In addition to rate ratios, the investigators also estimated incidence rate differences (NSAID incidence rate minus placebo incidence rate) for major vascular events (MVE) and upper GI complications (UGIC). Excess risks per 1000 person years of treatment were estimated by applying the rate ratios to hypothetical patient populations with high (2% per annum, or 20 per 1000 person years) or low (5 per 1000 person years) baseline rates of the events of interest. Numbers of either type of event expected to be fatal were also estimated. The analysis was predicated on the assumption that rate ratios are consistent across different levels of baseline risk. The results are shown in the following graph, reproduced from the paper.

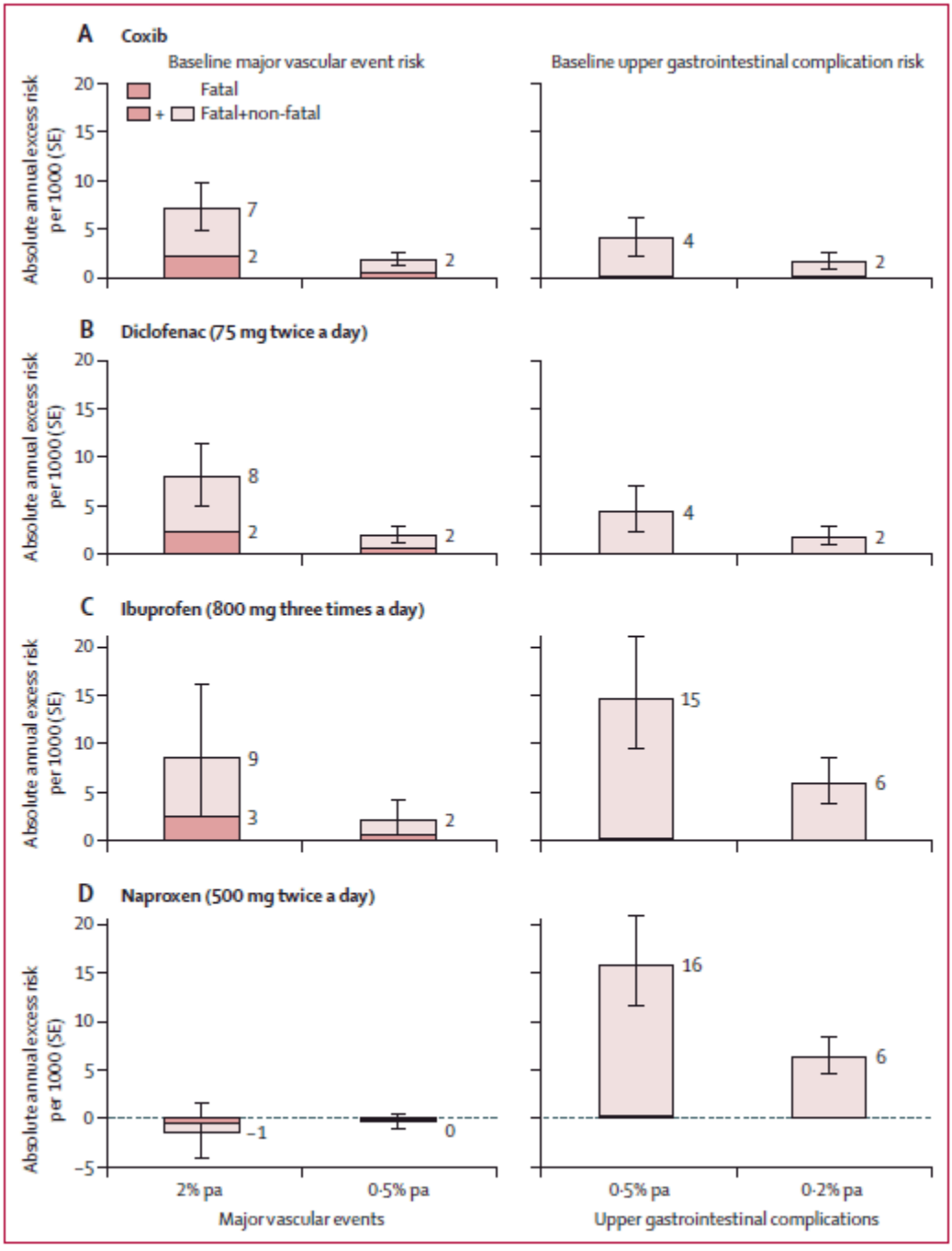


Figure 5: **Annual absolute effects per 1000 of coxibs and tNSAIDs at different baseline risks of major vascular events and upper gastrointestinal complications**

3.5 STUDY CONCLUSIONS

The investigators concluded that diclofenac and coxibs were associated with "small but serious" vascular risks, with roughly 3 excess major vascular events per 1000 person years of treatment, one of which was fatal. (This represents roughly 1 excess death per 500 patient-years of exposure.) Ibuprofen was associated with a two-fold increased risk in major coronary events (though not a statistically significant increase in major vascular events). Naproxen was not associated with major vascular events or vascular death. All treatments were associated with hospitalizations for heart failure and with upper GI complications, though coxibs had the lowest rate ratio for upper GI complications (followed by diclofenac). The authors urged that the null association of naproxen with vascular events be treated with caution, despite its hypothesized aspirin-like effect on platelets, for the following reasons: they could not adequately analyze the effect of naproxen on cardioprotection from low-dose aspirin; the anti-platelet effects of naproxen 1000 mg/day may not be present at lower doses; and an immediate anti-platelet effect may not counteract longer-term effects promoting atherosclerosis.

4 DISCUSSION

This meta-analysis has many important strengths, but foremost among them is use of randomized datasets. A number of observational studies have assessed cardiovascular risks of NSAIDs, as described in the 12-4-2012 DEPI II review, but all are subject to the possibility of unknown/unmeasured confounding factors, which randomization renders unlikely. Accordingly, risk estimates from randomized trial data are not subject to the same limitations as risk estimates from observational studies. The finding of cardiovascular risk for compounds other than naproxen in a dataset not subject to selection bias supports the hypothesis that past observational studies which showed protective effects from NSAID use may have been affected by "healthy user bias" (e.g., Ref#4 in the previous review[6]).

Another strength of the analysis was a sufficient number of events to characterize the case fatality rate of major vascular events and upper GI complications. However, it should be borne in mind that the mean age of these subjects was 61 years, so cardiovascular risks may have been more salient than they would have been in a young adult sample. The risk of fatal vascular events in terms of number needed to harm was roughly 1 in 500 person years, a much lower frequency of cardiovascular death than in some observational studies focusing on vulnerable populations.

Limitations of the analysis included the following. Some trials were missing individual patient data, so trial-level meta-analysis methods were necessary to permit use of all the trial data (the investigators could have elected to conduct a subgroup analysis using only patient-level data). Also, as described, comparisons to placebo for tNSAIDs had to be derived indirectly from tNSAID-coxib comparisons and coxib-placebo comparisons. Subgroup analyses according to patient baseline characteristics generally lacked sufficient statistical power, a problem exacerbated by the practice of treating patients with missing data as their own separate stratum. However, by inspection of the data displayed in the Webfigures, eliminating patients with missing data from specific subgroup analyses would probably not have materially affected most of those results.[7] Events were too sparse to determine to what extent the risk varies with duration of treatment. Most data on tNSAIDs pertained to one dose level; celecoxib was the only compound for which the data allowed a meaningful dose-response analysis. No associations were found with stroke, perhaps because the number of events was relatively smaller, though the point estimates were not as elevated as for other outcomes.

Only a proportion of the outcomes were validated by adjudication (that proportion is not specified in the paper), so misclassification of outcomes was possible. However, misclassification of outcomes would be expected to bias risk estimates towards the null unless the misclassification

was nonrandom, and there is no obvious basis to hypothesize differential misclassification. Another consideration regarding the outcome definition is that vascular death as defined by the Antiplatelet Trialists Collaboration will include some events not relevant to NSAID use (e.g., death from pulmonary embolism is considered a vascular cause of death[8]); again, including events not specifically related to NSAID toxicity in the numerators would be expected to bias the risk estimates towards the null.

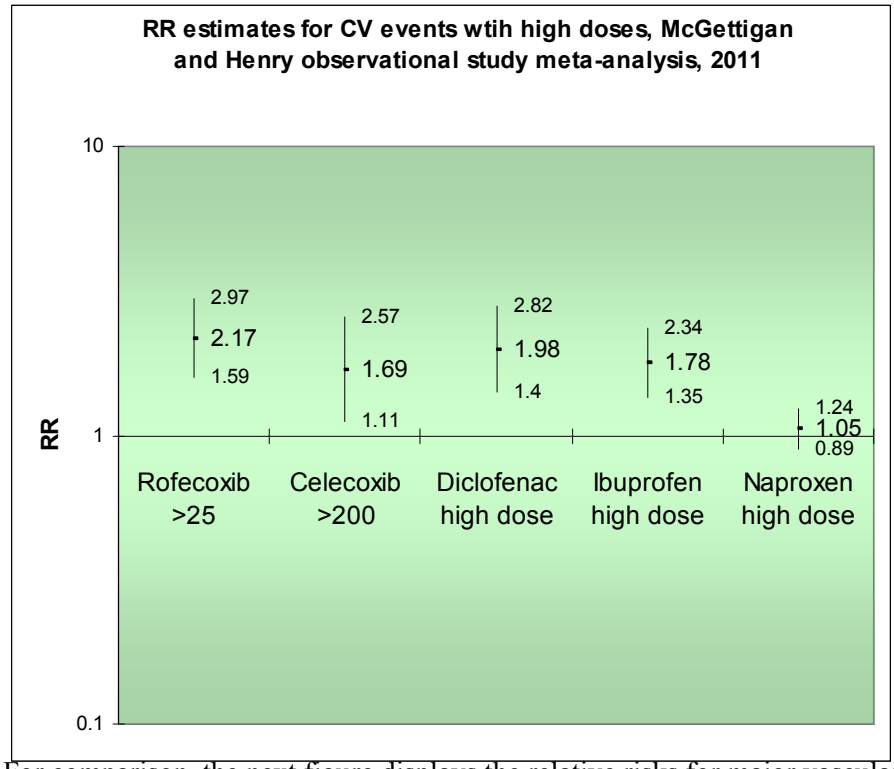
This analysis was not able to show a reduction in upper GI adverse events from concurrent gastroprotective medication, but the subgroup of patients receiving gastroprotective therapy at baseline was probably too small to measure such an effect. Another factor may have been compliance. A recent study raises concerns about long-term compliance with gastroprotective medication; in that study, NSAID-treated patients who discontinued their gastroprotective agent experienced more GI adverse events.[9]

In terms of compounds relevant to the U.S. market, the analysis provides data for celecoxib, ibuprofen, naproxen, and diclofenac. Although data on six different coxibs were analyzed, Webfigure 14 in the paper shows that 88% of the major vascular events in coxib-treated patients occurred with celecoxib or rofecoxib. Accordingly, those two compounds had the only meaningful individual rate ratio estimates, which were similar (1.36 with 95% CI 0.91-2.02 for celecoxib, 1.38 with 95% CI 0.99-1.94 for rofecoxib). However, of the 126 major vascular events with celecoxib treatment, 111 occurred at higher doses of 400 or 800 mg/day.

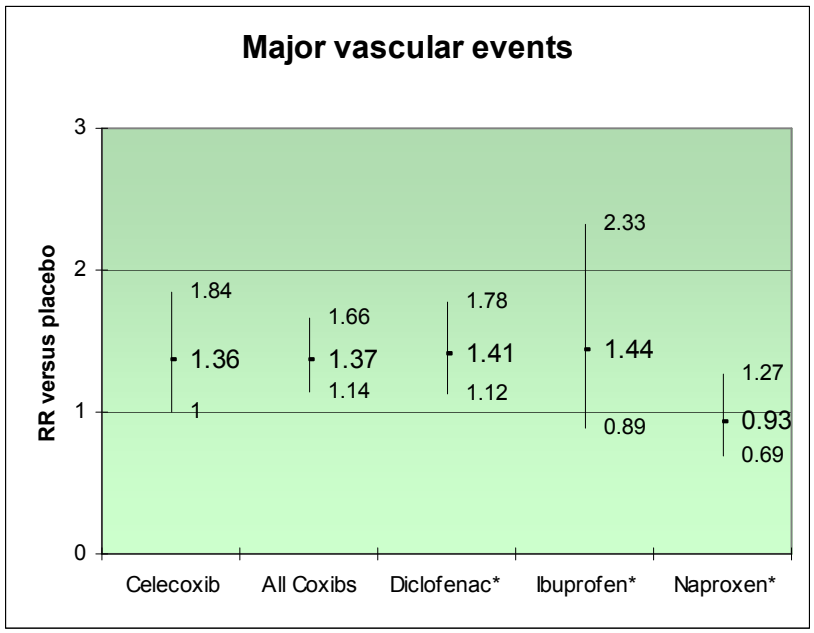
Regarding the CNT author's hypothesis that naproxen may have an inverse dose-response for cardiovascular risk, and that low dose naproxen might have shown a greater risk than 1000 mg/day, no observational studies described in the previous review reported such a directionality, though the ADAPT clinical trial found a cardiovascular risk from naproxen 440 mg daily.[10]

It may be instructive to examine how the results of this meta-analysis are, or are not, in agreement with the pharmacoepidemiology literature described in the previous DEPI II review. As noted, the CNT meta-analysis was not able to provide evidence on certain aspects of the cardiovascular risk evaluated in the published studies, such as the time course of the risk, the risk of stroke, the effect of concomitant aspirin, the effect of dose (for compounds other than celecoxib), and the risk from over-the-counter doses of naproxen and ibuprofen. The CNT meta-analysis did assess risks according to the patient's baseline risk factors, finding that the patient's modeled risk for either major vascular events or ulcer did not influence their relative risk of vascular or upper GI events with NSAID treatment, though statistical power for these subgroup comparisons was limited. With respect to risk by compound, the CNT results are in agreement with previous data indicating less cardiovascular risk for naproxen, and with data indicating comparable cardiovascular risks from diclofenac and coxibs. The high level of cardiovascular risk observed with ibuprofen 2400 mg/day in the CNT dataset was observed in the Danish national healthcare data (ref 64[11]) and the General Practice Research Database (ref 88[12]).

It may also be instructive to compare the compound-specific cardiovascular risks with the relative risk estimates from the 2011 meta-analysis of 51 observational studies by McGettigan and Henry.[13] The figure below shows the cardiovascular event relative risk for users of higher doses of rofecoxib, celecoxib, diclofenac, ibuprofen, and naproxen.



For comparison, the next figure displays the relative risks for major vascular events from the Oxford CNT meta-analysis of clinical trial data. There was no association with naproxen in either analysis.



*RR derived from indirect comparison

5 CONCLUSION

- Coxibs had a significantly higher risk of major vascular events compared to naproxen 1000 mg/day.
- Risk estimates for vascular events with coxibs, ibuprofen 2400 mg/day and diclofenac 150 mg/day were comparable.
- Relative risk for major vascular events appeared similar between patients with or without baseline cardiovascular risk factors, but the incidence differences (incidence among NSAID group minus incidence among placebo group) were greater in higher risk patients.
- No vascular risk was observed with naproxen (excepting heart failure).
- Coxibs had significantly lower risk of upper GI complications compared to naproxen 1000 mg/day or ibuprofen 2400 mg/day. The risk of GI events with diclofenac appeared comparable to that for coxibs.
- All treatments were associated with a statistically significant risk of hospitalization for heart failure.
- Vascular risks of celecoxib were dose related, with the risk at doses above 200 mg/day appearing similar to that for rofecoxib.
- A higher proportion of vascular adverse events than upper GI adverse events were fatal, in this sample of older adults treated with NSAIDs.
- Taking into account deaths from major vascular events and upper GI complications, among the treatments analyzed, the absolute risk increase for a fatal event was lowest with naproxen 1000 mg/day.

6 RECOMMENDATIONS

In order to reduce the population burden of drug-related deaths from NSAID toxicity, naproxen should be considered first line NSAID treatment in patients for whom the risk of cardiovascular adverse events is relevant. Accordingly, the class NSAID labeling should be amended to reflect the more favorable cardiovascular risk profile of naproxen. The labeling can also note that naproxen had a less favorable GI risk, but that GI events were less likely to be fatal than CV events.

The NSAID labeling should be updated with respect to the association with heart failure. Current NSAID labeling states, “Fluid retention and edema have been observed in some patients taking NSAIDs,” but it is now possible to make a stronger statement.

The recommendations from the 12-4-2012 DEPI II review should still be considered valid in the light of this new analysis, though the conclusion that diclofenac has a particularly unfavorable cardiovascular risk profile is now tempered by the finding that ibuprofen at a dose of 2400 mg/day had a comparable risk.

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

META-ANALYSIS REVIEW

TSI:	1230
Product Class:	Non-steroidal anti-inflammatory drugs (NSAIDs)
Classification of Drugs:	Analgesia
Date(s):	Consult received 02/07/2013
Document(s) reviewed:	"Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials"
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Eugenio Andraca-Carrera, Ph.D.
Concurring Reviewers:	Mat Soukup, Ph.D.
Medical Division:	Division of Anesthesia, analgesia, and Addiction Products (DAAAP)
Clinical Division Director:	Judith Racoosin
Project Manager:	Ayanna Augustus

Keywords: meta-analysis, cardiovascular safety

1 Introduction

The Coxib and traditional NSAID Trialists' (CNT) Collaboration conducted a meta-analysis of major vascular events and upper gastrointestinal complications based on individual participant data and trial-summary data from randomized clinical trials of COX-2 inhibitors (referred to as coxibs) versus placebo, traditional NSAIDs ("tNSAIDS", referring to non-coxibs NSAIDs) versus placebo, and NSAIDs versus other NSAIDs. The CNT reported the findings of their meta-analysis in a manuscript titled "Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials" dated 7th February 2013. In the present document, we conduct a statistical review of this manuscript, which we will refer to as the "2013 meta-analysis".

We will discuss the data sources, statistical methods and results of the 2013 meta-analysis and compare them to a similar meta-analysis reported by Kearney, Baigent, et al. (2006)[1], which we will refer to as the "2006 meta-analysis".

2 Outcomes

The outcomes of interest of the 2013 meta-analysis were major vascular events (nonfatal myocardial infarction, nonfatal stroke or vascular death), mortality, heart failure, and upper gastrointestinal complications (perforation, obstruction or bleed). The meta-analysis used adjudicated outcomes where available and un-adjudicated outcomes based on MedDRA codes otherwise.

Reviewer's Comment:
When possible, the use of adjudicated outcomes based on a pre-specified detection and adjudication process is advisable. We acknowledge that such a process is likely not feasible within the scope of the 2013 meta-analysis.

3 Data Sources

Trials longer than 4 weeks of duration and comparing at least one NSAID to placebo or to another NSAID were eligible to be included in the 2013 meta-analysis[1].

Table 1 shows the number of trials and person years used in the 2006 and 2013 meta-analyses. The 2006 meta-analysis used trial-level summary data only, whereas the 2013 meta-analysis used a combination of patient-level and trial-level data. A high percentage of the data used in the 2013 meta-analysis were patient-level, as shown in Table 1.

Analyses of vascular events comparing all coxibs to placebo in the 2013 meta-analysis included 52,628 total patient-years of exposure to both treatment arms, coxibs and placebo, and 482 total vascular events; which represent a 69% increase in total patient-years and a 47% increase in the

[1] Figure 1 in the 2013 article depicts the PRISMA flow diagram for how the final set of trials was selected.

number of vascular events over the 2006 meta-analysis (31,129 patient-years and 328 vascular events).

The tables included in both meta-analyses reports were insufficient to calculate exactly how many additional patient years were used in the 2013 meta-analysis comparing all coxibs to all tNSAIDs. Table 1 shows that the 2006 meta-analysis included 56,585 total patient-years of exposure comparing all coxibs to all tNSAIDs. The 2013 meta-analysis included 90,644 patient years comparing coxibs to diclofenac, 11,668 years comparing coxibs to ibuprofen, and 31,633 years comparing coxibs to naproxen. However, it is unclear how many trials in the 2013 meta-analysis included a coxib and more than one tNSAID treatment arms.

***Reviewer's Comment**:*
The 2013 meta-analysis manuscript did not list total patient-years and events by trial. Therefore, it is not possible to determine whether one or more trials contributed the majority of the available information for any pairwise treatment comparison. Large studies have the potential to largely influence parameter estimates in meta-analyses.

Table 1. Data sources for the 2006 and 2013 meta-analyses

		Trials with available data	Person Years	PY from Individual Patients' Data	Vascular events	
					COX 2	Comparator
2006	coxibs vs. placebo	121	31129	-	216	112
	coxibs vs. tNSAIDs	91	56585	-	340	211
2013	coxibs vs. placebo	184	52628	88%	307	175
	coxibs vs. diclofenac	33*	90644*	99%	386*	378*
	coxibs vs. ibuprofen	22*	11668*	99%	43*	41*
	coxibs vs. naproxen	48*	31633*	95%	167*	88*
	tNSAIDs vs. placebo	158	16305	49%	NA	NA

*Some trials may have included a coxib and more than one tNSAIDs treatment arm and therefore may have been counted in multiple rows on this table.

4 Statistical Methodology

The 2013 meta-analysis estimated rate ratios of the outcomes of interest through a combination of direct and indirect treatment comparisons. Rate ratios are defined as number of events divided by number of patient years of exposure. Rate ratios comparing coxibs versus placebo and coxibs versus tNSAIDs were estimated based on randomized clinical trials with direct comparisons of the treatments of interest. Rate ratios comparing tNSAIDs versus placebo were estimated through a combination of trials with a direct comparison of tNSAIDs versus placebo (16,305 patient-years according to Table 1) plus indirect comparisons based on randomized trials of coxibs versus placebo and coxibs versus tNSAIDs.

Direct comparisons (coxibs vs. placebo and coxibs vs. tNSAIDs) estimated the rate ratio of events of interest by calculating the observed and expected number of events under the null hypothesis of no difference between treatments (rate ratio of 1) in each trial. Under the null hypothesis, the sum of observed minus expected events has expectation equal to zero. The sum

of observed minus expected events across trials was used to estimate the overall rate ratio and its associated variance. This method is commonly used in meta-analyses [2, 3]. It is unbiased but not optimal to estimate the rate ratio when the true rate ratio is different from one [3]. When patient-level data is available for all trials, other methods exist that estimate the rate ratio with a smaller variance.

Reviewer's comment:
The statistical methodology used to estimate rate ratios based on trials with direct treatment comparisons is appropriate given that it combines summaries from both patient-level and trial level data. The observed minus expected method allows for a valid combination of rate ratio estimates based on the available data. If patient-level data were available for all trials, other statistical methods would be more efficient.

Indirect comparisons (tNSAIDs vs. placebo) estimated the rate ratio of events of interest through a simplified network meta-analysis approach. Let δ_1 be the log(rate ratio) between coxibs and placebo for an event of interest and δ_2 be the log(rate ratio) between coxibs and ibuprofen. The log(rate ratio) for the event of interest between ibuprofen and placebo can be estimated by $\delta_1 - \delta_2$ with corresponding variance: $\text{Var}(\log(\text{rate ratio})) = V_1 + V_2$.

Reviewer's comment:
The statistical methodology used to estimate rate ratios based on trials with indirect treatment comparisons can be thought of as the simplest possible network meta-analysis with a single path connecting A-B-C, where the interest lies in comparing A to C. The estimator of the variance of the rate ratio comparing A to C accounts for the fact that the comparison of these two treatments is indirect through B. This methodology is adequate for conducting indirect comparisons of two treatments. The methodology is well documented in the literature of network meta-analysis[4].

In general, the validity of indirect comparisons depends on the "internal validity and similarity of the included trials"[5]. When the conditions of internal validity and similarity hold, indirect and direct comparisons have been found to usually (but not always) agree with each other [5,6]. The authors argue that the indirect comparisons in their 2013 meta-analysis meet these conditions: "placebo-controlled and tNSAID controlled trials involved the same typical doses of coxibs. Secondly, the populations in these two sets of trials were demographically similar. Thirdly, fixed (high) daily dosages were used for the 3 main tNSAIDs studies" and "there was little heterogeneity in the rate ratios for treatment effects in different types of patients."

We found one aspect of the meta-analysis that may limit the interpretability of indirect comparisons:

- *According to the authors, the indication for treatment with an NSAID was rheumatoid arthritis or osteoarthritis in approximately 80% of the participants, but among trials of coxibs versus placebo the indication was the prevention of colonic adenomata or of Alzheimer's in approximately 25% of the participants.*

It is unclear whether combining trials for different indications compromises the interpretability of indirect comparisons between tNSAIDs and placebo. It is possible that these comparisons may still be considered valid and interpretable given that the authors found no heterogeneity in the rate ratios in different types of patients and that more than 75% of the trials were conducted in

patients with rheumatoid arthritis or osteoarthritis. However, one potentially informative analysis not included in the manuscript would involve indirect treatment comparisons between tNSAIDs and placebo based on trials for rheumatoid arthritis and osteoarthritis only.

In our opinion, the indirect comparisons between tNSAIDs and placebo in the 2013 meta-analysis reasonably meet the conditions to be considered valid. However, this is a subjective assessment. Indirect comparisons should be considered somewhat less reliable than direct comparisons.

5 Results

Table 2 shows a summary of the main results of the 2006 meta-analysis. Table 3 shows a summary of the 2013 meta-analysis. Both sets of results are consistent. To summarize, the 2013 meta-analysis obtained the following results:

- Coxibs appear to be associated with increased risk of major cardiovascular events, MI, vascular death, overall mortality, heart failure and upper GI complications compared to placebo.
- Coxibs appear to be associated with increased risk of major cardiovascular events and MI compared to naproxen, but not compared to ibuprofen or diclofenac.
- Diclofenac appears to be associated with increased risk of major cardiovascular events, MI, heart failure and upper GI complications compared to placebo*.
- Ibuprofen appears to be associated with increased risk of MI, heart failure and upper GI complications compared to placebo*, and possibly with increased risk of major cardiovascular events: RR 1.44, 95% CI 0.89-2.33.
- Naproxen appears to be associated with increased risk of upper GI complications compared to placebo* and to coxibs.
- Naproxen appears to be associated with increased risk of heart failure, but not with other CV outcomes compared to placebo*.
- No difference in the risk of strokes was detected between any two treatments and/or placebo.

*Comparisons between tNSAIDs and placebo are based on indirect evidence, as discussed earlier.

Table 2. Results from 2006 Meta-Analysis (RR and 95% CI)

	Major vascular events	MI	Stroke
coxibs vs. placebo	1.42 (1.13, 1.78)	1.86 (1.33, 2.59)	1.02 (0.71, 1.47)
coxibs vs. naproxen	1.57 (1.21, 2.03)	2.04 (1.41, 2.96)	1.10 (0.73, 1.65)
coxibs vs. any tNSAID	1.16 (0.97, 1.38)	1.53 (1.19, 1.97)	0.83 (0.62, 1.12)
diclofenac vs. placebo*	1.63 (1.12, 2.37)	-	-
ibuprofen vs. placebo*	1.51 (0.96, 2.37)	-	-
naproxen vs. placebo*	0.92 (0.67, 1.26)	-	-

Table 3. Results from 2013 Meta-Analysis (RR and 95% CI)

	Major vascular events	MI or CHD death	Stroke
coxibs vs. placebo	1.37 (1.14, 1.66)	1.76 (1.31, 2.37)	1.09 (0.78, 1.52)
coxibs vs. naproxen	1.49 (1.16, 1.92)	2.11 (1.44, 3.09)	1.14 (0.74, 1.73)
coxibs vs. ibuprofen	0.92 (0.58, 1.46)	0.81 (0.41, 1.61)	1.00 (0.44, 2.25)
coxibs vs. diclofenac	0.97 (0.84, 1.12)	1.04 (0.84, 1.28)	0.92 (0.71, 1.20)
diclofenac vs. placebo*	1.41 (1.12, 1.78)	1.70 (1.19, 2.41)	1.18 (0.79, 1.78)
ibuprofen vs. placebo*	1.44 (0.89, 2.33)	2.22 (1.10, 4.48)	0.97 (0.42, 2.24)
naproxen vs. placebo*	0.93 (0.69, 1.27)	0.84 (0.52, 1.35)	0.97 (0.69, 1.27)

Table 3 . (continued)

	Vascular death	Any cause death	Hospitalization for heart failure	Upper GI complications
coxibs vs. placebo	1.58 (1.00, 2.49)	1.22 (1.04, 1.44)	2.28 (1.62, 3.20)	1.81 (1.17, 2.81)
coxibs vs. naproxen	1.53 (0.89, 2.62)	1.23 (0.86, 1.75)	1.17 (0.76, 1.79)	0.37 (0.28, 0.49)
coxibs vs. ibuprofen	0.83 (0.32, 2.16)	0.78 (0.43, 1.42)	0.83 (0.42, 1.64)	0.40 (0.25, 0.64)
coxibs vs. diclofenac	0.96 (0.74, 1.23)	1.02 (0.84, 1.24)	1.23 (0.87, 1.73)	0.94 (0.72, 1.24)
diclofenac vs. placebo*	1.65 (0.95, 2.85)	1.20 (0.94, 1.54)	1.85 (1.17, 2.94)	1.89 (1.16, 3.09)
ibuprofen vs. placebo*	1.90 (0.56, 6.41)	1.61 (0.90, 2.88)	2.49 (1.19, 5.20)	3.97 (2.22, 7.10)
naproxen vs. placebo*	1.08 (0.48, 2.47)	1.03 (0.71, 1.49)	1.87 (1.10, 3.16)	4.22 (2.71, 6.56)

5.1 Secondary Analyses

Subgroup analyses in the 2013 meta-analysis found no variation in the estimated rate ratio for cardiovascular outcomes or upper GI complications between any NSAID and several baseline measurements, including baseline cardiovascular risk.

Analyses of temporal trends suggested that the risk of major cardiovascular events might be increased during the first 6 months for coxibs and diclofenac. However the available data was inconclusive.

The meta-analysis found evidence to suggest that the risk of upper GI ulcers is highest during the first 6 months of use of coxibs (RR 2.55, 99% CI 1.49-4.35), diclofenac (3.93, 99% CI 2.17-7.33), ibuprofen (5.73, 99% CI 3.16-10.39) and naproxen (6.31, 99% CI 3.74-10.65).

A statistically significant trend was found for increased risk of major vascular events associated with higher doses of Celecoxib compared to placebo.

6 Discussion

The 2013 meta-analysis conducted by the CNT was larger than the Kearney et al. 2006 meta-analysis[1] in terms of both number of patient-years and counts of events comparing coxibs to placebo, coxibs to tNSAIDs, and tNSAIDs to placebo. Whereas the 2006 meta-analysis was

based on summary level data only, the 2013 meta-analysis collected and used patient-level data from a large percentage of subjects as shown in Table 1.

The statistical methodology used to compare (directly) coxibs to placebo and coxibs to tNSAIDs in the 2013 meta-analysis is appropriate and is well documented in the literature of meta-analyses[2, 3]. More efficient methods exist when subject-level data is available for all subjects in a meta-analysis; however, the methodology used in the 2013 meta-analysis is appropriate for combining subject and trial-level data.

The statistical methodology used to compare (indirectly) tNSAIDs to placebo is a special case of a network meta-analysis. The methodology is valid conditionally on the assumptions of similarity of the participants in different trials and the comparability of the interventions. The authors found no evidence of heterogeneity of rate ratios across trials and noted that the clinical trials used in indirect comparisons had similar doses of coxibs and subjects with similar demographic characteristics. Therefore, we believe that the indirect comparisons of tNSAIDs versus placebo appear reasonably valid. However, these indirect comparisons should be interpreted with more caution than direct comparisons.

Two issues were not addressed in the 2013 meta-analysis that would help the interpretation of its results:

1. Indirect comparisons of tNSAIDS to placebo included trials for rheumatoid arthritis, osteoarthritis and Alzheimer's disease. The rheumatoid arthritis and osteoarthritis trials constitute the majority of the data used in these comparisons. A sensitivity analysis excluding trials for Alzheimer's would be useful to determine the impact of these trials on the estimated rate ratios.
2. The manuscript does not list the number of subjects, patient-years and number of events in each trial used in the meta-analysis. This information would be useful to assess the impact of large trials on the estimated rate ratios.

The results of the 2006 and 2013 meta-analyses are consistent. The 2013 meta-analysis found evidence of increased risk of major vascular events associated with coxibs vs. placebo (RR 1.37, 95% CI 1.14-1.66), coxibs vs. naproxen (RR 1.49, 95% CI 1.16, 1.92) and diclofenac vs. placebo (RR 1.41, 95% CI 1.12, 1.78). There was borderline statistically significant evidence of increased risk of major vascular events associated with ibuprofen vs. placebo (RR 1.44, 95% CI 0.89-2.33). There was no evidence of increased risk of major vascular events associated with naproxen vs. placebo (RR 0.93, 95% CI 0.69, 1.27). All NSAIDs were associated with increased risk of upper GI complications relative to placebo; however, the estimated rate ratio was highest among subjects on naproxen (RR 4.22, 95% CI 2.71-6.56) and ibuprofen (RR 3.97, 95% CI 2.22-7.10).

Note that the estimated rate ratios represent different estimated increases in absolute risk for subjects with different background risks. A rate ratio of major vascular events associated with coxibs versus placebo of 1.37 translates into 7.4 additional events per 1000 patient-years in a population with a high cardiovascular baseline risk of 20 events per 1000 patient-years, and only 1.9 additional events per 1000 patient-years in a population with a baseline risk of 5 events per 1000 patient-years. The interpretation of the rate ratios estimated by this meta-analysis should consider the baseline risk of the population of interest.

Overall, the 2013 meta-analysis was adequately conducted. The trial inclusion criteria were clear and documented. The CNT collected subject-level data for a large percentage of trials. The outcomes of interest included a combination of adjudicated events and MedDRA terms and therefore may involve some measurement error. However, it is likely unfeasible to conduct a similar meta-analysis with fully adjudicated outcomes. The statistical methodology was adequate given the nature of the data sources (i.e. subject-level and trial-level data). Overall, from a statistical perspective, the estimated rate ratios of major vascular events, myocardial infarction, stroke, death, heart failure, and upper gastrointestinal complications may be considered adequate estimates of the risk of these outcomes. We advise some caution in the interpretation of indirect comparisons as discussed above.

7 References

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Concur with review

Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Observational data on NSAIDs and thrombotic cardiovascular events

Date:	December 3, 2012
Reviewer(s):	Andrew D. Mosholder, MD, MPH Division of Epidemiology II
Team Leader	Elizabeth M. Maloney, M.S., Dr.P.H. Division of Epidemiology II
Division Director	Judy A. Staffa, Ph.D., R.Ph Division of Epidemiology II
Drug Name(s):	Nonsteroidal anti-inflammatory drugs (NSAIDs)
Subject	Observational data on thrombotic cardiovascular events, 2005-2011
OSE RCM #:	2011-45

TABLE OF CONTENTS

ABBREVIATIONS

AC	Advisory Committee
afib	atrial fibrillation
aHR	adjusted hazard ratio
AMI	acute MI
APTC	Antiplatelet Trialists' Collaboration
ASA	aspirin (acetylsalicilate)
CABG	coronary artery bypass graft
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
Cox PH	Cox proportional hazards analysis
CV	cardiovascular
CVA	cerebrovascular accident
CVE	cerebrovascular event
DDD	defined daily dose
DM	diabetes mellitus
DMARD	disease-modifying antirheumatic drugs
DSMB	data safety monitoring board
GPRD	General Practice Research Database of the UK
HF	heart failure
HR	Hazard ratio
HRT, HT	hormone replacement therapy
HTN	hypertension
ID	incidence difference
IRR	incidence rate ratio
MA	meta-analysis
MI	myocardial infarction
nsNSAID	non-selective NSAID
OA	osteoarthritis
OOH	out of hospital
OR	odds ratio
OTC	over the counter
PS	propensity score
RA	rheumatoid arthritis
RCT	randomized clinical trial
re-MI	rehospitalization for MI
SOS	Safety of Non-Steroidal Anti-Inflammatory Drugs Project (sponsored by EMA)
stat sig	statistically significant
THIN	The Health Improvement Network database (U.K.)
TIA	transient ischemic attack
tNSAID	traditional NSAID
VA	Veteran's Affairs
WHI	Women's Health Initiative study
y.o.	years old

EXECUTIVE SUMMARY

In May 2011, researchers using the Danish national health care database published a study finding that patients with a history of myocardial infarction (MI) had a significantly increased risk of death or re-infarction with non-steroidal anti-inflammatory drug (NSAID) use, as early as the first week of NSAID use. The Division of Anesthesia, Analgesia, and Addiction Products asked the Division of Epidemiology II to review this study, along with any other literature published since 2006 on the topic of thrombotic cardiovascular events with NSAID use. The FDA Medical Library performed a literature search in August 2011 to identify publications of other observational and epidemiologic studies of NSAID cardiovascular risks published since 2006. A total of 90 publications were returned in the search, of which 16 were duplicates, leaving 74 publications for review. This review summarizes the data in these 74 publications.

The publications are summarized in a table that is attached to this review. In addition, all the articles are available electronically in a shared directory folder: <\\fdsfs01\ode2\DAAAP\DAAAP-Safety\NSAIDs_CV>

The following summarizes some conclusions regarding the thrombotic cardiovascular risks of NSAIDs that can be put forward on the basis of this literature review.

- The NSAID-associated risk for death or re-infarction found in the Danish study is supported by other literature, though few studies specifically included a post-MI population.
- Dose response: The risk appears dose-related.
- Time course: The risk occurs without a latency period.
- Patient factors: Risks in absolute terms are considerably higher for vulnerable patients, such as those with heart disease, but NSAID use also increases cardiovascular events among apparently healthy patients.
- An increase in fatal cardiovascular outcomes with NSAID use, at a clinically relevant frequency, has been observed in both vulnerable populations and unselected populations.
- Risk by compound: Diclofenac appeared to have a level of risk overlapping with rofecoxib, while lesser risks were generally observed with naproxen.
- ASA: Naproxen and ibuprofen are believed to inhibit the cardioprotective actions of ASA, though naproxen may have cardioprotective effects in the absence of ASA. Some data suggest ASA can reduce NSAID cardiovascular risk.
- OTC use: There were no data on OTC dosages of ketoprofen. Two studies from Denmark showed associations with cardiovascular events for naproxen $\leq$ 660 mg/day. For ibuprofen $\leq$ 1200 mg/day, six studies found an increase in cardiovascular events.
- Stroke is associated with NSAID use.

With these findings in mind, the following recommendations are offered.

- Labeling: The NSAID class labeling enacted in 2005 is generally still valid, but specific statements can be updated.
    - The statement that the risk may be similar across NSAID compounds can be amended. There now seems to be a sufficient amount of evidence, from observational data and clinical trials, to conclude that among tNSAIDs, naproxen is likely to have a lesser cardiovascular risk and diclofenac a higher risk, particularly for MI.

- The statement that patients with cardiovascular risk factors are at greater risk can be clarified to indicate that the risk is not limited to such patients.
- The advice to use an NSAID for the shortest duration possible should be clarified to indicate that short term use does not guarantee avoidance of risk.
- Extending the existing contraindication in post-CABG patients to other high-risk patients (e.g., post-MI patients) should be considered.
- Labeling for naproxen and ibuprofen (prescription and OTC) should include the best current advice on how to avoid impeding the cardioprotective effects of ASA.

- To the extent that the cardiovascular risk with diclofenac is similar to that with rofecoxib, and rofecoxib was removed from the market for cardiovascular risks, the risk-benefit balance for diclofenac should be re-evaluated.
- The cardiovascular risk labeling for prescription ibuprofen should be extended to OTC ibuprofen (this should oblige a re-evaluation of its OTC risk-benefit balance). Strengthening the naproxen OTC cardiovascular risk labeling may also be considered, but there are fewer data indicating a risk for OTC naproxen.
- The report of the Safety of Non-Steroidal Anti-Inflammatory Drugs Project (SOS), and the report of the Oxford University-based Coxib and Traditional NSAID Trialists' Collaboration (CNT) meta-analysis, should be informative for NSAID labeling, and should be requested.

1 INTRODUCTION

In May 2011, researchers using the Danish national health care database published a study finding that patients with a history of myocardial infarction (MI) had a significantly increased risk of death or re-infarction with non-steroidal anti-inflammatory drug (NSAID) use, and that the risk appeared as early as the first week of NSAID use.[1] The Division of Anesthesia, Analgesia, and Addiction Products asked the Division of Epidemiology II to review this study, along with any other literature published since 2006 on the topic of thrombotic cardiovascular events with NSAID use.

In September 2004, the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial was halted early because of an excess of adverse cardiovascular events in the rofecoxib arm, and Vioxx was withdrawn from the market worldwide. The final analysis of the cardiovascular events in that trial indicated that the composite endpoint of non-fatal MI, non-fatal stroke, and death from cardiovascular, haemorrhagic, and unknown causes (Antiplatelet Trialists' Collaboration [APTC] combined endpoint) had a hazard ratio (HR) of 1.79 (95% CI 1.17–2.73) versus placebo treatment.[2] Although both nonfatal MIs and nonfatal strokes were increased with rofecoxib, most of the events (56%) were nonfatal MIs, the outcome with the strongest statistical association among the individual endpoints.

In April 2005, FDA announced that it was requesting class labeling for both prescription and over-the-counter NSAIDs regarding the risks of thrombotic cardiovascular events.[3] The class labeling that was enacted is shown here (source: Clinoril (sulindac) label).

> WARNINGS
>
> CARDIOVASCULAR EFFECTS--Cardiovascular Thrombotic Events
>
> Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective

and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see GI WARNINGS).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see CONTRAINDICATIONS)

The purpose of this review is to determine if new information from observational studies published in the years following enactment of the class labeling could inform the labeling regarding cardiovascular risks.

2 REVIEW METHODS AND MATERIALS

2.1 DOCUMENTS TO BE REVIEWED

The main source for this review was the literature search conducted by FDA Librarians Joyce Kitzmiller and Gwendolyn Halford. This search returned a variety of article types including commentaries, review articles, observational study reports, clinical trial reports, and meta-analyses; however, the references in the category of Epidemiologic Studies were the specific subject of this review.

The following is a description of the search strategy employed for Epidemiologic Studies, in Pubmed and Embase.

NSAID Search Strategy (8-11-11) in Pubmed:

Nsaids [ti/ab] OR nsaid [ti/ab] OR "anti-inflammatory agents, non-steroidal [mesh] OR Anti-inflammatory agents, non-steroidal [pharmacological action]

AND

Stroke [mesh] OR heart arrest [mesh] OR myocardial ischemia [mesh] OR intracranial embolism AND thrombosis [mesh] OR brain ischemia [mesh] OR Cardiovascular event(s) [ti/ab] OR "cardiovascular stroke" [ti/ab] OR "myocardial ischemia(s) [ti/ab] OR "myocardial infarction(s)" [ti/ab] OR "heart attack(s) [ti/ab] OR "myocardial arrest' [ti/ab] OR "cardiac arrest" [ti/ab] OR "cardiovascular death" [ti/ab] OR "cardiovascular sudden death" [tiab] OR "cardiovascular thrombotic event(s) [ti/ab]

Limits: Human, published in the last 5 years, English OR English Abstract

Search term: Epidemiologic Studies [mesh]. Excluded letters, comments, editorials. See http://www.ncbi.nlm.nih.gov/mesh?term=epidemiologic%20studies

Embase Targeted Search with Subheadings (08-29-11):

Limits 2006-2011, human, English

For NSAIDS and CV Events - Epidemiologic Studies:

Database Pubmed (2005-2011, English or Eng. Abstract, human)

Search terms:

NSAIDS [title/abstract] OR NSAID [title/abstract] OR Anti-inflammatory agents, non-steroidal [mesh] OR Anti-inflammatory agents, non-steroidal [pharmacological action]

AND

(stroke [mesh] OR heart arrest [mh] OR myocardial ischemia [mh] OR intracranial embolism and thrombosis [mesh] OR brain ischemia [mesh] OR cardiovascular event(s) [ti/ab] OR "cardiovascular thrombotic events" [ti/ab] OR ischemias [ti/ab] OR myocardial infarction(s)" [ti/ab]) OR "heart attack" [ti/ab] OR "myocardial ischemia(s)"[ti/ab] OR "heart arrest [ti/ab] OR "cardiac arrest" [ti/ab] OR "cardiovascular death" [ti/ab] OR "cardiovascular sudden death" [ti/ab] or stroke [ti/ab])

AND

Epidemiologic Studies [MeSH]

The abstracts returned by these searches were screened by the librarians and by the review team in DAAAP, yielding a final count of 90 references considered relevant for this project. These abstracts were provided to DEPI-II and form the basis for this review. After removal of duplicates, a total of 74 unique publications remained for review. The articles are available electronically in the shared directory folder <\\fdsfs01\ode2\DAAAP\DAAAP-Safety\NSAIDs_CV> Though the primary focus of this literature search was epidemiologic studies, articles describing clinical trial data were also reviewed if they were returned by the search.

2.2 CRITERIA APPLIED TO REVIEW

The 12-13-11 consult request from DAAAP, authored by Katherine Won, PharmD, MBA, Safety Regulatory Project Manager, asked DEPI-II to focus on the following questions in our review:

> "1. Are there data to better refine the understanding of time to event for cardiovascular risk (including stroke) with NSAIDs? Early hazard vs. increased risk with cumulative use (or both, depending on the population)?
>
> 2. Describe any data that suggest specific vulnerable populations (e.g., h/o MI, CV risk factors, post-operative- CABG or others) for NSAID-associated CV risk (including stroke)
>
> 3. Does use of NSAIDs in patients with history of MI increase the risk of recurrent MI or death?
>
> 4. Are there data to support differential CV risk (including stroke) across the specific NSAIDs?"

These questions provided a framework for review of the 74 publications.

Additionally, the Division of Nonprescription Clinical Evaluation requested special attention to any studies that analyzed non-prescription dosages of over-the-counter (OTC) NSAIDs (namely, ibuprofen $\leq$ 1200mg/d, ketoprofen $\leq$ 75 mg/d, and naproxen $\leq$ 660 mg/d).

Each publication was reviewed and information was abstracted to address the following topics:

Study design	Objective
Data source	Time frame
Population	Sample size
Exposure categories	Outcomes
Analysis	Results
Data on vulnerable subgroups	Risk by compound
Risk with OTC dosages	Strengths and Limitations

The information thus abstracted from the publications was summarized in a spreadsheet, with one entry (row) for each published study. This summary spreadsheet is attached as an appendix to this review. References with entries in the spreadsheet will be identified herein by the abbreviation "Ref" followed by the number. Additional information was obtained from relevant publications that were not among the 74 articles returned in this literature search, and these are referenced at the end of this document. In one case the corresponding author provided more data about the study results.

3 REVIEW RESULTS

A. Time course of risk

We begin by considering the first consult question, regarding the time course of cardiovascular risk with NSAID use. Studies from the literature search that appeared capable of providing meaningful data on the time course of cardiovascular events with NSAID use are highlighted below; studies that simply appeared to have insufficient power or which did not account for duration of NSAID use are omitted from this summary.

There are biologically plausible reasons for both an early increased onset and a delayed increase in thrombotic cardiovascular events with NSAID use. Reduction of prostacyclin synthesis via COX-2 inhibition may reduce vasodilation and promote platelet aggregation, effects which could create a short term risk; however, inhibition of COX-2 also may affect vascular remodeling, blood pressure and atherogenesis, thereby increasing cardiovascular risk over an extended period of time.[4] Consistent with this hypothesis, data from the APPROVe trial, of rofecoxib for the prevention of colon polyps, were considered "compatible with an early increase in risk that persists for one year after stopping treatment," though the authors conceded that the data were sparse.[5] For the APTC endpoint, and including all events after randomization, the event curves diverged from the origin without a significant time interaction. In contrast, for the narrower event category of thrombotic cardiovascular events, with censoring 14 days after the end of treatment, there was a statistically significant time x treatment effect, and the HR appeared to increase with time.

A number of studies analyzing exposure to various coxibs and tNSAIDs found no apparent latency of the cardiovascular risk. Notably, Schjerning Olsen et al. (Ref#1) analyzed the risk of death or reinfarction among NSAID users with a history of MI and found that the risk was present from the first week of treatment. The table below lists the initial risk window for which a positive risk was found, by drugs and specific study.

Table 1. Observational studies finding no latency of NSAID-related cardiovascular risk

Initial time period associated with risk	Reference (drugs with risk)
5.8 days (first quartile for duration of use)	74 (rofecoxib)
1 week	1 (multiple)
1-2 weeks	68 (multiple)
1 month	6 (multiple) 11 (naproxen & ibuprofen) 15 (coxibs)
60 days	83 (rofecoxib)
1st prescription	88 (tNSAIDs)

Four studies found a stronger association with cardiovascular events during early exposure compared to subsequently (Ref#s 8, 11, 15, 74).

Authors of Ref#88, however, argued that the initial risk of NSAID therapy could be due to protopathic bias; the hypothesis being that patients who need to initiate NSAID therapy may have higher baseline cardiovascular risk at the time due to rheumatoid arthritis or similar confounders.

In contrast, eight observational studies (Refs# 1, 7, 12, 17, 21, 53, 68, 83) and one clinical trial meta-analysis (Ref#44) found no time-dependency of the risk. Ref #1 reported no clear time-related pattern of events in post-MI patients by week of exposure through 14 weeks. Ref# 7 studied healthy patients in the same Danish data system used in Ref#1, and reported no difference in risk for the first few days versus the remainder of treatment, though these data were not shown in the publication. Ref # 68 found elevated MI odds ratios across multiple NSAID exposure periods (1-14, 15-30, 31-90, and 91-180 days). Refs# 17, 53, and 44 also found no time-relatedness for risk, though they compared broader risk windows than the aforementioned studies. Finally, Refs # 12, 21, and 83 reported an absence of time dependency from inspection of event plots.

Other studies found a stronger association of adverse cardiovascular events with longer use (Refs# 10, 13, 32, 62, 75). Ref#88, though showing a positive risk with the initial prescriptions, also found that the unadjusted relative risk for MI increased linearly with duration of exposure.

With respect to the risk after discontinuation, the data are mixed. Ref#88 found that for long-term NSAID users the elevated hazard of MI persisted post-treatment, but the authors' interpretation was that represented persistent confounding rather than a long term risk from NSAID use. Ref#1 found that the risk persisted after discontinuation only for rofecoxib. Ref#62 found an elevated risk among long-term NSAID users, for both current and past use. However, other studies reported a stronger association with current use than recent or past use (Refs#15, 68, 87), and Ref#74 found that the relative risk for rofecoxib returned to around one in as little as one week after discontinuation. It should be recalled that data from two placebo-controlled trials, APPROVe and study 078 in patients with mild cognitive impairment,[6] showed a persistent cardiovascular risk from rofecoxib after the end of treatment

McGettigan and Henry reported that in their systematic review of NSAID observational studies, which partially overlaps with the present literature review, 9 out of 12 studies analyzing new users of NSAIDs showed an elevated cardiovascular risk during the first month.[7]

In sum, various time patterns for the cardiovascular risk were identified (i.e., studies found different contours to the hazard function). This may reflect not only variability in study designs and samples but also perhaps different mechanisms at work for long term versus short term risks. However, though some data pointed to a higher risk with longer treatment, there was little or no evidence for an absence of risk early in treatment; i.e., use of an NSAID for only a short period of time does not eliminate the risk, and in fact Refs#1, 68, and 74 found a significant risk within days to weeks of NSAID initiation. As pointed out in the DCaRP review of Ref#1,[8] data from a placebo-controlled trial of valdecoxib for post-CABG pain tends to support the immediacy of the risk, since an increased risk of cardiovascular events was observed from the second day of therapy.

B. Vulnerable subpopulations

We next consider the consult question regarding evidence addressing the cardiovascular risks in vulnerable subpopulations. Note that there is some overlap with the consult question regarding the risk for death or recurrent MI specifically in patients with a past history of MI; findings related to that more narrowly defined topic will be considered in a subsequent section.

The current NSAID class labeling includes a contraindication for one vulnerable group of patients, those who recently underwent coronary artery bypass graft (CABG) surgery, because of an increase in MI and stroke in randomized, controlled trials. In a study of parecoxib and valdecoxib after CABG there was a relative risk of 3.7 for serious cardiovascular events, and a number needed to harm of roughly 70 (calculated from the data in the published report).[9]

One principle we must bear in mind when surveying the data on risk in subpopulations is that it is important to specify the metric of risk; i.e., is it a relative measure such as a risk ratio or hazard ratio, or is risk being described in absolute terms such as attributable risk (i.e., the incidence difference), or number-needed-to-harm (NNH), the number of patients needed to be treated to produce one excess adverse event. As an example, the relative risk (RR) of a cardiovascular outcome with NSAID use compared to nonuse might be identical in both high risk and low risk subgroups, but the NNH would be much smaller in the high risk subgroup, due to its higher background rate of cardiovascular events. In such a case, it would be correct to say that the risk ratio is similar, but the risk difference is higher, in the vulnerable population versus a healthy population.

The following table highlights those studies with informative data regarding vulnerable subgroups of patients. Studies in which there appeared to be insufficient power for subgroup analysis are not shown.

Table 2. Summary of findings regarding vulnerable subpopulations

Ref	Vulnerable subgroup	Drugs	Finding regarding subgroup
1	post MI*	Coxibs and tNSAIDs	Elevated risk of death and re-MI from first week
1	80+yo post MI	Diclofenac	Highest HR in first week
2	DM, HTN, past cardiovascular or cerebrovascular disease	Celecoxib and tNSAIDs	OR for stroke consistent across subgroups
6	DM, and users of ACE/ARB/furosemide	NSAIDs	IRRs similar to general population, but differences in incidences (attributable risk) higher
8	Pts hospitalized for MI, revascularization, or unstable angina*	NSAIDs	Naproxen had "better cardiovascular safety"
9	Pts with history of cardiovascular disease	NSAIDs	Rofecoxib increased risk for cardiovascular events, naproxen protective
11	CHD, HTN, arthritis, age 65+	Celecoxib, rofecoxib, diclofenac, naproxen	No effect modifications on ORs
12	Hx of CVA/age 65+	Rofecoxib	No effect modifications on HR for stroke/MI but greater attributable risk
13	Gender, age, hx of CAD	NSAIDs	MI RR higher in younger pts and pts with CAD
17	Age, vascular risk score	NSAIDs	HR for stroke not influenced by age or risk score
18	Pts with afib following cardiothoracic surgery*	NSAIDs	No association with cardiovascular outcomes (Authors stated, "We may have been underpowered…")

19	Multiple	NSAIDs	Interaction exacerbating risk (particularly with ibuprofen and rofecoxib): age 80+, HTN, prior MI, prior CVD, RA, renal disease, COPD. Attributable risks in the range of several events per 100 person years.
21	Past MI	Coxibs	MI risk increased only in subgroup with past MI
24	Past MI	Rofecoxib	MI RR numerically higher than for patients with no past MI
26	CAD in OA pts	NSAIDs	Increased risk of MI but lower mortality overall versus nonuse
29	HTN	Rofecoxib	Higher HR of hospitalized stroke/MI than for normotensive subgroup
42	Baseline CV risk groups	High dose celecoxib in RCTs	HR for CV events varied with baseline risk
43	Baseline CV risk groups	Coxibs and tNSAIDs	Relative increase in CV events not dependent on baseline CV risk
45	High baseline CV risk	Lumiracoxib, ibuprofen, naproxen	Without ASA, naproxen CV risk lower vs lumiracoxib; with ASA, ibuprofen higher risk than lumiracoxib
47	CV risk factors	etoricoxib RCTs (naproxen comparison)	RR similar, but event rates higher, with at least 2 CV risk factors
64	post MI*	Rofecoxib, celecoxib, ibuprofen, diclofenac, other NSAIDs	One excess death per 45 patient years of treatment or less, depending on drug
65	HF*	Rofecoxib, celecoxib, ibuprofen, diclofenac, naproxen, other NSAIDs	One excess death per 53 patient years of treatment or less, depending on drug
67	ASA users	NSAIDs	Higher OR for MI among ASA users
75	Age 65+	Coxibs	Higher HRs for CV events (vs ibuprofen)
83	CV risk groups	Coxibs and tNSAIDs	Higher event rates with high CV risk, but RRs similar (positive risk with rofecoxib and lower risk with naproxen)
85	RA*	Coxibs and tNSAIDs	No association with MI

*Entire sample had this characteristic

In general, from the published reports listed above, vulnerable patient populations often show a higher attributable risk of cardiovascular events with NSAID use compared to the general population, though their relative risk may not differ much from lower risk populations. (A few exceptions can be noted. Ref#26 found an increase in cardiovascular events among OA patients using NSAIDs, but a decrease in total mortality, even for rofecoxib; the authors did not have a hypothesis regarding this apparently paradoxical finding. Ref#85 described a study of RA patients and found an increase in CV events with corticosteroids, but not NSAIDs; the RA patient population is generally thought to have higher CV risk so this study may have been underpowered for NSAIDs. Ref#18 found no CV risk in cardiothoracic surgery patients, but the authors acknowledged a statistical power limitation.)

A few studies found evidence of an interaction between baseline risk and risk from NSAID use, indicating that the relative risk was in fact higher in the presence of elevated baseline risk (e.g., Ref#19).

Notwithstanding the few exceptions, the presence of a fairly consistently increased relative risk, but with a higher attributable risk in vulnerable patient populations, has clinical (and

labeling) implications. A number of the studies found attributable risks for vulnerable populations in the range of several events per 100 person-years of NSAID use; absolute risks of such magnitude often call for a risk management strategy (and in the case of post-CABG patients, the risk is such that NSAID use has been contraindicated). Another implication has to do with advice for patients considered to have low cardiovascular risk.

From the data reviewed, it cannot be said with any confidence that the cardiovascular risks of NSAIDs are limited to patients with pre-existing atherosclerotic disease or other known cardiovascular risk factors, though the risk in absolute terms (for example, when expressed as NNH) does appear to be of greater magnitude for such patients.

C. Post-MI patient population

We consider next the consult question, "Does use of NSAIDs in patients with history of MI increase the risk of recurrent MI or death?"

This question was prompted by Ref#1, a study in the Danish national health care system database of the outcomes of death or reinfarction (reMI) with NSAID use by patients with a prior MI. This study has some overlap with Ref#64, and with a recently published study by Schjerning Olsen et al.,[10] which both used the same database. In addition, Ref#65 was a study of a related question, the cardiovascular risk of NSAIDs among heart failure patients, also in the Danish national healthcare database.

Of these Danish studies, the first to be published was Ref#64, which employed both a case-crossover analysis and a cohort design to study all-cause mortality and re-MI among NSAID users with a past MI. Both outcomes were associated with NSAID use, and the excess rate of death by compound is shown below.

Table 3. Number needed to harm (in person-years) for mortality, post-MI patients, Ref#64

Compound	Person-years of exposure producing one excess death
Rofecoxib	13
Celecoxib	14
Diclofenac	24
Ibuprofen	45

Ref#1 was a cohort study in the same database that analyzed these same outcomes but with a focus on the time-to-event by week of NSAID use. The investigators found that the risk of death and the combination endpoint of death or reMI was elevated (versus the population as a whole) from the very first week of NSAID use. By compound, diclofenac had the strongest association and naproxen the weakest. One important limitation of the study was lack of information regarding indication, which could have been a confounder; however, the authors reported that when patients with RA (an indication known to be associated with cardiovascular risk) were excluded from the sample, the results did not materially change. The authors also pointed out that across drugs the relative magnitude of the risk paralleled the degree of COX-2 inhibition, which they argued would be independent of indication. It should

be noted that there was an error in the way the units appear on the figures in Ref#1; the y-axis units should be per 1000 patient-days rather than patient years.[11]

The 2012 paper by Schjerning Olsen et al. also concerned a study of users of NSAIDs who had a previous MI, again in the Danish national healthcare database, though with a somewhat larger sample drawn from a longer time frame. As with the previous publication, NSAID use was associated with death from any cause, and in addition, was associated with an outcome of death from coronary artery disease or nonfatal re-MI. Unlike the previous publication, this study analyzed the association with respect to the time elapsed from the initial MI, and found that the risk did not vary materially through 5 years of follow-up time.

Ref#65 is a study from the same Danish data source which found similar results to the above in population of NSAID users with chronic heart failure.

An obvious question is whether these findings, of a strong association of these events with NSAID use in the post-MI population, and fairly modest NNHs for fatal outcomes, can be corroborated in other data sources. A limited number of other published studies examined cardiovascular risks in patients status post MI. Ref#26 described a nested case-control study of U.S. veterans with OA, assessing the association of NSAID use with outcomes of cardiovascular and cerebrovascular events, and death from any cause. Post-MI patients were not specifically studied although there was a subgroup defined by diagnoses of angina and ischemic heart disease. NSAID use was associated with both cerebrovascular and cardiovascular events, with or without prior coronary heart disease, but NSAID use was associated with fewer deaths from all causes. The authors offered no definite hypothesis to explain this apparently paradoxical set of findings. Ref#21 described a study, also in U.S. veterans, assessing the association of acute MI with use of etodolac, celecoxib, and rofecoxib (versus naproxen). In this study, use of a coxib was associated with acute MI only among the subgroup of patients with a prior MI. Ref#8 described an international study, combining data from three separate databases, to assess the risk of MI or death from coronary heart disease among NSAID users recently hospitalized for MI, revascularization, or unstable angina. The study analyzed risk by specific NSAID and found an association with short term (<90 day) use of ibuprofen, diclofenac, celecoxib and rofecoxib; but not with naproxen, which the authors felt had the most favorable cardiovascular risk profile. No associations were statistically significant for the smaller subgroup of patients with a prior MI. Finally, Ref#24 assessed the risk of MI in elderly patients with a prior MI, and found an increased risk with celecoxib and rofecoxib (but not for other NSAIDs).

On balance, there is evidence that NSAIDs increase the risk of re-MI and death among patients with a past MI, with the most robust data coming from the Danish national healthcare system, and pointing to a relatively high level of risk if judged by NNH. This finding has been corroborated to a certain extent in other databases. The paradoxical finding of Ref#26, showing an increase in cardiovascular events but a decrease in mortality, is not readily explained.

D. Risk by compound

We turn next to the question of whether the observational studies show a difference in the degree of risk associated with different NSAID compounds. The articles were reviewed for data which might provide comparative risk estimates for different NSAID compounds. This review was necessarily qualitative, although below are some results from a quantitative meta-analysis. References which provided some degree of informative comparison of cardiovascular risk by compound are highlighted in the following table.

Table 4. Cardiovascular risk in selected observational studies by specific NSAID compound

Ref	Outcome/Special Population (if any)	Higher risk estimate	Lower risk estimate
1	Death/reMI in post-MI patients	Diclofenac	Naproxen (no association)
2	Stroke	Parenteral NSAIDs esp. ketorolac	Not well differentiated
7	Death/reMI in healthy patients	Coxibs	No association with naproxen, ibuprofen
8	Serious CHD in CHD pts	Diclofenac, ibuprofen, high dose coxibs	Naproxen “had better cardiovascular safety”
9	Composite CV	Rofecoxib, Valdecoxib, Indomethacin	Naproxen (protective in CVD pts)
12	MI & ischemic stroke	Rofecoxib	Naproxen, celecoxib (only 3 compounds studied)
13	Nonfatal MI	Piroxicam, diclofenac	Naproxen, ibuprofen (risk correlated with COX-2 inhibition)
14	Stroke	Rofecoxib, Naproxen	Multiple
17	Stroke	Rofecoxib, Valdecoxib	Multiple
19	Composite CV/Medicare patients	Rofecoxib	All others: HR <1 (stat sig for celecoxib, valdecoxib, naproxen, other tNSAIDs)
21	MI	Rofecoxib, Celecoxib	Naproxen, etodolac (only 4 compounds studied)
24	MI in elderly post-MI patients	Rofecoxib, Celecoxib	Multiple
24	MI in elderly patients with no past MI	Rofecoxib	Multiple
32	MI in patients w/o risk factors	Rofecoxib, Celecoxib, Diclofenac	Naproxen, ibuprofen (only 5 compounds studied)
43	MI, stroke (>65 y.o.)	Rofecoxib	Other compounds had similar increase vs nonuse
44	MI in RCT meta-analysis	Coxibs	tNSAIDs; valdecoxib protective
50	RCT MA of cardiovascular events	Ibuprofen, Coxibs, Diclofenac	Naproxen "seemed least harmful" (see text)
53	MI	Coxibs, Diclofenac	No association for ibuprofen, naproxen, other NSAIDs
64	Death/post MI pts (Denmark)	Rofecoxib, celecoxib, high dose ibuprofen & high dose diclofenac	Low dose ibuprofen (protective), low dose diclofenac
64	Re-MI/post MI pts (Denmark)	Not well differentiated	Not well differentiated
65	Death / HF pts (Denmark)	High doses of all, esp. diclofenac	Low dose ibuprofen & naproxen
65	MI / HF pts (Denmark)	High dose diclofenac	Not well differentiated

68	MI	Not well differentiated	
69	MI (MA of 16 observational studies)	Diclofenac, Rofecoxib	Naproxen, celecoxib. Without ASA, naproxen protective
70	CV events	Meloxicam, Rofecoxib	Celecoxib (only 3 drugs analyzed)
73	RCT MA of cardiovascular events	Coxibs, High dose ibuprofen Diclofenac	Naproxen (see text)
83	MI or stroke in Medicare patients	Rofecoxib	Naproxen protective
86	MI or stroke	Rofecoxib	Celecoxib, tNSAIDs (only 3 groups)
87	CV events	Celecoxib	Naproxen protective vs celecoxib
88	MI	Diclofenac, ibuprofen and naproxen risk similar when adjusted for length of use	

While it is difficult to draw generalizations from these somewhat disparate data, use of naproxen was frequently associated with a numerically lower risk estimate in these studies, and in some cases naproxen use was associated with a frank reduction in cardiovascular events. However, in two of three studies examining stroke alone, this apparent advantage of naproxen was not evident (Ref# 2, 14), so perhaps stroke has a different pattern of risk by compound versus the more frequent outcome of MI.

Another generalization from these results is that among non-coxib compounds, diclofenac was frequently found to have one of the higher risk estimates.

A number of authors have addressed the question of differential cardiovascular risk by NSAID compound. In their observational study described in Ref#13, Garcia Rodriguez and colleagues found that their relative risk point estimates for individual drugs correlated with the percent of in vitro COX-2 inhibition in whole blood, irrespective of COX-1 inhibition, with the exception of naproxen, which they argued is the only NSAID inhibiting COX-1 at a level that impacts platelet function in vivo (with the possible exception of ibuprofen).

Hernandez-Diaz and colleagues performed a meta-analysis of 16 observational studies of NSAIDs and the risk of MI (Ref#69). There was some overlap with the studies reviewed in this literature search. They derived summary relative risk estimates from these observational studies by drug, and their results are summarized below. Diclofenac had the highest risk estimate, higher even than for rofecoxib, and there was no association for celecoxib or naproxen. They reported evidence of a dose response effect for rofecoxib, but not celecoxib.

Table 5. Summary MI relative risk estimates from observational studies of NSAIDs, Hernandez-Diaz et al., 2006.

Compound	No. of studies	Summary RR	95% CI
Naproxen	11	0.98	0.92-1.05
Ibuprofen	8	1.07	1.02-1.12
Celecoxib	8	0.96	0.90-1.02
Rofecoxib	8	1.26	1.17-1.36
Diclofenac	4	1.44	1.32-1.56

In addition, the authors subgrouped data on naproxen and ibuprofen according to studies which included or excluded users of ASA. These results are shown below; the data suggest a protective effect in the absence of ASA, particularly for naproxen, with a positive risk for ibuprofen with allowed ASA.

Table 6. Summary MI relative risk estimates from observational studies of NSAIDs by ASA use, Hernandez-Diaz et al., 2006.

Compound	No. of studies	Summary RR	95% CI
Naproxen—ASA allowed	9	1.03	0.96-1.10
Naproxen—no ASA use	4	0.83	0.72-0.90
Ibuprofen—ASA allowed	9	1.10	1.04-1.16
Ibuprofen—no ASA use	4	0.88	0.78-1.01

More recently, McGettigan and Henry[7] performed a meta-analysis of 51 observational studies of cardiovascular risk with NSAIDs, and found that the summary risk estimate was greatest for etoricoxib and least for valdecoxib; however, the across-drug comparisons were confounded by study type: etoricoxib data was all from case-control studies and valdecoxib data all from cohort studies. Considering only compounds included in at least 10 studies, they found that rofecoxib and diclofenac had the highest pooled relative risk estimates for cardiovascular events, and naproxen the lowest. A portion of Table 1 from their article is reproduced below, with compounds ranked according to the number of studies contributing the summary risk estimate.

Table 7. Summary risk estimates for cardiovascular events from observational studies of NSAIDs, McGettigan and Henry 2011.

Compound	No. of studies	Summary RR	(95% CI)
Naproxen	41	1.09	(1.02, 1.16)
Ibuprofen	38	1.18	(1.11, 1.25)
Celecoxib	35	1.17	(1.08, 1.27)
Rofecoxib	34	1.45	(1.33, 1.59)
Diclofenac	29	1.40	(1.27, 1.55)
Indomethacin	14	1.30	(1.19, 1.41)
Piroxicam	8	1.08	(0.91, 1.30)
Meloxicam	7	1.20	(1.07, 1.33)
Etodolac	5	1.55	(1.28, 1.87)
Valdecoxib	5	1.05	(0.81, 1.36)
Etoricoxib	4	2.05	(1.45, 2.88)

The authors also conducted pair-wise comparisons among the compounds (those data are not shown here). Here is the conclusion of McGettigan and Henry with respect to differences in risk by compound (note with respect to their reference to over-the-counter diclofenac that they are based outside the U.S.):

> This review suggests that among widely used NSAIDs, naproxen and low-dose ibuprofen are least likely to increase cardiovascular risk. Diclofenac in doses available without prescription elevates

risk. The data for etoricoxib were sparse, but in pair-wise comparisons this drug had a significantly higher RR than naproxen or ibuprofen. Indomethacin is an older, rather toxic drug, and the evidence on cardiovascular risk casts doubt on its continued clinical use.[13]

With respect to indomethacin, in this literature search, it was one of the less studied tNSAIDS; three studies found positive associations of indomethacin with cardiovascular events (Refs# 2, 9, and 68), and in fact, in Ref#9 indomethacin had some of the highest risk estimates among either tNSAIDs or coxibs.

Kearney and colleagues, at the Clinical Trial Service Unit and Epidemiological Studies Unit, Oxford University, conducted a meta-analysis of cardiovascular events in randomized clinical trials of coxibs (Ref#73). Though the focus was on coxibs, the data on celecoxib, the only currently marketed coxib in the U.S., was limited. However, they were able to derive summary rate ratios for vascular events for three tNSAIDs, and these are shown below.

Table 8. Summary risk estimates versus placebo for vascular events in NSAID clinical trials, Kearney et al. (Ref #73)

Compound	Summary RR	95% CI
Naproxen	0.92	0.67-1.26
Ibuprofen	1.51	0.96-2.37
Diclofenac	1.63	1.12-2.37
Coxibs (combined)	1.42	1.13-1.78

In addition, cardiovascular risk was elevated for coxibs versus naproxen, but was not statistically significant for coxibs versus non-naproxen NSAIDs (p-value for risk heterogeneity = 0.001). (A project to expand this clinical trial meta-analysis is currently under way, and results should be available soon.[12]) Consistent with this analysis by Kearney et al., Trelle et al. (Ref#50) concluded from their meta-analysis of cardiovascular events in NSAID large scale randomized trials that naproxen "seemed least harmful."

Van Staa and co-authors argued in Ref#88 that apparent differences in the level of thrombotic cardiovascular risk among compounds are most likely due to confounding by underlying disease severity. In their GPRD cohort study of MI, diclofenac was more prominently associated with MI (RR 1.21) than ibuprofen or naproxen (RR 1.04 and 1.03, respectively). However, risk also increased with total number of NSAID prescriptions, and they argued that when stratified by the number of previous prescriptions the risks for those three compounds appeared similar. They also argued that such differences in the patient population could account for the findings of Kearney et al. and McGettigan and Henry, suggesting a higher risk with diclofenac than ibuprofen or naproxen. However, while channeling might cause bias in the observational data used by McGettigan and Henry, it seems unlikely to have affected a randomized data set such as was used by Kearney et al.

As this review was being finalized, the European Medicines Agency (EMA) announced their conclusion that the cardiovascular risk from diclofenac is similar to that from COX-2 inhibitors.[13]

On balance, there is evidence from observational studies and clinical trials indicating a lower thrombotic cardiovascular risk, and in some instances a protective effect, with naproxen, perhaps consistent with some degree of platelet inhibition. Ibuprofen at lower dosages may also have a lesser thrombotic cardiovascular risk. Among the other tNSAIDs, there is evidence implicating diclofenac as having a higher cardiovascular risk, similar to that of

rofecoxib. One limitation of the preceding summary is the possibility that some less extensively studied drugs (e.g., indomethacin) might also have higher levels of cardiovascular risk, but that this is not as well documented in the literature because they are less frequently included in studies. The potential for interference with the cardioprotective effect of ASA by both ibuprofen and naproxen[14] should be borne in mind when interpreting these results.

E. Non-prescription NSAIDs

Three NSAIDs are approved in the U.S. for over-the-counter (OTC) use: ibuprofen at doses up to 1200mg/d, ketoprofen at doses up to 75 mg/d, and naproxen at doses up to 660 mg/d. The literature references were surveyed for data specifically addressing the cardiovascular risk of these compounds at these dose ranges; summaries of the data appear in the spreadsheet under the column describing OTC use.

a. OTC Ketoprofen

There were no data on the cardiovascular risk of OTC ketoprofen dosages. Ref#2 found an association between ischemic stroke and use of ketoprofen, but dose was not analyzed. Ref#68 found a statistically significant association for MI with recent use of ketoprofen, and a borderline significant association for current use, but again dose was not analyzed. No other data on cardiovascular events with ketoprofen were available from this literature search.

b. OTC Ibuprofen

A number of studies provided data on doses of ibuprofen of 1200 mg/day or less, though all studies were from outside the U.S., perhaps because the widespread OTC use of ibuprofen in this country would make exposure difficult to ascertain. The following table summarizes the risk estimates from the various studies that examined this dose level of ibuprofen. Statistically significant findings are bolded.

Table 9. Observational data on cardiovascular events with nonprescription ibuprofen dosages

Reference	Population and source	Outcome	Reference group	Risk estimate by mg/day (95% CI)
1*	Post MI (Denmark)	Cardiovascular death	Nonuser	<1200 HR **1.11** (1.03-1.20) >1200 HR **2.56** (2.27-2.88)
		Coronary death / re-MI	Nonuser	<1200 HR **1.17** (1.09-1.26) >1200 HR **2.01** (1.77-2.28)
2	Taiwan	Ischemic stroke	Control period (case-crossover)	<600 avg OR 1.26 (0.96–1.66) 600+ avg OR **1.51** (1.35–1.69)
		Hemorrhagic stroke	Control period (case-crossover)	<600 avg OR **1.72** (1.06–2.81) 600+ avg OR **1.51** (1.23–1.86)
7 and [15]	Healthy (Denmark)	Any death plus MI (main sample)	No use	<=1200 HR **0.92** (0.86-0.97) >1200 HR **1.84** (1.62-2.08)
		Any death plus MI (case crossover analysis)	Control period (case-crossover)	<=1200 OR **1.12** (1.02-1.23) >1200 OR 1.10 (0.94-1.30)
		Coronary death or nonfatal MI	Control period (case-crossover)	<=1200 OR **1.45** (1.19-1.77) >1200 OR 1.44 (0.91-2.27)
		Coronary death or nonfatal MI	No use	<=1200 HR **0.72** (0.65-0.80) >1200 HR 1.16 (0.92-1.47)

		Coronary death or nonfatal MI	Matched controls/no use	<=1200 HR **1.24** (1.12-1.37) >1200 HR **1.94** (1.54-2.45)
		Fatal or nonfatal stroke	Control period (case-crossover)	<=1200 OR 1.21 (0.95-1.53) >1200 OR 1.36 (0.84-2.19)
		Fatal or nonfatal stroke	No use	<=1200 HR **0.88** (0.79-0.98) >1200 HR **1.45** (1.14-1.86)
		Fatal or nonfatal stroke	Matched controls/no use	<=1200 HR **1.39** (1.24-1.54) >1200 HR **2.22** (1.74-2.84)
13	Age 50-84 (THIN)	MI	Nonuse	<1200 RR 1.00 (0.80-1.25) >1200 RR 1.56 (0.90-2.71)
53	Age 40+ (GPRD)	MI	Nonuse	<=1200 RR 0.99 (0.81-1.21) >1200 RR 1.14 (0.74-1.77)
64	Post MI (Denmark)	Death	No use	<=1200 HR **0.75** (0.61-0.92) >1200 HR **2.20** (1.95-2.48)
		re-MI	No use	<=1200 HR **1.28** (1.03-1.60) >1200 HR 1.22 (0.99-1.51)
		Death (case crossover)	Control periods (case-crossover)	<=1200 OR **0.57** (0.45-0.74) >1200 OR **1.65** (1.33-2.04)
		re-MI (case crossover)	Control periods (case-crossover)	<=1200 OR 1.41 (0.95-2.08) >1200 OR 1.26 (0.89-1.78)
65	Heart failure (Denmark)	Death	Nonuse	<= 1200 HR 0.99 (0.94-1.04) >1200 HR **2.83** (2.64-3.02)
		MI	Nonuse	<= 1200 HR **1.31** (1.15-1.48) >1200 HR **1.47** (1.15-1.89)
		Hospitalized for HF	Nonuse	<= 1200 HR **1.16** (1.09-1.23) >1200 HR **1.18** (1.04-1.33)
		Death	Control periods (case-crossover)	<= 1200 HR **0.89** (0.79-0.99) >1200 HR **6.43** (5.26-7.86)
		MI	Control periods (case-crossover)	<= 1200 HR 1.28 (0.98-1.63 >1200 HR **4.51** (2.28-8.91)
		Hospitalized for HF	Control periods (case-crossover)	<= 1200 HR **1.36** (1.19-1.56) >1200 HR **1.86** (1.33-2.60)
87	The Netherlands	MI	Remote NSAID use	<= 1200 OR 1.66 (0.92-3.00) >1200 OR **1.51** (1.06-2.14)
88	Age 40+ (GPRD)	MI	Past NSAID use	<1200 RR **1.18** (1.01-1.36) 1200 RR **1.15** (1.05-1.24) 1201-2399 RR **1.38**(1.17-1.62) >=2400 RR **2.16** (1.16-4.01)

*Data on dose provided by corresponding author

Six of the studies, using three different data sources, found a positive cardiovascular risk with an OTC dosage of ibuprofen; three studies did not find a statistically significant association, though one of these (Ref#87) yielded an OR point estimate of 1.66.

The Danish studies found a positive risk for OTC dosage ibuprofen in both healthy patients and patients with cardiac disease. A limitation of the Danish database is that prescribed dosage has to be imputed. A peculiarity of the Danish national healthcare data was that when all-cause mortality was analyzed or included in the composite outcome, OTC dose ibuprofen often showed lower risk. This may be due to

confounding; perhaps users of low-dose ibuprofen had better health care for non-cardiovascular conditions. With cardiovascular death specifically, there was an increased risk with OTC dose ibuprofen in Danish post-MI patients (Ref#1 above). In Ref#7 involving patients with no hospitalizations of any kind for 5 years, comparisons to the nonuser reference group showed a protective effect, but this was absent in the perhaps better controlled case-crossover analysis in which patients served as their own controls. Note that additional results from that study were published separately.

Conceivably, patients taking aspirin for cardioprotection, which may not be evident in health care claims databases, could have an increase in cardiovascular events with ibuprofen due to the interaction between ibuprofen and aspirin.[16] This effect might be important in studies of high-risk patients, but would not be as applicable to studies of healthier patients (e.g., Ref#7).

McGettigan and Henry[7] reported a summary relative risk estimate for cardiovascular events with low dose ibuprofen (most commonly defined in the studies as up to 1200 mg/day) of 1.05 (0.96-1.15), based on meta-analysis of 11 observational studies. The 11 studies were not identified, but almost certainly would have included some from the present literature review. The authors found a substantially higher relative risk for ibuprofen doses above 1200 mg/day (1.78, 1.35-2.34).

In sum, there is evidence from several observational studies that although the risk appears dose-related, OTC dose ibuprofen can be associated with adverse thrombotic cardiovascular events. This is biologically plausible, for while the cardiovascular risk appears dose related, there is no obvious reason to expect a threshold in the dose-response curve below which ibuprofen has no risk.

c. OTC Naproxen

Fewer observational studies (Ref#s 1, 7, 13, 53, 65) provided data on OTC doses of naproxen (up to 660 mg/day). In the study in Ref#1, naproxen > 500 mg/day was associated with increased risk of cardiovascular death in post-MI patients, but for lower doses the HR was close to one.[17] Ref#7, in the same Danish national database, found that in a healthy patient population there was no association with death or MI for doses either above or below 500 mg/day (though the HR point estimate for higher doses was 1.3); and in fact, deaths from any cause were statistically significantly lower with doses < 500 mg/day, similar to the aforementioned ibuprofen results. However, a subsequent analysis of the same sample, published separately, showed an association of naproxen < 500 mg/day with stroke.[18] Ref#13 and Ref# 53 found no association between MI and naproxen at doses either above or below 750 mg/day, in the THIN and GPRD databases, respectively; in both studies power was an issue. Finally, Ref#65, a study of heart failure patients conducted in the Danish national database, showed that doses up to 500 mg/day were associated with MI (HR 1.47, 95% CI 1.02-2.10).

From their analysis of 10 observational studies which subgrouped naproxen exposures by dose, McGettigan and Henry[7] reported a summary cardiovascular risk estimate of 0.97 (0.87-1.08) for low-dose naproxen (inconsistently defined across the studies), and 1.05 (0.89-1.24) for high dose naproxen.

Overall, observational data on OTC doses of naproxen in this literature search is limited. Two studies found a positive cardiovascular risk, one for MI in patients with heart failure, and one for stroke in a healthy sample. It has been hypothesized that

naproxen could have potentially cardioprotective aspirin-like activity, based on its inhibition of COX-1 and its relatively long duration of action (Ref#13). However, in the ADAPT trial for prevention of Alzheimer's dementia, long-term dosing with naproxen 440 mg/day showed a statistically significant increase in adverse cardiovascular events relative to placebo.[19] This risk was actually numerically higher in the subgroup not using ASA, though the test for an interaction with ASA was not statistically significant.

F. Other issues

a. Dose-response

The current labeling for NSAIDs (see above) recommends using the lowest possible dose as one way to reduce NSAID cardiovascular risk. The articles in the search were reviewed for evidence supporting a dose-response relationship for thrombotic cardiovascular events with NSAIDs. Studies that were selected because they were informative regarding dose response are highlighted in the following table.

Table 10. Studies addressing the dose-response relationship for cardiovascular events

Reference	Population and source	Outcome	Reference group	Pattern indicating dose response?
1*	Danish post-MI patients	MI or coronary death	Nonusers	Yes: rofecoxib, celecoxib, ibuprofen, diclofenac, naproxen
2	Taiwan	Stroke	Case-crossover	Equivocal: diclofenac, ibuprofen, mefenamic acid
7	Healthy patients (Denmark)	Death or MI	Nonusers	Yes: ibuprofen, diclofenac, celecoxib (naproxen: no risk)
8	Multinational data	MI or coronary death	Nonusers	Equivocal: naproxen, ibuprofen, diclofenac, celecoxib, rofecoxib
11	Canada	MI	Case-control	Equivocal for all (power to analyze by dose limited)
13	Age 50-84 (THIN)	MI	Nonuse	Yes, for all drugs pooled. Also, RR slow release > immediate
24	Elderly (Canada)	MI	Nonuse	Yes for rofecoxib, and for celecoxib in patients with past MI
28	Elderly (Canada)	MI	Low dose diclofenac	Yes for rofecoxib, other dose strata underpowered
33	Australia	Cases=MI/unstable angina	Controls hospitalized for other reasons	Low dose celecoxib/rofecoxib protective, high dose + risk
42	Celecoxib RCT MA	Combined CV events	Placebo	Celecoxib risk: 400 mg bid>200 mg bid> 400 mg qd
44	Coxib RCT MA	MI	Placebo	Yes for celecoxib
53	GPRD	MI	Nonuse (case-control)	Yes for rofecoxib, celecoxib, etoricoxib. No for diclofenac, ibuprofen, naproxen.
64	Danish post-MI patients	Re-MI or all cause death	Nonuse	Death: rofecoxib, celecoxib, ibuprofen, diclofenac showed clear dose response pattern. Re-MI: less apparent

65	Danish HF patients	Death, MI, HF	Nonuse	Death: strongly dose-related for rofecoxib, celecoxib, diclofenac, ibuprofen, naproxen. MI: only diclofenac HF: only rofecoxib
69	Meta-analysis of observational studies	MI	Nonuse	Yes for rofecoxib; other NSAIDs not analyzed by dose
73	RCT MA	Serious vascular events	Placebo	Celecoxib (dose-response p-value = 0.03)
87	The Netherlands	MI	Remote use	Yes for celecoxib, diclofenac; equivocal for rofecoxib, ibuprofen
88	Age 40+ (GPRD)	MI	Past NSAID use	Yes for ibuprofen, diclofenac; equivocal for naproxen

*Data on dose provided by corresponding author

From this summary, there is evidence for thrombotic cardiovascular events being dose related with both coxibs and tNSAIDs. Observational data can be suboptimal for assessing dose-response, since confounding of higher doses with greater disease severity is possible, but a dose-response relationship has also been seen in clinical trial datasets where such bias is less likely. Another limitation of this survey of dose-response findings is that failure to discern a dose-response pattern in a particular study may be due to a true absence of dose-relatedness, or it may be a Type 2 error (e.g. lack of statistical power). Nonetheless, these results tend to support the current advice in the labels recommending the lowest feasible dose to keep the cardiovascular risks as low as possible.

b. Use of anti-platelet agents

The class labeling states that data are lacking regarding thrombotic cardiovascular risks from NSAIDs with concomitant ASA. Even fewer data are available regarding concomitant use of other anti-platelet agents. With respect to naproxen and ibuprofen, there is evidence that those NSAIDs could interfere with the antiplatelet, cardioprotective action of ASA.[20 21 22] A large observational study of patients who had been hospitalized for cardiovascular disease and were using cardioprotective ASA found that concomitant ibuprofen, but not other NSAIDs, increased all-cause mortality;[23] in contrast, a study of MI in a veteran population found a reduced risk of MI for ibuprofen plus ASA compared to ASA use alone.[24] A case-control study of MI in a Medicaid population found that ASA use ameliorated the risk of MI with coxibs and some tNSAIDs, partially ameliorated the risk with indomethacin, but did not measurably change the cardiovascular risk with ibuprofen.[25]

The articles from the literature search were reviewed for data to address this topic.

- Ref#1: ASA use was a covariate, and 51% of nonusers and 38-45% of users of different NSAIDs received ASA. However, no separate analysis addressing ASA use was conducted.
- Ref# 2: In this case crossover study of stroke, ASA users had a statistically significant lower risk with oral and parenteral tNSAIDs.
- Ref# 21 reported no reduction in MI risk from rofecoxib, celecoxib, naproxen or etodolac with concomitant antiplatelet therapy.

- In Ref #24, point estimates for MI risk were lower with concomitant ASA for celecoxib and rofecoxib, approaching statistical significance (p=0.07 in subgroups with or without a past MI).
- Ref# 35: The OR for intracranial hemorrhage with NSAIDs was not affected by use of aspirin, but power was limited.
- Ref #38: In this cohort study of elderly NSAID users, point estimates (HRs) for MI were higher with ASA use for rofecoxib, celecoxib, ibuprofen, and diclofenac, but not for naproxen.
- Ref #39: In this meta-analysis of celecoxib clinical trial data, the subgroup analysis by aspirin users versus nonusers appeared underpowered, though cardiovascular deaths were statistically significantly lower among aspirin nonusers receiving celecoxib compared to tNSAIDs.
- Ref #42: Another celecoxib clinical trial meta-analysis reported an increased cardiovascular risk either with or without baseline aspirin use.
- Ref #45 describes data on cardiovascular outcomes from large (N=18,325 total) twin randomized trials of lumiracoxib versus ibuprofen or naproxen. Among ASA users, ibuprofen, but not naproxen, increased cardiovascular events relative to lumiracoxib; conversely, among ASA nonusers, lumiracoxib and ibuprofen had similar risk while the risk was lower for naproxen. The authors suggest that ibuprofen may have higher risk in the presence of ASA because it antagonizes the antiplatelet action of ASA; while in the absence of ASA, naproxen may be supplying some cardioprotective antiplatelet effect because of its inhibition of COX 1.
- Ref# 47: This clinical trial meta-analysis of etoricoxib trials found generally higher cardiovascular event rates among ASA users, consistent with the hypothesis that these patients were using ASA for cardioprotection, but comparisons between treatment assignments were underpowered.
- Ref# 67 described a case-control study of MI with NSAID use, chiefly ibuprofen and naproxen. The investigators conducted an exploratory subgroup analysis by use of ASA; the following graph reproduced from the article shows the ORs for MI by subgroup. The results suggest a reduction in MI risk with ASA, and an antagonism of that protective effect by NSAIDs, along with an increase in MI with NSAID use in the absence of ASA, though not statistically significant.

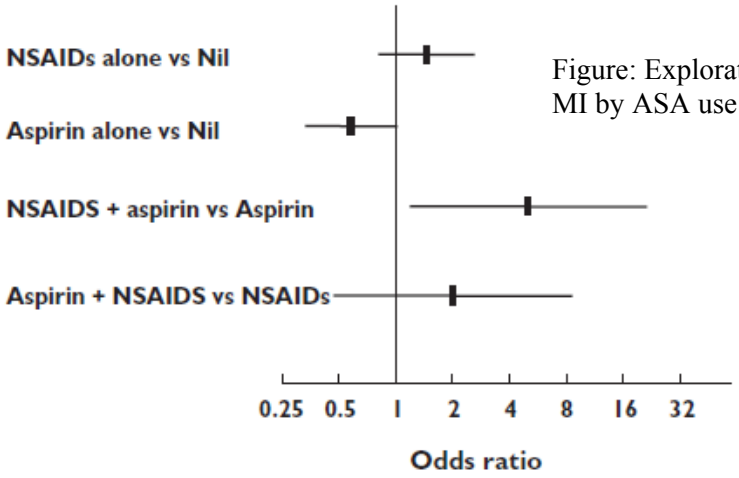

Figure: Exploratory analysis of ORs for MI by ASA use Source: Figure 2, Ref 67

- Ref#69: In this meta-analysis of MI risk in observational studies, the authors reported, without ASA, a cardioprotective effect of naproxen and a neutral effect of ibuprofen, and with ASA, a neutral effect of naproxen and a positive risk with ibuprofen.
- Ref#73: In this clinical trial meta-analysis, for coxibs the relative risk for cardiovascular events was similar for patients using or not using ASA at baseline.
- Ref#78 included a subgroup analysis of naproxen users with or without concomitant ASA, but the risk estimates lacked enough precision to be informative.
- Ref#88: The risk of MI was similarly elevated with ibuprofen, diclofenac, and naproxen, with or without concomitant ASA.

In sum, evidence regarding the amelioration of NSAID-related cardiovascular risk by concomitant antiplatelet therapy is mixed. Most studied has been concomitant ASA, with very little data available on other antiplatelet agents. There is evidence from some studies that ASA may ameliorate the cardiovascular risks of NSAIDs, although there is also evidence that ibuprofen and naproxen can interfere with the antiplatelet action of ASA. However, Ref#88 reported an increase in MI from ibuprofen in the absence of ASA. Other studies failed to show a reduction in NSAID cardiovascular risk by ASA. There are perhaps competing influences at work, since patients taking ASA may often be at higher cardiovascular risk than ASA nonusers. Accordingly, data from RCTs (e.g., Ref#73) may be the most informative.

c. Stroke as an outcome

The Safety of Nonsteroidal Anti-inflammatory Drugs (SOS) project conducted a meta-analysis of observational studies of NSAIDs and stroke.[26] The authors derived pooled risk estimates from 6 studies showing associations for rofecoxib (RR 1.64, 1.15-2.33) and diclofenac (RR 1.27, 1.08-1.48), but no associations for naproxen, ibuprofen, or celecoxib. The risk estimates for ischemic strokes were similar, and there was inadequate data for separate risk estimates of other types. The authors also pointed out the possibility of protopathic bias for subarachnoid hemorrhage, since a premonitory headache may lead to NSAID use.

The following selection of references with data on stroke from this literature search is not all-inclusive but seeks to highlight those studies that are more informative regarding the outcome of stroke.

Table 11. Selected references from literature search with data on NSAIDs and stroke risk

Reference	Population and source	Outcome	Reference group	Finding
2	Taiwan	Ischemic Stroke	Case-crossover	Statistically significant ORs >1 for oral use of all compounds individually (celecoxib, ketorolac, ketoprofen, diclofenac, piroxicam, naproxen, ibuprofen, melixicam, sulindac, mefenamic acid, indomethacin); ORs similar, ranging from 1.26-1.90 across compounds. Even higher ORs with parenteral use (ketorolac, diclofenac, ketoprofen)
2	Taiwan	Hemorrhagic Stroke	Case-crossover	Generally similar to ischemic stroke results; OR point estimates higher for hemorrhagic stroke than ischemic stroke for several drugs especially ketorolac, naproxen, parenteral ketorolac, parenteral ketoprofen)
7 and [19]	Healthy (Denmark)	Fatal or nonfatal stroke	Case-crossover (see [19] for other analyses)	Naproxen 1.91 (1.04-3.50) Ibuprofen 1.29 (1.02-1.63) Diclofenac 1.71 (1.29-2.25) Celecoxib 1.20 (0.59-2.46) Rofecoxib 1.14 (0.62-2.12)
14	Prospective study of volunteers >55 y.o. in The Netherlands	Stroke	Nonusers	HR higher for COX-2 selective than any NSAID. Individual drugs with positive associations: diclofenac (aHR1.60, 1.00-2.57), naproxen (aHR 2.63, 1.47-4.72), rofecoxib (aHR 3.38, 1.48-7.74); limited power for other compounds.
17	Tenn. Medicaid patients 50-84 y.o.	Stroke	Nonuse	Rofecoxib, valdecoxib only compounds with statistically significant association
39	Celecoxib clinical trials meta-analysis	Nonfatal stroke	Nonselective NSAID controls	Celecoxib with lower rate of stroke vs. tNSAIDs, statistically significant with investigator-reported events prior to adjudication
43	Veterans 65+ y.0.	Cerebrovascular accident	No NSAID use	Positive associations for all compounds (rofecoxib, celecoxib, etodolac, nabumetone, ibuprofen, naproxen); HR varied by COX-2 selectivity
50	Clinical trial meta-analysis	Stroke	Placebo	Rate ratios: Naproxen 1.76 (0.91 to 3.33) Ibuprofen 3.36 (1.00 to 11.60) Diclofenac 2.86 (1.09 to 8.36) Celecoxib 1.12 (0.60 to 2.06)

				Etoricoxib 2.67 (0.82 to 8.72) Rofecoxib 1.07 (0.60 to 1.82) Lumiracoxib 2.81 (1.05 to 7.48)
70	Long term users of rofecoxib, celecoxib, & meloxicam in Taiwan	Stroke	Meloxicam	Celecoxib HR 0.78 (0.63-0.96) (Most celecoxib use < 200 mg/d) Rofecoxib HR 0.91 (0.76-1.09)
73	Clinical trial meta-analysis	Stroke	Placebo	No association with stroke found for coxibs pooled (though MI risk was increased)
83	Medicare	Stroke	Nonusers	Rofecoxib only NSAID with positive association

Some generalizations from this survey of results for the specific outcome of stroke can be put forth. MI as an outcome is likely to be more common than stroke; this was seen in the data from the APPROVe trial mentioned previously. Accordingly, statistical power to assess risks of MI will generally be greater than for stroke when both outcomes are analyzed in the same data set. Nonetheless, there is clearly evidence of an association with stroke for NSAIDs. The pattern of risk by compound, in which rofecoxib or diclofenac tend to have higher risk estimates and ibuprofen or naproxen lower, is generally not as apparent in the data for stroke alone (see also the recent Australian study described below), although Ref#14 found a relationship of stroke risk to COX-2 selectivity.

One might hypothesize that naproxen, because of its aspirin-like antiplatelet action, might be particularly associated with hemorrhagic stroke (as is ASA[27]). Only Ref#2 had sufficient numbers of hemorrhagic stroke outcomes for a meaningful separate analysis; for several compounds, including naproxen, the point estimate was higher than for ischemic stroke. Similarly, a study of Australian veterans published after this literature search, using prescription event sequence symmetry analysis, showed numerically higher risk estimates for hemorrhagic strokes than ischemic strokes for naproxen and most other NSAIDs analyzed.[28] In this study, for all strokes ibuprofen had the lowest risk estimate, but risk estimates for other NSAIDs (coxibs and tNSAIDs) were generally similar.

4 DISCUSSION

This review has several limitations that must be kept in mind. First, most of the studies reviewed were observational in nature, and non-randomized data always carries the possibility of bias (confounding) that is not adequately adjusted for in the analysis. Findings which are also observed in randomized trial data or in RCT meta-analyses may be viewed with more confidence. Secondly, the literature search was truncated at 2006, and while certain key references published before 2006 emerged in the course of the review, there was no systematic attempt to review the literature prior to 2006. Another limitation stems from the fact that many of the observational studies were conducted outside the U.S. and so may have included NSAIDs that are not marketed here. This might be particularly an issue in studies that pooled data for various drugs, since the pooled data may not closely reflect drugs available in the U.S.

5 CONCLUSION

The following are some summary statements that can be offered on the basis of this literature review.

- Dose response: There are observational data indicating that the thrombotic cardiovascular risk from NSAID use is dose-related. There is some evidence of this dose-response effect from clinical trials with celecoxib.
- Time course of risk: Observational data exists showing an essentially immediate onset of measurable cardiovascular risk. Other data suggests a delayed time course, or a risk persisting after NSAID treatment. Conceivably, different pharmacologic mechanisms could be involved at different time points.
- Healthy patients: There is evidence of an increased cardiovascular risk from NSAID use by apparently healthy patients.
- Vulnerable populations: Observational data indicate that the cardiovascular risk in absolute terms (attributable risk) is considerably higher in vulnerable patients, such as those with heart disease, though the relative risk may or may not be higher in such patients.
- The NSAID-associated risk for death or re-infarction found in the Danish study is supported by other literature, though few studies specifically included a post-MI population.
- An increase in fatal cardiovascular outcomes with NSAID use, at a clinically relevant frequency, has been observed in both vulnerable populations and unselected populations.
- With respect to risk by compound, in general, diclofenac appeared to have a degree of risk overlapping with rofexocib, while lesser risks were often observed with naproxen.
- Evidence regarding the amelioration of NSAID-related cardiovascular risk by concomitant antiplatelet therapy is mixed, though some data indicate that ASA might reduce NSAID cardiovascular risks.
- Some data indicate a possible cardioprotective effect of naproxen in the absence of concomitant ASA.
- Naproxen and ibuprofen are believed to inhibit the cardioprotective actions of ASA. However, interference with ASA is not likely to account for the entirety of their cardiovascular risk.
- Some findings indicate that naproxen may have a lower cardiovascular risk than ibuprofen, while ibuprofen may have a lower gastrointestinal (GI) toxicity than naproxen. (The possibility of amelioration of NSAID GI toxicity by proton pump inhibitors has been proposed, but that topic was beyond the scope of this literature review.)
- Over-the-counter use: There were no data on over-the-counter (OTC) dosages of ketoprofen, and sparse data on OTC dosages of naproxen, although two studies from Denmark showed positive associations with cardiovascular events at OTC naproxen doses. For ibuprofen, however, evidence from six studies indicated an increase in cardiovascular events at doses $\leq$ 1200 mg/day.
- Stroke appears to be a less frequent event than MI, but is also associated with NSAID use. The aforementioned pattern of relative hazards among the compounds (i.e., rofecoxib and diclofenac with a higher risk, ibuprofen and naproxen with a lower risk) is not as evident in the data for stroke.

6 RECOMMENDATIONS

- The NSAID class labeling enacted in 2005 is on the whole still valid when viewed alongside the more recently available data. Specific statements that could be updated include the following.
    - The statement that "All NSAIDs, both COX-2 selective and nonselective, may have a similar risk" can be amended, now that there is emerging evidence to the contrary, because to the extent that specific compounds have greater or lesser cardiovascular risk, that would be important to communicate to prescribers and patients. There now seems to be a sufficient amount of evidence, from observational data and clinical trials, to conclude that among tNSAIDs, naproxen is likely to have a lesser cardiovascular risk and diclofenac a higher risk. This pattern is more obvious in the data for MI than stroke, but MI is the more common event.
    - The statement that patients with cardiovascular risk factors are at greater risk can be clarified to indicate that the risk is not limited to patients with such risk factors.
    - It could be clarified that the advice to use an NSAID for the shortest duration possible is not based on the absence of a cardiovascular risk during a short latency period, but is simply a prudent way to limit patient exposure.
    - Extending the existing contraindication in post-CABG patients to other high-risk patients (e.g., post-MI patients) should be considered.
    - Prescription and OTC labeling for naproxen and ibuprofen should include the best current advice on how to avoid impeding the cardioprotective effects of ASA.
- To the extent that the cardiovascular risk with diclofenac is similar to that with rofecoxib, which was removed from the market for its cardiovascular risks, the risk-benefit balance for diclofenac should be re-evaluated.
- Cardiovascular risk labeling for prescription ibuprofen should be extended to OTC ibuprofen, though this will probably oblige re-assessment of its OTC risk-benefit balance. Strengthening the naproxen OTC cardiovascular risk labeling may also be considered, but there are fewer data indicating a risk with OTC naproxen.
- Risk communication should be undertaken to raise awareness of these risks among prescribers and patients.
- A request should be made through our EMA contacts for the report of the Safety of Non-Steroidal Anti-Inflammatory Drugs Project (SOS).
- The report of the Oxford University-based Coxib and Traditional NSAID Trialists' Collaboration (CNT) meta-analysis of NSAID clinical trial data on cardiovascular events should be informative for NSAID labeling, and should be obtained.

APPENDICES

The summary listing of NSAID cardiovascular outcome studies identified in the FDA Medical Library literature search is attached.

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#	Reference, Study Design & Objective	Data source and time frame	Population & Sample Size	Exposure and dose (mg/d) groups	Outcomes & Analysis	Results	Time to event	Vulnerable subgroups (including pts s/p MI)	Risk by compound	Data on OTC use (ibuprofen ≤ 1200mg/d, ketoprofen ≤ 75 mg/d, naproxen ≤ 660 mg/d)	Strengths & Limitations	Comments
1	**Schjerning Olsen** Cohort study to determine how duration of NSAID use affects risk of death or reinfarction post-MI	Danish National Patient Registry 1997-2006	All pts > 30 y.o. with initial MI during study period. N=83,677 pts with MI, 63% male, mean age 68, of whom 48,270 used an NSAID post-MI	Any NSAID; celecoxib, rofecoxib, diclofenac, ibuprofen, naproxen, other NSAIDs	All cause mortality and recurrent MI analyzed with Cox PH, with exposure as a time-dependent covariate (through 14 wks)	HR for death/re-MI 1.45 (1.29-1.62) at wk 1, and 1.55 (1.46-1.64) > 90 days	Incidence of death and death/recurrent MI elevated from week 1 overall. By compound, mortality risk in first week most prominent for diclofenac	All pts had hx of MI. Excluding pts with rheumatic disease did not materially affect findings. For diclofenac, 80+ y.o. had higher death HR in first week than other age groups	COX2 inhibition correlated with measured risks. Diclofenac: highest risk for death/re-MI at wk 1, HR 3.26 (2.57-3.86). Naproxen: statistically weakest association but also smallest sample (HR point estimates similar to other drugs)	Data not shown though risk described in text as "clear dose-dependent"	Strengths: National sample. Ibuprofen only OTC NSAID in Denmark. Limitations: Outcomes not adjudicated. GI bleeding not assessed, but thought to worsen MI prognosis. Possibly unmeasured confounders (e.g., indication) but effect size would have to be large (>2-fold RR).	Hazard observed from first few days of use, esp.for diclofenac (with a HR greater than rofecoxib). Attributable risk of significance since pts with MI are already at higher mortality risk. Authors observed
2	**Chang** Case-crossover study to evaluate cerebrovascular safety of selective and nonselective NSAIDs in a high risk population (i.e., Taiwanese)	Taiwan National Health Insurance Database 2006	Pts 20+ y.o. hospitalized with ischemic or hemorrhagic stroke (including subarachnoid and intra-cerebral hemorrhages) N=28,424 pts with ischemic stroke, 54% male, mean age 69; & N=9456 pts with hemorrhagic stroke, 58% male, mean age 63	Celecoxib, nonselective NSAIDs, ketorolac, ketoprofen, diclofenac, piroxicam, naproxen, ibuprofen, meloxicam, sulindac, mefenamic acid hi/lo, indomethacin	Principle discharge dx of ischemic or hemorrhagic stroke; Conditional logistic regression, adjusted for time varying confounders, comparing exposures 1-30 and 91-120 days prior to stroke	Ischemic stroke: OR 1.71 (1.63-1.80) for oral nonselective NSAIDs; Hemorrhagic stroke: OR 1.80 for oral nonselective NDSAIDs. Risk greater with parental use (OR 3.5 for ischemic stroke)	For parenteral use, sensitivity analysis suggested risk greater within 7 days	Risk estimates "uniform" with diabetes, hypertension, prior cardiac or cerebrovascular disease. Risk of ischemic stroke was reduced by aspirin use.	Ischemic stroke: OR>1 for all oral compounds (range: 1.20 (1.05-1.48) for celecoxib, 1.90 (1.39-2.60) for ketorolac) Hemorrhagic stroke: similar results, wider CLs, ketorolac highest OR (2.69) OR did not diminish with intermittent use vs daily use for compounds where this was analyzable. Risk greater with parental use (esp. ketorolac)	Ibuprofen 600+ mg/d: OR ischemic 1.51 (1.35–1.69), OR hemorrhagic 1.51 (1.23–1.86). Ibuprofen <_600mg/d, OR ischemic 1.26 (0.96–1.66), OR hemorrhagic 1.72 (1.06–2.81). Ketoprofen associated with ischemic stroke, dose response not analyzed. Naproxen associated with both outcomes, dose not analyzed.	Strengths: National database. Large sample of patients with events. Case control design limits confounders to time-dependent variables. Limitations: Outcomes not adjudicated. Sample not ethnically diverse. Theoretically, possible confounding by indication, though not obvious what that would be (migraine, perhaps). Data on certain risk factors such as smoking and OTC use missing.	Examined ischemic and hemorrhagic strokes. Some association with all compounds studied; greatest risk with parenteral use.
3	**Choi** Case-control study to investigate possible selection bias in a case-control study of NSAIDs and hemorrhagic stroke	33 hospitals in South Korea 2002-2004	Aged 30-84, s/p subarachnoid (SAH) or intracerebral hemorrhage (ICH), able to complete interview; age- and gender- matched controls from community or hospital. N=940 cases (42% female, mean age 57); with 940 community controls and 940 hospital controls	Exposure = Non-aspirin NSAID use reported within 14 days of index date	Hemorrhagic stroke (SAH and ICH); Conditional logistic regression, adjusted and unadjusted	Unadjusted OR for exposure = 1.18 (0.80-1.73) with community controls; 0.67 (0.45-0.98) with hospital controls; adjustment did not materially change results	Not assessed (14 day window of exposure)	Protective effect versus hospital controls most significant with neurology and neurosgy pts. Pts s/p MI not analyzed.	Not specifically analyzed	Not presented	Strengths: Large number of cases Limitations: Main focus of study was phenylpropanolamine. Only survivors were cases. Compound or dose specific risk not assessed. Exposure duration not assessed	Community control analysis underpowered (CL 0.80-1.73). Authors concluded selection bias explained protective effect found with hospital controls (i.e., hospital pts were more likely than source population for cases to be using NSAIDs)
4	**Mangoni BJCP 2010** Nested case-control study investigating association of NSAIDs and MI, heart failure (HF), and mortality in an elderly sample	Australian Department of Veterans Affairs databases 1-1-2002 to 30-2006	War veterans, their spouses, and dependents aged 65+ as of 1-1-2002. Cases: N = 83,623 pts with MI, HF, death from any cause. Contols: N = 1,662,099 (matched 20:1)	Any NSAID, non-selective NSAID, meloxicam/prioxicam/sulindac combined, specific NSAIDs	Conditional logistic regression to calculate adjusted ORs for use within 2 yrs, and use within 30 days	OR fo 20+ NSAID Rxs in past 2 years: MI = 1.10 (1.01-1.19), All cause mortality = 0.74 (0.69-0.79), NS for peripheral arterial disease, HF, arrhythmia, cardiac arrest	Similar results for use within 30 days of event (MI risk increased but mortality decreased)	Adjusted for risk factors but did not stratify by them. Patients with one of the outcomes or a cancer diagnosis or cancer therapy within 2 yrs were excluded.	Generally similar results by category of NSAID but power limited. Heavy users of meloxicam and diclofenac had significantly lower total mortality	Not presented	Strengths: Examined several different cardiovascular outcomes in a high risk (i.e., older) population. Large number of cases and controls for analysis. ORs adjusted for risk factors. Limitations: Cases not adjudicated. Not adjusted for baseline health care utilization, which could affect number of NSAID Rxs.	Mortality reduction despite increase in MI possibly attributable to "healthy user" effect, especially since level of health care utilization was not accounted for in analysis

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5	**Mangoni PDS 2010** Nested case-control study investigating association of NSAIDs and stroke. Companion study to previous one	Same as previous	Population same as previous study. Cases = 5233 pts with iscemic stroke and 1391 with hemorrhagic stroke. 19 matched controls for each case.	Same as previous study	Hospitalization for ischemic or hemorrhagic stroke. Statistical analysis plan as per previous study.	No positive association with ischemic strokes and slight protective effect for 1 or 2 NSAID Rxs in past 30 days (OR 0.89, 0.81-0.98). No statistically significant ORs for hemorrhagic stroke.	2 yr and 30 day exposure risk windows were evaluated	Adjusted for risk factors but did not stratify by them. Patients with one of the outcomes or a cancer diagnosis or cancer therapy within 2 yrs were excluded.	Infrequent use of diclofenac and meloxicam within 2 years lowered risk of ischemic stroke compared to no use.	Not presented	Same as previous study. Hemorrhagic stroke analysis perhaps underpowered (all CLs included unity).	Tendency towards protective effects in the results may represent healthy user bias (see comments for previous study).
6	**Pratt** Cohort study of risk of serious events with NSAIDs in high-risk patients	Australian Dept. of Veterans Affairs database. Study period 8-1-2000 through 6-30-2005; 4-mo baseline prestudy period	Two cohorts of high-risk patients: (1) DM patients as identified by use of insulin or oral hypoglycemics (N=16,573); or (2) users of ACEIs, ARBs or frusemide (N=17,865). Reference group were users of at least one other medication (N=128,750). Patients predominantly male with mean ages 75+	Any NSAID, COX-2 inhibitors	Primary hospital diagnosis of congestive heart failure (CHF), GI ulcer, acute renal failure, AMI, hypertension, within 30 days of first NSAID Rx. Adjusted incidence rate ratios calculated with Poisson regression.	NSAID use: increased RR for every outcome except hypertension in reference group; increased RR for every outcome except CHF in ACE/ARB/frusemide group, increased RR for ulcer and AMI in DM group	First 30 days on drug was only exposure analyzed	For AMI, aIRRs: 1.31 (1.12-1.53) reference group, 1.54 (1.20-1.98) ACE&c group, 1.40 (1.09-1.80) DM group; unexposed incidence rates ~3x higher in DM and ACE&c groups vs. reference group	>70% of NSAIDs used were COX-2 inhibitors. For COX-2 inhibitors analyzed separately results were similar for total hospitalizations, but were not presented by specific outcomes.	Not presented	Strengths: Stratified by comorbid diseases. Focus on at-risk population (older with comorbidities). Limitations: Outcomes not adjudicated. Only one risk period (first 30 days) examined. Results reflect mainly of users of COX-2 inhibitors. Difficult to assess adequacy of adjustments to IRRs.	Primary focus was on outcomes of any hospitalization, and on GI ulcers
7	**Fosbol** Cohort study to evaluate risk of death or MI with NSAID use by healthy individuals	Danish National Patient Registry 1997-2005	Individuals aged 10+ without hospitalizations x 5 yrs before NSAID Rx, and no use of selected drugs for chronic medical conditions (N=1.03 mil, 58% male, median age 39) Subgroup with no hospitalizations x 10 yr	Ibuprofen, diclofenac, rofecoxib, celecoxib, naproxen; high vs low prescribed dose	MI or death from any cause. Two analyses: Cox proportional hazards with NSAID use a time-dependent variable, and case crossover comparing 0-30, 60-90, and 90-120 day windows before event	Elevated HRs with high doses of all, and statistically significant for all except naproxen (Protective HRs with low dose ibuprofen and naproxen.) ORs in case-crossover elevated for all except naproxen. Additional results published separately in Fosbol et al., Circ Cardiovasc Qual Outcomes 2010.	Per text of article (data not shown): no significant differences in first few days of treatment versus later treatment; post treatment, risk returned to baseline except for rofecoxib, for which risk persisted.	Not analyzed (healthy population)	For each compound, lower dose had lower risk, with some evidence of protective effects from low doses of ibuprofen, diclofenac, naproxen, but not coxibs.	Main population, HR for death from any cause: ibu ≤1,200 mg 0.78 (0.73–0.84); ibu >1,200 mg 1.77 (1.55–2.02); nap ≤500 mg 0.70 (0.58–0.86); nap >500 mg 1.25 (0.90–1.72). However, OR for composite endpoint in case crossover analysis elevated for ibu ≤ 1200 mg/d	Strengths: General agreement between two analytic methods (Cox PH and case-crossover) Limitations: Ibuprofen available over the counter during latter part of the study period, but results did not differ with or without data from that time. Results for stroke endpoint were omitted & published separately (Fosbol et al., Circ Cardiovasc Qual Outcomes 2010).	Deaths outnumbered MIs so composite results generally reflect pattern for all-cause mortality. Strong dose dependency for risk observed. Low dose naproxen associated with less risk. Authors comment that public health burden of excess deaths with NSAID use in Denmark comparable to Danish traffic fatalities.

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8	**Ray 2009** Cohort study to assess cardiovascluar safety of NSAIDs in patients recently hospitalized for coronary heart disease	Three databases: Tennessee Medicaid, Saskatchewan Health, UK GPRD. 1999-2004	48,566 patients 40-89 y.o. enrolled for 1 yr without evidence of cardiovascular or other life-threatening dx, and hospitalized for MI, unstable angina, or coronary artery revascularization.	Outpatient Rxs for naproxen (hi dose cutoff 1000+), ibuprofen (hi dose >1600), diclofenac (hi dose 150+), celecoxib (hi dose >200), rofecoxib, indomethanic, valdecoxib. Follow-up began 45 days after admission.	Outcomes: Serious Coronary Heart Disease (=MI or out-of-hospital cardiac death) & Serious Cardiovascular Disease (=MI, stroke, or death from any cause). Analysis: adjusted Poisson regression.	No associations found vs nonuser except for diclofenac/serious cardiovascular disease/death, IRR 1.38 (1.18-1.61). IRRs favored naproxen over other NSAIDs though not always statistically significant.	Generally, an inverse duration-risk relationship was observed. Short term (<90 days) greater risk than longer term use, for ibuprofen, diclofenac, celecoxib, rofecoxib.	(Entire study population at elevated risk.) No clear pattern of higher risk among subgroups of MI, angioplasty, and upper tertile CV risk score	Generally, naproxen with lower risk than diclofenac, ibuprofen, or high dose coxibs	Not analyzed by these dosage levels. Generally few differences by hi vs. lo dose	Strengths: High risk population studied. Limitations: Many analyses with differing reference groups, patient subgroups, and endpoints. Data combined from 3 different countries and health care systems. First 45 days after qualifying event excluded because of no inpatient NSAID use data. Only medical records in GPRD available for review.	Authors concluded naproxen has best cardiovascular risk profile. Accompanying editorial notes that adding all-cause mortality to endpoint reduced the IRRs for rofecoxib, perhaps due to fewer GI bleeding deaths?
9	**Roumie** Retrospective cohort study to assess cardiovascular risk with NSAID use	Tenn. Medicaid 1999-2005	Non-institutionalized beneficiaries aged 35-94 y.o. Pos. CV hx: N=18972 NSAID users and N=60784 nonusers. Neg CV hx: N=118213 NSAID users and N=380434 nonusers. Pts predominantly female and white, mean age 45 for Neg CV hx and 54 for Pos CV hx	Celecoxib, rofecoxib, valdecoxib, ibuprofen, naproxen, indomethacin, diclofenac; stratified by modal doses and use <90 days vs 90+ days. Other NSAIDs excluded	Outcomes: Hospitalized AMI and stroke, and out of hospital death from coronary heart disease (determined via linked death certificates). Adjusted Cox PH analysis (yielding aHR)	Neg CV hx: rofecoxib, valdecoxib, indomethacin had statistically sig. increased aHRs (all below 1.5). Pos CV hx: only rofecoxib with increased aHR. Naproxen with aHR = .88 (.79-.99) in prevalent users. No consistent pattern for higher risks with hi vs lo doses	No consistency of risks with respect to use < or ≥ 90 days	See under Results; entire sample was stratified by pos or neg CV hx. Further stratification by age groups was underpowered.	See under Results; of compounds still marketed, only indomethacin showed increased risk; naproxen showed decreased risk in CV pts.	ketoprofen not studied; hi-lo dose cut-offs for ibuprofen and naproxen exceeded OTC doses	Strenghts: stratified by CV hx. Limitations: could not adjust for indication (e.g., severity of arthritis); nonuser comparison group makes confounding by indication possible.	Funded by Pfizer.
10	**Turajane** Hospital based retrospective cohort study to assess CV and GI risks of nonselective NSAIDs vs coxibs in elderly OA pts	Police General Hosp. inpt and outpt records, Bangkok, Jun 2004-Jun 2007	Age 60+ y.o., with OA, and without hx of selected GI events, MI, or heart failure. N=1030.	Diclofenac, dflunisal, sulindac, prioxicam, indomethacin, loxoprofen, meloxicam, nimesulide, naproxen, celecoxib, etoricoxib. In-hospital prescriptions.	MI and CHF. Only outcomes with inpatient drug exposure analyzed. Adjusted OR	ORs for celecoxib and etoricoxib versus traditional NSAIDs <1 but not statistically significant.	Drug exposure time increased risk (OR 1.05, p=0.00, reference not stated)	Not analyzed with respect to drug exposure	Analyzed only celecoxib & etoricoxib vs. all traditional NSAIDs	Not presented	Strengths: studied OA population only to reduce confounding by indication Limitations: Inpatient drug use only, no analysis by individual compounds except coxibs	Offered limited inferential value regarding CV risks of NSAIDs. The authors speculated that reduced ORs with coxibs may be due to preferrential use of traditional NSAIDs in pts with CV risks. Celecoxib and etoricoxib significantly reduced risk of GI events vs older NSAIDs; gastroprotective agents also reduced GI events

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11	**Varas-Lorenzo** Combined population based cohort study and nested case-control study of MI and sudden cardiac death with NSAIDs	Saskatchewan Health 11-15-1999 to 12-31-2001	Enrollees 40-84 y.o. not residing in N.H. and without major non-CV diseases. N=3252 cases (see outcome) and N=20002 randomly selected controls	Hi-lo dose (mg/d) cutoffs: celecoxib 200, rofecoxib 25, diclofenac 100, naproxen 1000, ibuprofen 1800, indomethacin 100	Main analysis current use (<7 days of index event) vs non-use. AMI hospitalization or out of hospital coronary heart disease death. Sample of hospitalized MI charts reviewed	No statistically significant ORs versus nonuse for composite endpoint after full multivariate adjustment	Short term (0-30 days), but not >30 day use, of naproxen and ibuprofen had stat sig OR	Authors analyzed effect modification by comorbidities or elderly age for most commonly used drugs (celecoxib, rofecoxib, diclofenac, naproxen), no significant finding.	No statistically significant ORs for individual drugs versus nonuse for composite endpoint after full multivariate adjustment. When limited to new users, ibuprofen associated with primary outcome (OR 2.20, 1.06-4.58).	Low dose cutoffs higher than for OTC use for ibuprofen and naproxen, ketoprofen not studied	Strengths: Well known database, some charts adjudicated. Limitations: Statistical power limited. Restricted formulary use of coxibs prior to Jun 2000.	Study appears underpowered for number of covariates used in analysis; simpler model adjusted for age and sex alone found positive associations. Authors argue that results show coxibs and tNSAIDs have similar risks; i.e., despite mostly null comparisons. Sponsored by Pfizer.
12	**Cunnington** Retrospective database study of coxib cardiovascular risk in OA	Life-link medical & pharmacy claims database; includes fee-for-service and PPO settings. Exposures from 1999-2002	Pts with OA (N=80826) of which 29287 were chronic users of a study drug; RA pts and pts with other chronic illnesses excluded.	Chronic (≥90 d) use of celecoxib, rofecoxib, or naproxen.	Outcome: hospitalization for AMI or ischemic stroke. Follow up starting after 91 days. Adjusted Cox PH analysis	Use > 90 days was compared to nonuse+short-term NSAID use (< 90 days). Positive association for rofecoxib (HR 1.25, 1.04-1.50) but not naproxen or celcoxib	No significant effect reported for duration of use (only use >90 days analyzed)	Authors state no evidence of effect modification for rofecoxib. Attributable risk from rofecoxib versus short-term use= 3 per 1000 PY for younger low risk subgroup, 19 per 1000 PY in high risk group	See Results	Not presented	Limitations: Only use for 90+ days considered. No adjudication of outcomes. Strengths: heterogeneous indication (limited to OA)	Only finding was positive risk from rofecoxib. Sponsored by GSK
13	**Garcia Rodriguez** Nested case-control study of nonfatal MI and NSAID use, to correlate risk with in vitro measures of COX2 inhibition	THIN database in UK. Jan 2000-Oct 2005	Pts 50-84 y.o. without cancer. N=8852 cases and N=20000 randomly selected controls (incidence density sampling) matched on sex, age, year	25 individual tNSAIDs and coxibs	MI diagnosis with survival >1 mo. Unconditional adjusted logistic regression, taking OR as estimator of RR	Current use of any NSAID vs nonuse RR=1.34 (1.23-1.47). Weaker COX-2 inhibitors (ibuprofen, meloxicam, celecoxib, etoricoxib) had RR =1.18; stronger COX-2 inhibitors (rofecoxib, indomethacin, diclofenac, piroxicam) had RR 1.60 (p<0.01).	Trend towards higher RR with longer exposure (up to 3+yrs)	RR higher in females, younger pts, and pts with CV risk factors, but CLs overlapped	Only overall associations: diclofenac (RR 1.67, 1.44-1.94) & rofecoxib (RR 1.46, 1.10-1.92). Slow release hi dose (150 mg) diclofenac with greatest point estimate (RR 2.09, 1.43-3.06)	No association for low or high dose ibuprofen (cutoff 1200), or naproxen (cutoff 750)	Strengths: Many compounds analyzed Limitations: Many underpowered comparisons, since RR> 1 for multiple drugs but stat. sig. for only 2. Fatal MI excluded.	Authors found a statistically siginificant linear correlation between % inhibition of whole blood COX-2 and point estimates of RR. Sponsored by Pfizer. See #61 for additional analyses.

#	Reference, Study Design & Objective	Data source and time frame	Population & Sample Size	Exposure and dose (mg/d) groups	Outcomes & Analysis	Results	Time to event	Vulnerable subgroups (including pts s/p MI)	Risk by compound	Data on OTC use (ibuprofen ≤ 1200mg/d, ketoprofen ≤ 75 mg/d, naproxen ≤ 660 mg/d)	Strengths & Limitations	Comments
14	**Haag** Prospective population-based cohort study to assess risk of stroke with NSAIDs	Rotterdam Study: prospective long term follow up study of volunteers 55+ y.o. living near Erasmus Medical Center. 1990-2004	N=7636 subjects with no hx of stroke (mean age 70 yrs, 61% female)	Current vs. past vs. never users analyzed. COX-1–selective: Indometacine, Piroxicam, Ketoprofen, Flurbiprofen, Apazone. Nonselective: Diclofenac, Naproxen, Ibuprofen,Nabumetone, Sulindac. COX-2–selective: Rofecoxib, Celecoxib, Meloxicam, Etoricoxib, Valdecoxib	Strokes (ischemic or hemorrhagic) during follow-up identified from database and adjudicated with medical records. User status defined at time of event. Adjusted Cox PH with never use reference.	Current users of NSAIDs experienced 61 strokes (aHR 1.77, 1.29-2.41). Ischemic stroke aHR 1.92, 1.29-2.87. Unadjusted HRs lower.	not analyzed	Not analyzed	Association greater for COX-2 selective than nonselective; no association with COX-1 selective. Stronger associations for ischemic strokes alone. Individual drugs with positive associations: diclofenac (aHR1.60, 1.00-2.57), naproxen (aHR 2.63, 1.47-4.72), rofecoxib (aHR 3.38, 1.48-7.74); limited power for other compounds. Changing reference group to subgroup with at least 1 NSAID Rx gave comparable results. Naproxen, rofecoxib also associated with ischemic strokes alone.	Not presented. (Authors stated that doses above vs. below "DDD" showed no obvious differences, but power was limited)	Strengths: linked health care records minimized loss to follow-up. Data on clinical covariates such as BP, BMI, smoking, total cholesterol, available. Adjusted for ASA use. Limitations: Only 61 current user events, most (n=48) involving nonselective NSAIDs, limited power for subanalyses. 273 out of 807 total strokes could not be classified (ischemic vs. hemorrhagic). Some study drugs not marketed in U.S.	Authors point out that 2x increase in strokes with naproxen (vs pbo) was also seen in ADAPT trial, and that in VIGOR trial rofecoxib and naproxen arms had similar incidences of stroke, lending credence to their naproxen finding
15	**Hammad** Population-based cohort study to address time course of risk of AMI with NSAID use	GPRD 1997-2004	New NSAID users (n= 283136)with >1 yr in GPRD aged 40-84 y.o. with no major CV or other illnesses	Coxibs vs. noncoxib COX-2 inhibitors (meloxicam, etodolac, diclofenac) vs tNDSAIDs	AMI confirmed by record review. COX PH adjusted for demographic, CV risk factors. Remote NSAID users reference group. First month of exposure vs. longer exposure	Versus remote use: Positive associations similar for coxibs (aHR 2.11, 1.04-4.26) and noncoxib COX-2 inhibitors (aHR 2.24, 1.13-4.42), nonsignificant for tNSAIDs	HR for combined COX2 inhibitor group higher for 1 month of use than > 1 mo (difference not statistically significant). Recent use: no association found	Not analyzed	Not analyzed by individual compound	Not analyzed	Strengths: Records reviewed by study authors. Limitations: did not include OOH deaths. Dose and individual compounds unanalyzed.	Suggests risk returns to baseline post exposure. Confirms findings in Levesque et al. CMAJ 2006 of immediate onset of risk.
16	**Nadareishvili** Nested case-control study to determine risk factors for stroke in RA pts	National Data Bank for Rheumatic Diseases (registry of US rheumatology pts) Jan 1999-Jul 2006	N=16990 adult RA pts and N=5141 noninflammatory rheumatic disorder pts	Exposure to NSAIDs determined from pt self report on semiannual survey, yielding 6-month windows for exposures	Cases were 269 pts aged 25-100 with initial stroke (fatal or nonfatal) confirmed by chart review. Incidence density sampling of matched controls. Conditional logistic regression.	Rofecoxib use within 6 mo OR 2.28, 0.97-5.38	not analyzed	not analyzed	Association with rofecoxib (see results). Celecoxib use at baseline OR > 1 but with CL including 1. Low dose ASA OR=3.60 (2.09-6.22)	Not analyzed	Strengths: collected data on many clinical characteristics. Limitations: drug use data collected only every 6 months by pt self report. Only data on celecoxib and rofecoxib presented in results. Most strokes unclassified as to ischemic or not.	ASA association likely to be confounding by indication; authors included ASA use as indicator of past CV disease

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17	**Roumie 2008** Retrospective cohort study to assess stroke risk with NSAID use	Tenn. Medicaid 1999-2004	Non-institutionalized beneficiaries aged 50-84 y.o. without prior stroke or other serious illnesses (n=336906)	Celecoxib, rofecoxib, valdecoxib, ibuprofen, naproxen, indomethacin, diclofenac; stratified by modal doses and use <90 days vs 90+ days. Other NSAIDs grouped	Hospitalization for ischemic or hemorrhagic stroke. Sample of 250 charts reviewed, PPV for any stroke 97%. Proportional hazards regression adjusted for covariates and vascular risk score	4354 stroke hospitalizations (89% ischemic). "Celcoxib aHR 1.04 (0.87, 1.23), rofecoxib aHR 1.28 (1.06, 1.53), valdecoxib aHR 1.41 (1.04, 1.91) No noncoxib NSAIDs with statistically significantly increased risk. Low dose higher risk for valdecoxib and rofecoxib	Little difference for <90 vs 90+ days	No statistically significant effect of age or vascular risk	See Results	not analyzed	Strengths: Validated outcomes. Includes review of 6 other observational studies of NSAIDs and stroke. Limitations: Sample sizes for individual compounds limited. Did not account for out of hospital stroke deaths	Found association only for 2 compounds no longer marketed
18	**Ruffin** Nested cohort study examining NSAID use and CV events after cardiothoracic surgery (CTS)	Subjects in Atrial Fibrillation Suppression Trials (AFISTs): randomized trials of therapies to reduce AF post CTS (first trial published 2001)	Pts 50+y.o. undergoing CABG and/or valve surgery. N=555, 77% male, mean age 68 y.o.	Use of any NSAID postoperatively except prophylactic ASA. NSAID use was prescribed by clinicians as needed, not protocol-defined	Stroke or MI determined by review of clinical records. Multivariate logistic regression.	N=13 strokes, 2 with NSAID use. N=12 MIs, 3 with NSAID use. Adjusted OR for stroke 1.10, 0.21-5.66. Adjusted OR for MI 1.70, 0.40-7.10.	Not analyzed	Not assessed. All pts had undergone cardiothoracic sgy.	Not analyzed	Not analyzed	Strengths: Randomized controlled trial data. Access to clinical records and data. Limitations: NSAID use not randomized. Small number of events. Authors stated, "We may have been underpowered" for stroke, MI	Other findings included less postoperative AF and fewer blood transfusions with postoperative NSAID use. The authors commented that power was limited, but the elevated point estimates for the MI and stroke ORs warrant further study.
19	**Solomon** Cohort study to explore risk factors for CV events among older NSAID users	Medicare drug benefits program in PA, 1999-2004. Secondary cohort from similar Medicare program in NJ	Coxib users (N=76,082), tNSAID users (N=53,014), & nonusers (N=46,558). Mean age 78-80 y.o., >80% female	New users of celecoxib, rofecoxib, valdecoxib, iclofenac, ibuprofen, naproxen, any other tNSAID combined. All doses combined.	Outcome: Hospitalization for MI, stroke, CHF, or out-of-hosp. cardiac death. Reference group: users of thyroid hormone or glaucoma medication. Cox PH.	Increased risk with rofecoxib (aHR 1.22, 1.14-1.30); point estimates below one for all others, and stat sig <1 for celecoxib, valdecoxib, naproxen, other tNSAIDs	not analyzed	Risk factors: age 80+, hypertension, prior MI, prior study outcome, RA, renal disease, COPD. Large increments in absolute risk: typically several events per 100 person years in these subgroups	See under Results. Calculated attributable proportion as measure of interactions. Excess risk in vulnerable subgroups most pronounced for rofecoxib and ibuprofen (age 80+, prior MI, prior CVD, COPD)	Not analyzed	Strengths: examined vulnerable subgroups Limitations: did not account for dose or duration	Partially funded by Pfizer
20	**van Staa** Simulation analysis using GPRD data to estimate CV harms and GI benefits of coxibs	GPRD, no time frame given	Coxib users (N=155,439)	Rofecoxib, celecoxib, other	Estimated how many CV events observed were attributable to coxib use and how many GI events had been prevented by coxib use, based on clinical trial data	Projected benefits of coxibs in reducing GI events offset by CV events especially in patients with CV risk	not analyzed	Not applicable	Not applicable	not analyzed	Limitations: simulation study	First author from MHRA

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21	**Warner** Retrospective cohort study of risk of AMI with etodolac	Dallas VA Medical Center 10-1-1998 to 9-30-2004	Male veterans who received a study drug; N=38,601.	Etodolac, naproxen, rofecoxib, celecoxib	Acute MI as adjudicated by cardiologists. Logistic regression.	N=100 confirmed MIs With naproxen as ref. rofecoxib OR 2.16 (1.04-4.46); celecoxib OR 2.18 (1.09-4.35); etodolac OR 1.32 (0.81-2.16).	Plotted; by inspection, cumulative incidence increased linearly for all 4 drugs	In pts with previous MI, OR for coxibs 4.26 (1.17-15.6)	See Results	not analyzed	Limitations: single site. Only 4 durgs and 1 outcome assessed. Strengths: adjusted for antiplatelet therapy; patients obtain ASA at no charge, making OTC use less likely	Authors concluded etodolac has favorable risk:benefit profile (low GI toxiity shown in a companion study), and CV risk of NSAIDs low in pts without a previous MI
22	**Wolfe** Cohort and nested case-control study of RA patients to assess risk factors for first MI	National Data Bank for Rheumatic Diseases (registry of US rheumatology pts) Jan 1999-Jul 2006	N=17,738 RA pts and N=3,001 noninflammatory rheumatic pts	Only data on celecoxib and rofecoxib presented. Exposures by patient self report at 6 month intervals.	Adjudicated fatal and nonfatal MI.	In RA subjects no association with current rofecoxib (OR 1.2, 0.8-1.8) or celecoxib (OR 1.1, 0.8-1.4)	No association whether exposure current or "ever"	Not assessed with respect to coxib use	See Results	not analyzed.	Strengths: data on many clinical characteristics. Limitations: drug use data collected only every 6 months by pt self report. Only data on celecoxib and rofecoxib presented in results	Companion study to Reference 16. Paradoxically, low dose ASA associated with MI (confounding by indication?)
23	**Afilalo** Analysis of clinical trial data to assess long term stroke risk with rofecoxib	APPROVe study: randomized placebo controlled clinical trial of effects of rofecoxib on colon polyps	Pts with history of colon polyps. N= 1,287 rofecoxib 25 mg/d and N= 1,287 placebo	rofecoxib 25 mg/d or placebo for three years with follow-up post-treatment	Adjudicated cases of ischemic stroke	RR for ischemic stroke at 3 yrs 1.99 (0.74-5.39); with 1 year post-treatment follow-up RR 2.91 (1.15-7.39)	See results. All 5 strokes during 1 yr post-treatment follow up were in rofecoxib subjects	not analyzed	Rofecoxib only compound studied	not relevant	Strengths: randomized dataset Limitations: only one compound studied	Authors note this is the first clinical trial data to replicate association with stroke found in observational data, suggest risk may extend past actual duration of exposure
24	**Brophy** Nested case-control study to assess risk of MI with NSAIDs with respect to past history of MI	Quebec universal health insurance database, 1-1-1999 to 6-30-2002	Random sample of Quebec residents >65 y.o. dispensed NSAID during study period (N=125,000)	Non-ASA NSAIDs, naproxen, celecoxib, rofecoxib, meloxicam. Nonuser controls (up to 20) matched on age and yr	First hospitalization for AMI. Conditional logistic regression.	Adjusted RR rofecoxib 1.28 (1.10-1.49), celecoxib 1.08 (0.94-1.25) Nonsignificant increase in RR with higher doses of coxibs	not analyzed	Adjusted RR for previous MI patients: rofecoxib 1.59 (1.15-2.18), celecoxib 1.40 (1.06-1.84). Only rofecoxib associated with MI in pts with no past MI	RR point estimates lower with concomitant ASA (test for interaction p=0.07 for celecoxib, 0.25 for rofecoxib)	not analyzed	Strengths: examined previous MI patients. Limitations: statistical power limited and many point estimates did not reach statistical significance	
25	**Garcia Rodriguez Egan FitzGerald** Nested case-control study of the relationships between NSAID use, hormone replacement therapy (HT), and MI	GPRD 1997-2000	Female patients aged 50-84. Cases had MI (including nonfatal or death from coronary heart disease) (N=1673); controls randomly selected (N=7005)	Any one of 21 tNSAIDs (75% of tNSAID users received dilofenac, ibuprofen or naproxen). HT was any form of estrogen with or without progestin.	Adjusted ORs for MI (including deaths) with exposure to HT, tNSAIDs, both	With no HT or NSAID as reference, adjusted ORs: for current HT & no NSAID 0.64 (0.48-0.85). Current NSAID, no HT 1.02 (0.84-1.24). Current HT and NSAID 1.71 (1.05-2.78)	Results appeared similar when subgrouped by NSAID duration less than or greater than 2 mos. though subgroup sample size small	Not analyzed	All tNSAIDs combined in analysis. For ASA, nonuse or dose 75 mg/day + HT showed OR<1, but ASA 150 mg/d + HT OR 1.41 (0.47-1.22)	not analyzed	Strengths: GPRD database includes much clinical information, including nonprescription ASA. Limitations: did not examine NSAIDs by compound or dose	Authors argue that WHI study showed cardioprotection by HT for perimenopausal (but not older) women, and that NSAID use may antagonize this effect
26	**Lee Bartle Weiss** Nested case-control study of OA pts examining tNSAID and coxib use, cardiovascular risk, and total mortality	U.S. VA system 10-1-2001 to 9-30-2004	Users of a single NSAID without past MI or stroke, stratified by previous coronary artery disease (CAD+, n=16,869, mean age 72; CAD-, n=11,912, mean age 70).	Celecoxib, rofecoxib, naproxen, ibuprofen, diclofenac, etodolac, indomethacin, other.	All cause mortality, cardiovascular events (MI, angina), cerebrovascular events	Cerebrovascular and cardiovascular events elevated; total mortality reduced, all varieties of exposures	Exposure any time during follow-up was counted	Generally, ORs elevated with or without CAD. However, rofecoxib did not increase risk in CAD pts, only in pts without CAD	Elevated ORs for all compounds combined for cardiovascular/cerebrovascular events. For all cause mortality, ORs for all individual compounds < 1, many statistically significant.	Not analyzed	Strengths: VA system captures fairly complete clinical information. Limitations: exposure could have been remote in time from outcome	Authors had no ready explanation for reduction in total mortality with NSAID use

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27	**Moore, Derry & McQuay** Review of rates for cardiovascular and GI events in NSAID clinical trials	Six meta-analyses of NSAID clincial trials	99,400 exposed person-years	Placebo, celecoxib, etoricoxib, lumiracoxib, rofecoxib, valdecoxib,NSAID	Antiplatelet Triallists Collaboration endpoint (fatal/nonfatal MI, stroke, CV death); GI events	Rates for different treatments ranged from 0.8-2.0 events per 100 person years. Authors concluded that serious CV events occurred at equal rates with coxibs or tNSAIDs (and that GI events were less frequent with coxibs).	not analyzed	Not analyzed	Rofecoxib, among the coxibs, had the most elevated CV event rate versus tNSAIDs	not analyzed	Strenghts: used clinical trial data. Authors contended that patient populations were similar so rates could be compared across studies. Limitations: compared raw event rates across trial meta-analyses without stratification, thereby discarding randomized structure of data, so validity of comparisons dubious	Authors made no within-trial comparisons because they felt absolute event rates are more important. Sponsored by Pfizer. Did not include any observational data.
28	**Rahme et al. 2007** Retrospective cohort study to characterize risk of hospitalized MI in elderly NSAID users	Quebec health insurance database 1999-2002	NSAID users 65-80 y.o. (N=283,799)	Rofecoxib, celecoxib, ibuprofen, diclofenac. Hi/lo dose cutoffs 25 mg, 200 mg, 1600 mg, 150 mg, respectively	Hospitalized MI (ICD9 410.x). Cox regression	Relative to diclofenac <150 mg/day, only rofecoxib > 25 mg/day had statistically significant increase in MI (adjusted HR 1.64, 1.21-2.23). However, in general higher doses tended to have higher crude rates	Short duration ibuprofen lower risk than short duration diclofenac (aHR 0.79,0.41-0.95), otherwise no significant findings	Subgroup of pts with OA: similar results	See Results	\	Strengths: large sample of geriatric patients. Limitations: Comparisons appeared statistically underpowered. Naproxen may have been a more useful reference group, but authors felt naproxen would not make a good comparator because of its antiplatelet activity (?)	Sponsored by Merck.
29	**Spalding et al.** Retrospective cohort study of cardiovascular risk, NSAID use, and hypertension (HTN)	Northeastern U.S. Blue Cross/Blue Shield plan Jan 1999- Jun 2001.	Adults with RA or OA (N=31,743)	Pts required to have 2 or more NSAID Rxs. Rofecoxib, celecoxib, nonselective NSAIDs (naproxen, ibuprofen, diclofenac/misoprostol).	Hospitalization for MI or stroke. Cox PH.	Coxib users had generally more CV risk factors. After adjustment, rofecoxib risk higher than nonusers (1.62, 1.21-2.16), celecoxib aHR 1.23 (nonsig.), nsNSAIDs 1.05 (nonsig.) Naproxen HR 1.01 vs nonuse.	Not examined	Rofecoxib risk higher with HTN.	See Results	not analyzed	Strengths: examined subpopulation of HTN pts. Limitations: requiring 2 NSAID Rxs may have introduced immortal time, though authors counted events during first Rx.	Sponsored by Pfizer. Authors concluded that HTN elevates coxib CV risk and that celecoxib should be safer than rofecoxib because of its milder BP effects
30	**Cheng** Literature review of observational studies of nsNSAIDs and CV risk	Publications 1966-2006	16 observational studies	Not applicable	Review article	Concluded that findings varied from study to study, some showing increased risk, some decreased risk						
31	**Huang et al.** Cohort study of CV events in long term NSAID users	Taiwan National Health Insurance Database 2001-2003	Adults using NSAIDs continuously for ≥180 days (N=16,326)	Etodolac, nabumetone, ibuprofen, naproxen, celecoxib	Hospitalization for MI, angina, CVA, TIA. Cox PH with celecoxib as reference group.	No increases in events relative to celecoxib for other NSAIDs studied.	At least 6 months of continuous use was required	Pts at higher risk regardless of NSAID use with a positive history of cardiovascular disease or other CV risk factors	No differences found	Not analyzed	Strengths: population-based with close to universal capture of Taiwanese patients. Limitations: requirement for 6 months of use may have lead to depletion of susceptibles	Confirmed know risk factors for CV events but provided no data on additional risk from NSAIDs, (i.e., with celecoxib as reference group).

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32	**Jick et al.** Nested case-control studies assessing long term CV risk of five NSAIDs	GPRD Cases of MI in NSAID users from Jan 2001-Sep 2005	GPRD patients aged 30-79. N=859 cases with first MI	Rofecoxib, celecoxib, ibuprofen, naproxen, diclofenac; exposure categorized by prescription number. Matched controls = pts with only 1 Rx of that NSAID	First MI. Conditional logistic regression; each NSAID analyzed separately	Rofecoxib: signifiant RR only for 20+ Rxs (3.1, 1.1-8.9). Celecoxib & ibuprofen: no significant RRs. Naproxen: 2-4 Rxs RR 2.2 (1.2-4.0) Diclofenac: RR >2 after 10 or more Rxs	See under Results	Cases and controls with risk factors for MI were excluded	RRs greatest for longer term rofecoxib and diclofenac use	not analyzed	Strengths: GPRD database includes much clinical information. Limitations: sample sizes limited; reference group was one month of NSAID exposure, which may not be risk-neutral	
33	**McGettigan et al.** Case-control study assessing risk of acute coronary syndrome (ACS) with NSAIDs	Three hospitals in New South Wales Aug 2003-Sep 2004	Cases were pts with ACS (=MI or unstable angina), N=328; Controls (N=478) = pts hospitalized but with no NSAID-related CV or GI events, frequency matched on age and sex	Exposure determined by pt recall on interview. Doses categorized as hi or lo by median dose among controls	Multiple logistic regression.	No associations overall with celecoxib, rofecoxib, or other NSAIDs. Test for interaction across doses suggests lo dose coxibs protective, hi dose confer risk. Positive association with ASA and antiplatelet drugs.	Assessed exposure within one week of event	Not analyzed	See results.	Not analyzed.	Strengths: interview allowed data collection on OTC use. Limitations: sample size limited, only one week risk window assessed.	Described as an interim study report; goal 1200 cases
34	**Schaeverbeke et al.** Review article with recommendations for monitoring cardiovascular risk factors among NSAID users	Not applicable										Not relevant (review article) Article in French, abstract in English
35	**Choi et al.** Case-control study of hemorrhagic stroke (HS) with NSAID use	2002-2004 Cases recruited from 33 Korean hospitals	940 pts with HS who survived and could communicate 30 days after event, aged 30-84 yrs, no trauma or past stroke. Matched to 940 community controls	Exposure ascertained by interviewers unaware of study hypothesis	HS (classified as intracranial hemorrhage or subarachnoid hemorrhage). Conditional logistic regression	No association (OR 1.12, 0.76-1.87)	Exposure determined within 14 days of event only	Not analyzed	No differences for COX2 inhibitors vs nonselective	Not analyzed; excluding ASA users did not affect results	Strengths: interview allowed data collection on OTC use and other covariates. Limitations: statistical power (CL 0.76-1.87); excluded cases resulting in death or inability to verbalize, excluded exposures more than 14 days previously.	Authors comment that a previous study reporting association of NSAIDs with HS may have been confounded by heavy ASA use
36	**Feng et al.** Randomized placebo controlled safety clinical trial of celecoxib in GI disorders	2004-2006 RCT with subjects selected from 12 villages in Linqu Co., China	Aged 35-64 with H. pylori and pre-malignant GI disorders (N=1024)	2 yrs of celecoxib 200 mg BID or pbo; (also received H pylori therapy or pbo in 2x2 factorial design)	MI and stroke, either fatal or nonfatal.	4 CV events in 463 celecoxib pts versus 5 in 473 pbo pts (HR 0.84, 0.23-3.15). No difference in peptic ulcer rates	not analyzed	Not analyzed	Not applicable	Not applicable	Strengths: randomized trial. Limitations: little statistical power	Approved by IRB in Peking. Potential clinical benefits to subjects participating in this 2-yr safety study not explicitly stated

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37	**Lee et al.** Statistical analysis comparing two coxib clinical trials with respect to CV events	Adenomatous Polyp Prevention on Vioxx trial (APPROVe) and Adenoma Prevention with Celcoxib (APC) trial	1287 rofecoxib treated patients and 1356 celecoxib treated patients	APPROVe: 1287 rofecoxib patients, 1299 pbo. APC: 1356 celecoxib patients, 679 pbo	Indirect RR comparison using formula $lnRR_{ab} = lnRR_{ac}$ minus $lnRR_{bc}$ Outcomes=MI, sudden cardiac death, stroke, unstable angina, thromboembolism	APPROVe: 48 events rofecoxib, 30 pbo. APC: 48 events celecoxib, 13 pbo. Indirect RR celecoxib vs rofecoxib = 0.95 (0.76-1.19)	3 yr trials; time to event not analyzed	not analyzed	Not applicable	Not applicable	Strengths: uses RCT data. Limitations: time-to-event not analyzed, indirect comparison of two drugs	Authors concluded the two coxibs have similar CV risk
38	**Rahme and Nedjar** Retrospective cohort study to assess MI and GI bleeding risks of NSAIDs in the elderly	Apr 1999-Dec 2002. Administrative data for Quebec.	Patients 65+y.o. who filled at least one Rx for NSAID or acetaminophen, without prior MI or GI bleeding (N=510,871)	Rofecoxib, celecoxib, ibuprofen, diclofenac, naproxen, with or without ASA	First hospitalization for AMI or GI bleeding. Cox regression with acetaminophen as reference.	Statistically significant HRs for rofecoxib, rofecoxib+ASA, celecoxib+ASA, acetaminophen+ASA	not analyzed	Celecoxib risk of AMI higher in OA pts	Celecoxib with lowest risk of combined outcome of AMI/GI bleeding. Naproxen+ASA with lowest HR for AMI (1.03, 0.67-1.58)	Not analyzed	Strengths: examined concomitant ASA use Limitations: no data on OTC NSAID or ASA use. Many HRs lacked precision (i.e., wide confidence limits)	MI risk with ASA plus acetaminophen possibly confounding by indication
39	**White et al.** RCT MA of celecoxib clinical trials for CV events	39 RCTs completed by Oct 2004	23,030 celecoxib pts, 4057 pbo, 13,990 tNSAIDs	Celecoxib RCTs with doses of 200-800 mg/d	Adjudicated APTC outcomes. Cochran-Mantel-Haenszel	No increase in CV events with celecoxib vs pbo (RR 1.11, 0.47-2.67), vs tNSAIDs, lower rate of nonfatal stroke (RR 0.51, 0.23-1.10), higher rate of MI (RR 1.76, 0.93-3.35). CV mortality lower with celecoxib than tNSAIDs in ASA nonusers	Analyzed graphically (Kaplan-Meier plots)	Not analyzed	Not applicable, analysis of celecoxib trials only.	Not presented	Strengths: randomized dataset Limitations: statistical power appears limited from width of CLs. Does not include several relevant trials (APC, PreSAP, ADAPT)	Sponsored by Pfizer, with co-authors from Pfizer. Authors concluded that celecoxib showed no CV risk relative to placebo or other NSAIDs.
40	**Ross et al**. Cumulative MA of rofecoxib RCT data on cardiovascular events	Authors were expert plaintiff witnesses in Vioxx litigation, allowing them access to Merck's clinical trial data.	30 RCTs enrolling 20,152 subjects	rofecoxib 12.5 to 50 mg/day	Subject-level MA, Cox PH stratified by trial; outcomes= death from any cause plus thrombotic CV events	RR versus pbo 1.39 (1.07-1.80)	not analyzed	Not analyzed	Rofecoxib only compound	Not applicable	Strengths: used RCT data Limitations: rofecoxib only drug studied	Authors concluded that a cumulative RCT MA of cardiovascular events would have showed CV risk prior to when the APPROVe trial was halted by DSMB
41	Duplicate of 40											Duplicate of 40
42	**Solomon et al.** MA of long-term celecoxib RCTs to assess CV risk relative to dose and baseline risk factors	Six celecoxib pbo-controlled RCTs of at least 3 yr duration	Total N=7950; total person yrs = 16070; subjects had conditions other than arthritis	Celecoxib 400 mg QD, 200 mg BID, & 400 mg BID	CV death, MI, stroke, heart failure, thromboembolic event. Cox models stratified by trial	HR 1.6 (1.1-2.3) overall; HR highest for 400 mg BID 3.1 (1.5-6.1); but 200 mg BID HR higher than for 400 mg QD	Depicted graphically (Kaplan-Meier plots)	Pts with higher baseline CV risk had higher HR (p-value for interaction 0.03). Dose relationship most pronounced with high baseline CV risk. Baseline ASA use--no impact.	Only celecoxib trials included	Not applicable	Strengths: used RCT data Limitations: celecoxib only drug studied, composite endpoint lacked specificity, only RCTs for off-label indications, no data on 200 mg/d dose	Sponsored by National Cancer Institute

#	Reference, Study Design & Objective	Data source and time frame	Population & Sample Size	Exposure and dose (mg/d) groups	Outcomes & Analysis	Results	Time to event	Vulnerable subgroups (including pts s/p MI)	Risk by compound	Data on OTC use (ibuprofen ≤ 1200mg/d, ketoprofen ≤ 75 mg/d, naproxen ≤ 660 mg/d)	Strengths & Limitations	Comments
43	**Abraham et al.** Retrospective cohort study assessing risk of MI or CVA in elderly pts by COX2 selectivity	VA national admimistrative databases 2000-2002	U.S. Veterans 65+ years old, prescribed a study drug (N=384,322)	Selectivity groups--Poor: naproxen, ibuprofen. Moderate:celecoxib, etodolac, meloxicam, nabumetone. High: rofecoxib, valdecoxib	Outcomes: AMI, CVA. Cox PH with propensity score as covariate.	985 MIs, 586 CVAs. With poor selective NSAIDs as reference, average CV risk pts: MI: no NSAID HR 0.7 (0.5-0.8), high selective HR 1.5 (1.1-1.9). CVA: no NSAID HR 0.6 (0.5-0.7), high selective HR 1.6 (1.2-2.2).	Exposure assessed daily from pharmacy data. Time with no NSAID also analyzed.	For MI and CVA, aHR not much changed by low vs average CV risk subgroups, though incidence rates lower in low risk group	Relative to no NSAID, all compounds had elevated risk (with aHR c.i.s excluding 1 except nabumetone), rofecoxib the highest, for MI and CVA. Type of stroke (ischemic/hemorrhagic) did not vary significantly by COX2 selectivity (but few hemorrhagic strokes to analyze).	Not analyzed. Average median dose/day: ibuprofen 1800 mg, naproxen 1000 mg	Strengths: Included non-use person time by NSAID users (semi case-crossover design). Included data on use of lo dose ASA among other covariates. Limitations: apparently excluded out-of-hospital deaths	All compounds associated with MI and CVA but risk higher with COX2 selectivity.
44	**Chen and Ashcroft** MA of RCTs of coxibs for MI risk	55 RCTs of coxibs with at least 1 MI reported. Used public domain data.	Total subjects=99,087. Study population varied (arthritis, colon adenoma, dementia)	Celecoxib, etoricoxib, lumiracoxib, rofecoxib, valdecoxib, tNSAID, pbo	Fatal or nonfatal MI. Mantel-Haenszel ORs by trial level, with continuity correction	Increased risk with any coxib vs pbo, any coxib vs tNSAID, any coxib vs naproxen	All trials at least 4 weeks in length. Meta-regression showed no relationship to duration.	Not analyzed	Rofecoxib vs naproxen OR 5.39 (2.08-14.02), other coxibs not statistically significant vs naproxen except in aggregate. Valdecoxib vs diclofenac protective, OR 0.14, 0.03-0.73. No significant difference between rofecoxib vs celecoxib but sample small (2 trials). Celecoxib >200 mg/d vs pbo OR 2.25, 1.06-4.77)	Not applicable	Strengths: randomized datasets. Limitations: small number of outcomes, outcome reporting not standardized across trials	
45	**Farkouh et al.** Post hoc subgroup analysis of cardiovascular event data from large lumiracoxib RCT	Therapuetic Arthritis Research and Gastrointestinal Event Trial ("TARGET")	N=18325 pts 50+ y.o. with OA. Subgrouped by CV risk, low dose ASA use	1 yr RCT comparing lumiracoxib 400 mg/d, naproxen 1000 mg/d, ibuprofen 2400 mg/d. Stratified into two substudies (lumiracoxib vs ibuprofen, lumiracoxib vs naproxen	CV death, MI, or stroke; CHF as secondary outcome	High CV risk using ASA: ibuprofen vs lumiracoxib HR 9.08 (1.13-72.76), naproxen similar to lumiracoxib. High CV risk not on ASA: naproxen protective vs. lumiracoxib (HR =0, p=0.027) while ibuprofen, lumiracoxib similar	Not analyzed per se	In pts at high CV risk not on ASA, naproxen protective vs lumiracoxib (HR undefined because of zero denominator, p=0.027)	See Results, also, ibuprofen with higher event rates for CHF than lumiracoxib (HR 9.9, p=0.03), lumiracoxib and naproxen event rates similar (HR 1.03, NS). Low dose ASA did not alter this pattern.	Not applicable	Strengths: randomized trial, included data on low dose ASA. Limitations: limited statistical power. Lumiracoxib event rates higher in the naproxen sub-study; not clear why the two arms could not be combined for a safety analysis.	Authors concluded that ibuprofen, but not lumiracoxib, antagonizes ASA cardioprotection, while naproxen may provide cardioprotection in high risk pts not receiving ASA. Includes co-authors from Novartis
46	**Chen and Ashcroft** MA of RCTs of coxibs for CVE risk. Companion to #44	40 RCTs of coxibs. Used public domain trial-level data.	Total N=88,116, various populations (arthritis, colon adenoma, dementia)	Celecoxib, etoricoxib, lumiracoxib, rofecoxib, valdecoxib, tNSAID, pbo	Fatal or nonfatal cerebrovascular events including TIA. Mantel-Haenszel ORs by trial, with continuity correction	No association vs pbo for any coxib or overall (overall OR 1.03, 0.71-1.50).	Trials at least 4 wks in duration. Meta-regression found no relationship to duration above or below 6 mos.	Meta-regression found no relationship to indication studied	ORs: Coxibs vs naproxen 0.94 (0.60-1.46). Coxibs vs non-naproxen NSAIDs 0.82 (0.54-1.20). Coxibs vs diclofenac 0.62 (0.37-1.03). Coxibs vs ibuprofen 0.91 (0.47-1.75)	Doses not stated except for coxibs	Strengths: randomized datasets. Limitations: small number of outcomes, outcome reporting not standardized across trials	Diclofenac risk numerically higher than coxibs, borderline significant. Authors conclude CV risk with coxibs likely does not include CVE
47	**Curtis et al.** Pooled analysis of RCT data on etoricoxib CV events	12 RCTs of etoricoxib at least 4 weeks in duration	Sample size stated as approximate person-years for etoricoxib (~6500). Arthritis, back pain patients.	Etoricoxib 60+ mg/d, naproxen 1000 mg/d, ibuprofen 2400 mg/d, diclofenac 150 mg/d, pbo	Thrombotic CV events including TIA, but hemorrhagic CVEs excluded. Simple pooling.	Three comparisons (etoricoxib vs pbo, etoricoxib vs non-naproxen NSAIDs, etoricoxib vs naproxen) found no association although highest point estimate was vs naproxen	Analyzed graphically (Kaplan-Meier plots)	No apparent effects on RR of indication, baseline CV risk, use of anti-platelet therapies.	Etoricoxib was only study drug	Not applicable	Strengths: RCT data. Limitations: statistical power limited, used crude pooling rather than MA statistical techniques	Authors concluded that excess in CV events relative to naproxen was likely to be a valid finding despite marginal statistical significance. Authors from Merck.

#	Reference, Study Design & Objective	Data source and time frame	Population & Sample Size	Exposure and dose (mg/d) groups	Outcomes & Analysis	Results	Time to event	Vulnerable subgroups (including pts s/p MI)	Risk by compound	Data on OTC use (ibuprofen ≤ 1200mg/d, ketoprofen ≤ 75 mg/d, naproxen ≤ 660 mg/d)	Strengths & Limitations	Comments
48	**Madan et al.** Retrospective chart review of prostate cancer pts treated with high dose celecoxib	VA hospital in NJ, 1/1/1999-1/1/2005	Metastatic hormone refractory prostate cancer (N=67)	34 pts received celecoxib 400 mg BID, 33 did not and were controls	MI or CVA	Among 34 celecoxib treated pts, 2 MIs and 2 CVAs; among 33 controls, 1 MI and 2 CVAs	Only one event during current use of celecoxib	Not applicable	Not applicable (celecoxib only)	Not applicable	Strengths: examined unique patient population Limitations: sample size.	Authors concluded that CV risks should not be a barrier to using celecoxib in advanced prostate cancer
49	**Sakamoto and Soen** Pooled analysis of clinical trials comparing loxoprofen and celecoxib	12 open label and double blind trials of either loxoprofen or celecoxib or both	All studies conducted in Japan. Rheumatology and orthopedic pts. Various diagnoses.	Celecoxib up to 400 mg/d, loxoprofen 180 mg/d	GI events, serious CV events	Serious CV events in 2/2398 celecoxib treated pts and 3/1190 loxoprofen treated pts (NS). Celecoxib had fewer GI events.	Not analyzed	Not applicable; authors note ischemic heart disease less prevalent in Japan than in the West	Only compared celecoxib to loxoprofen	Not applicable	Strengths: clinical trial data. Limitations: pooled data across double blind and open label trials, loxoprofen not marketed in U.S.	
50	**Trelle et al.** RCT MA of cardiovascular safety of NSAIDs	Publically availabe data from NSAID RCTs through July 2009, plus some unpublished data on celecoxib and lumiracoxib	RCTs with two or more arms having at least 100 person-years of follow-up. 31 RCTs included. Total N=116429	Ibuprofen, diclofenac, rofecoxib, celecoxib, etoricoxib, naproxen, lumiracoxib (any dose)	MI, Stroke, CV death, any death, APTC composite outcome of nonfatal MI, nonfatal stroke, CV death. Bayesian random effects model, omitting trials with zero events	(vs. pbo): Rofecoxib and lumiracoxib highest RRs for MI, ibuprofen and diclofenac highest RRs for stroke, etoricoxib and diclofenac highest RRs for CV death	Not analyzed	Not analyzed	Vs pbo, the following drugs and outcome pairs had positive associations: Naproxen, none; Ibuprofen, stroke, APTC; Diclofenac, stroke, CV death, any death; Celecoxib, none; Etoricoxib, CV death; Rofecoxib, MI, any death, APTC; Lumiracoxib, stroke, APTC.	Not analyzed	Strengths: RCT data. Limitations: some trial data unavailable, events not adjudicated	Authors concluded that the least harmful of the 7 compounds appeared to be naproxen
51	Duplicate of 43											
52	**Abraham et al. 2008** Retrospective cohort study of mortality in elderly veterans using NSAIDs	Nationwide VA system data 1/1/2000 to 12/31/2002	Veterans aged 65+ prescribed an NSAID without NSAID use in prior 6 months (N=474495, 98% male)	tNSAIDs, coxibs, ASA at dose of ≥325 mg/d	Deaths from upper GI events, MIs, CVAs. Cox PH adjusted for PS	6920 pts died with current NSAID use. NSAID users who suffered a nonfatal upper GI event, MI, or CVA had elevated 30-day mortality afterwards	Mortality increased with cumulative % time on NSAID or coxib, reduced with increasing cumulative % time on PPI	Not analyzed	Not analyzed	Not analyzed	Strengths: large sample Limitations: all pts exposed, no direct comparisons	Difficult to know what conclusions to draw other than confirming the expected increase in mortality after a serious CV or GI event
53	**Andersohn et al.** Nested case-control study of AMI with coxibs	GPRD 6/1/2000-10/31/2004	Pts with at least 1 NSAID Rx and 40+ y.o. (N=486378)	Cases=fatal or nonfatal AMI Controls matched on age, sex, practice, yr. Rofecoxib, celecoxib, etoricoxib, valdecoxib, diclofenac, ibuprofen, naproxen	Conditional logistic regression to calculate adjusted ORs as estimates of rate ratios (RRs)	3643 cases, 13918 controls. Fully adjusted RRs: celecoxib 1.56 (1.22-2.00), diclofenac 1.37 (1.17-1.59), etoricoxib 2.09 (1.10-3.97) (valdecoxib only 2 cases)	No consistent effect of duration of use grouped by <3 mo, 3-12 mo, >12 mo	No significant modifications in RRs by age, gneder, CV risk factors, though RRs in under 60s numerically higher	Celecoxib risk elevated at both doses above and below 200 mg/d (but higher >200). Diclofenac--little difference above or below 100 mg/d	Ibuprofen no association above or below 1200 mg/d, naproxen no association above or below 750 mg/d	Strengths: GPRD captures much more relevant clinical data than claims database Limitations: sample size	Authors conclude that AMI is a risk of all coxibs, possibly dose dependent

#	Reference, Study Design & Objective	Data source and time frame	Population & Sample Size	Exposure and dose (mg/d) groups	Outcomes & Analysis	Results	Time to event	Vulnerable subgroups (including pts s/p MI)	Risk by compound	Data on OTC use (ibuprofen ≤ 1200mg/d, ketoprofen ≤ 75 mg/d, naproxen ≤ 660 mg/d)	Strengths & Limitations	Comments
54	**Brownstein et al**. Ecological study correlating hospitalizations for MI to volume of Rxs for coxibs	Partners Healthcare System in MA (includes Brigham and Women's Hosp. and Mass. Gen. Hosp.) 1997-2005	System represents 12% of all Massachusetts inpt care	National prescription volumes for rofecoxib and celecoxib	Hospitalized AMI in Partners Healthcare System. Cumulative sum and interrupted time series analyses	During period of heaviest use of coxibs, MI inpt stays increased 18.5%, and mean age of MI pts decreased by roughly 1 yr; both trends reverted towards baseline after rofecoxib withdrawn	Not applicable	Not applicable	By Poisson regression, positive relationship between MI admissions and prescription volume for both coxibs, but stronger for rofecoxib ($p<0.001$) than celecoxib ($p=0.02$)	Not applicable	Strengths: included periods of both rising and diminishing coxib use. Though ecological studies usually hypothesis-generating, association between CV events and coxibs already known. Limitations: ecological correlations are subject to many potential unmeasured biases	Authors argue that surveillance for trends in MI hospitalizations might have provided corroboration for suspicions regarding coxibs and CV events
55	Duplicate of 24											
56	**Caldwell et al**. MA of RCTs with celecoxib to assess CV events	6 RCTs of celecoxib reporting data on CV events. Public domain data sources through 2005.	Combined N=12780	Doses of 200-800 mg/d pooled	1. Fatal or nonfatal MI 2. fatal or nonfatal CVE 3.CV mortality 4.composite. Inverse variance weighting with continuity correction	OR MI vs pbo 2.26 (1.0 to 5.1), absolute risk difference 7 per 1,000 (c.i. 2 -12 per 1,000). No statistically significant associations for other outcomes. Similar results when pbo and active controls pooled	Not analyzed; trials 6+ wks in duration	Not analyzed	Only celecoxib analyzed	Not analyzed	Strengths: randomized data. Limitations: did not analyzed dose effect due to sparse data. Pooled active controls and pbo in secondary analysis, even though these may not be "poolable"	Authors feel this study, though lacking in detailed analyses, confirms positive risk with celecoxib
57	Duplicate of 2											
58	Duplicate of 47											
59	Duplicate of 7											
60	**Garcia Rodriguez et al. 2011** MA of RCTs and observational studies to compare risk of fatal vs. nonfatal MI with NSAIDs	Publications of RCTs and observational studies listed in PubMed from Jan 1990-Mar 2010	6 observational studies and 9 RCTs reporting data on fatal and nonfatal MI. RCTs had to have duration of at least 6 months and at least 1500 subjects	Any tNSAID or coxib in observational studies. All RCTs were of coxibs	Nonfatal MI or CHD death. Random effects summary estimates of RR.	Observational studies: RR 1.30 (1.20–1.41) for nonfatal MI; for CHD death RR 1.02, 0.89–1.17. RCTs: RR for nonfatal MI 1.61 (1.04–2.50); 0.86 (0.51–1.47) for CHD deaths.	Not analyzed	Subgroup of 2 observational studies of pts with CV disease also showed higher risk for nonfatal MI compared to fatal CHD events	Not analyzed	Not analyzed	Strengths: used a variety of data sources Limitations: used only published data. Pooled nonselective and COX2 selective NSAIDs. How well were fatal CHD events ascertained?	Authors argue that their results are reassuring since fatal MI not increased
61	**Duplicate of 13**											
62	**Garcia Rodriguez et al letter 2009** Nested case-control study of nonfatal MI and NSAID use (supplementary analysis of #13)	THIN database in UK. Jan 2000-Oct 2005	Pts 50-84 y.o. without cancer. N=8852 cases and N=20000 randomly selected controls (incidence density sampling) matched on sex, age, year	Any NSAID. Exposure: nonuse (reference), current use, past use (within 7-365 days)	Nonfatal MI. Unconditional adjusted logistic regression, taking OR as estimator of RR	Current NSAID use RR 1.34 (1.23-1.47). Past use RR 1.11 (1.03-1.20). Past use of > 1 yr duration RR 1.58 (1.27-1.96)	RR for current users of >1 yr duration 1.45 (1.27-1.65); duration 1-12 mos RR 1.34 (1.15-1.55); duration up to 1 mo RR 1.14 (0.93-1.39).	Not analyzed	Not analyzed	Not analyzed	Strengths: much clinical data available, large sample of MI cases. Limitations: pooled all NSAID exposures, did not examine fatal MI or other CV outcomes	Authors feel their results support duration of exposure as contributing to the risk, even in former users. Sponsored by Pfizer

#	Reference, Study Design & Objective	Data source and time frame	Population & Sample Size	Exposure and dose (mg/d) groups	Outcomes & Analysis	Results	Time to event	Vulnerable subgroups (including pts s/p MI)	Risk by compound	Data on OTC use (ibuprofen ≤ 1200mg/d, ketoprofen ≤ 75 mg/d, naproxen ≤ 660 mg/d)	Strengths & Limitations	Comments
63	**Garcia Rodriguez et al BMJ 2011** Nested case-control study to evaluate CV events after discontinuing ASA	THIN database in UK. 2000-2007	Pts 50-84 y.o. with a first prescription for aspirin for cardioprotection. N=39,513	ASA 75-300 mg/d. Current and former use analyzed. 5000 controls selected with incidence density sampling	Non-fatal MI or CHD death. Unconditional logistic regression	ASA users who discontinued in past 1-6 mos at higher risk than current ASA users (RR 1.43, 1.12 to 1.84). Per 1000 patients/ yr ~4 excess cases of non-fatal MI with discontinuation	Not applicable	No clear relationship to age or gender	not applicable	Not applicable	Strengths: THIN database includes much detailed clinical data Limitations: did not consider concomitant NSAID use	Reaffirms cardioprotection from ASA but limited relevance to NSAIDs
64	**Gislason et al.** Cohort and case-crossover study of death and rehospitalization for MI among NSAID users with a past MI. Overlaps with #1	Danish National Patient Registry and prescription data, 1995-2002	Pts at least 30 y.o. hospitalized for first MI (N=58,432, of which 36% had at least one NSAID Rx during follow-up)	Rofecoxib, celecoxib, ibuprofen, diclofenac, other. Upper limits of low dose (mg/d) = 25 rofecoxib, 200 celecoxib, 1200 ibuprofen, 100 diclofenac	Any death, or rehospitalization for MI (reMI). Cox PH with exposure as time-dependent covariate. Case-crossover analysis with conditional logistic regression.	9,773 reMIs, 16,573 deaths. HR for death with current exposure: 2.80 (2.41-3.25) rofecoxib, 2.57 (2.15 to 3.08) celecoxib, 1.50 (1.36 to 1.67) ibuprofen, 2.40 (2.09 to 2.80) diclofenac, and 1.29 (1.16 to 1.43) other NSAIDS. Positive associations for all 4 drugs with re-MI also. In case-crossover, positive associations for death with high doses of all 4 drugs, and low doses of coxibs, and positive associations with re-MI for all 4 compounds overall	Not analyzed, but Cox model adjusted for length of treatment (range of mean duration by drug from 20-83 d)	Entire sample post-MI pts	HRs for death were higher with high dose for all 4 drugs; in fact for both ibuprofen and diclofenac HRs for low dose <1. All 4 drugs associated with re-MI also, but dose relationship not as obvious as for deaths. NNH for death in person-years of exposure: rofecoxib 13, celecoxib 14, ibuprofen 45, diclofenac 24, others 143	Ibuprofen up to 1200mg/d: HR for death 0.75 (0.61–0.92), for re-MI 1.28 (1.03-1.60). In case-crossover analysis, OR for death 0.57 (0.45-0.74), re-MI 1.41 (0.95-2.08)	Strengths: Focus on high-risk population, completeness of data, use of two analytic techniques Limitations: did not examine deaths due specifically to CV events. Did not account for indication of NSAID. Prescribed dose not available, daily dose estimated.	Dose-dependent pattern to results. NNHs for excess deaths small. OTC dose ibuprofen lowered mortality
65	**Gislason et al.** Cohort and case-crossover study of death and CV hospitalizations among NSAID users with CHF	Danish National Patient Registry and prescription data, 1995-2004	Pts at least 30 y.o. hospitalized for HF (N=107,092, of which 34% had at least one NSAID Rx during follow-up)	Rofecoxib, celecoxib, ibuprofen, diclofenac, naproxen, other. Upper limits of low dose (mg/d) = 25 rofecoxib, 200 celecoxib, 1200 ibuprofen, 100 diclofenac, 500 naproxen	All deaths, or hospitalization for MI or HF. Cox PH with exposure as time-dependent covariate. Separate case-crossover analysis.	57% of cohort died, 8% hospitalized for MI. 38% for HF. Death: pos. risk with all exposures except low dose ibuprofen and low dose naproxen. Higher dose for all compounds had the higher risk. MI: pos. risk with all drugs, apparently dose-related for rofecoxib and diclofenac. HF: pos. risk all drugs, dose related with rofecoxib	Cox PH model considered pts at risk only with current exposure and was adjusted for duration of exposure. Case-crossover analysis used 30 day risk window.	No interactions found with respect to types of HF pharmacotherapy, previous MI. For death outcome subgrouped by predicted risk of death within 1 yr, HR>1 in all three tertiles (naproxen in low risk tertile had lowest HR)	Estimated person-yrs of exposure needed to produce one excess death (unadjusted, combining doses): rofecoxib 9, celecoxib 14, ibuprofen 53, diclofenac 11, naproxen 51, others 43	Subgrouping naproxen and ibuprofen by dose changed HRs for MI and HF by little; for all deaths: naproxen ≤500 HR 0.88 (0.73-1.05); naproxen >500 HR 1.97 (1.64-2.36); ibuprofen ≤ 1200 HR 0.99 (0.94-1.04); ibuprofen > 1200 HR 2.83 (2.64-3.02)	Strengths: comprehensive clinical data available, consistency of associations across multiple endpoints, vulnerable population. Limitations: events not adjudicated; did not examine time to event, indication not accounted for, did not examine cardiovascular mortality specifically	Authors speculated that celecoxib may have its greatest CV risk in CV vulnerable pts. OTC doses of naproxen and ibuprofen had lowest mortality risks. Estimated NNH fairly low
66	Duplicate of 14											

#	Reference, Study Design & Objective	Data source and time frame	Population & Sample Size	Exposure and dose (mg/d) groups	Outcomes & Analysis	Results	Time to event	Vulnerable subgroups (including pts s/p MI)	Risk by compound	Data on OTC use (ibuprofen ≤ 1200mg/d, ketoprofen ≤ 75 mg/d, naproxen ≤ 660 mg/d)	Strengths & Limitations	Comments
67	**Hawkey et al.** Case-control study of NSAID use among pts with first MI	Queen's Medical Center, Nottingham; Nov 1998-Dec1999	All admissions for first nonfatal MI (n=205). Matched community controls (sampled from same clinical practice as case) and hospital controls (admitted same day with no MI)	Exposure within 7 days of MI and use of ASA determined from interviews.	Multivariate logistic regression	ORs NonASA NSAID: 1.77 (1.03, 3.03) vs community controls; 2.61 (1.38, 4.95) vs. hospital controls. ORs 5.00 (1.18, 21.28) and 7.66 (0.87, 67.48), respectively, in ASA users	Previous use (from 1 yr to 7 days before index date): no association	Not analyzed per se. Authors interpreted higher ORs among ASA users as evidence of interference with cardioprotection by ASA, but ASA users might be a more vulnerable subgroup	Eliminating naproxen did not change OR very much.	Not analyzed	Strengths: cases clinically adjudicated, data on OTC ASA use obtained by interview. Limitations: inaccuracies of pt recall, insufficient sample to examine individual drugs	Sponsored by Boehringer Ingelheim
68	**Helin-Salmivaara et al.** Case-control study of NSAID use and first hospitalized MI	Finnish Hospital Discharge, Special Reimbursement, and Prescription Registers, 2000-2003.	N=33,309 pts hospitalized for first MI. Controls matched from general population on age, gender, catchment area, index date (N=138,949)	Any NSAID, conventional NSAIDs (indomethacin, ibuprofen, diclofenac, naproxen, piroxicam, ketoprofen, tolfenamic acid), semi-selective NSAIDs (etodolac, nabumetone, numesulide, meloxicam); Coxibs	Conditional logistic regression	Adjusted ORs for current use were 1.3-1.5 and statistically significant for all categories. Lower OR for recent use, no association past use (past use protective for coxibs)	Current use= on drug at time of MI; recent use=1-30 days prior; past use = 31 days to 2 years prior. Stratifying by duration of use (1-14d, 15-30d, 31-90d, 91-180d) did not materially affect OR point estimates	Age: for indomethacin, diclofenac, naproxen, nimesulide, and rofecoxib, statistically significant pos risk only for pts >76 yrs	Few differences in ORs by individual compounds; etoricoxib highest and celecoxib lowest OR point estimate	Not analyzed	Strengths: completeness of data in Finnish national database; ability to obtain results on many individual compounds. Limitations: outcomes not adjudicated, duration of treatment inferred from DDDs	Able to examine many individual compounds independently.
69	**Hernandez-Diaz et al.** Systematic review of observational studies on NSAIDs and MI	Publications in MEDLINE 2000-2005	16 case-control and cohort studies that included risk estimates for MI vs nonuse.	tNSAIDs, coxibs	Weighted summary RRs for MI with 95% CI per DerSimonian & Laird method. ORs taken as equivalent to RRs	Pooled MI RRs: 1.09 (1.06–1.13) tNSAIDs, 0.98 (0.92–1.05) naproxen, 1.07 (1.02–1.12) ibuprofen,1.44 (1.32–1.56) diclofenac	Insufficient data to analyze	Limited data in RA (most in OA)	Pooled MI RR 0.96 (0.90–1.02) celecoxib, 1.26 (1.17–1.36) rofecoxib. Dose effect for rofecoxib but not celecoxib. Apparent protective effect for ibuprofen and naproxen when ASA users excluded	Not analyzed	Strengths: good summary of observational studies 2000-2005. Limitations: validity of pooling ORs and RRs across studies may be questioned	One co-author from Pfizer
70	**Huang et al**. Cohort study of CV events in long term users of celecoxib, rofecoxib, meloxicam	Taiwan National Health Insurance Database 2001-2003	Pts prescribed celecoxib, rofecoxib, or meloxicam for >180 d (N=9602 total, roughly 3/4 aged 64+)	Meloxicam, celecoxib (92% at dose <=200 mg/d), and rofecoxib (excluding doses 50 md/d)	Hospitalizations for MI, angina, CVA, TIA. Cox PH with meloxicam as reference.	HR AMI celecoxib/meloxicam = 0.78 (0.63-0.96). HR stroke celecoxib/meloxicam 0.81 (0.70-0.93). 92% of celecoxib daily dosages 200 mg or less. No other statistically significant comparisons	Not analyzed per se; all pts were users for at least 180 d	Hx of same outcome in past year was a strong risk factor for all 4 outcomes, but interaction with drug exposure not analyzed	See results; no statistically significant differences for rofecoxib vs meloxicam	Not applicable	Strengths: Comprehensive national data. Analyzed subpopulation of long term users implicated in APPROVe trial data. Limitations: no data on high dose rofecoxib, sparse data on high dose celecoxib. Possible depletion of susceptibles over 180 run-in period. No data on OTC use, OOH fatal events	Appears to have some overlap with ref. 31. Authors concluded that meloxicam, a semi-selective NSAID, has CV risks
71	Duplicate of 32											

#	Reference, Study Design & Objective	Data source and time frame	Population & Sample Size	Exposure and dose (mg/d) groups	Outcomes & Analysis	Results	Time to event	Vulnerable subgroups (including pts s/p MI)	Risk by compound	Data on OTC use (ibuprofen ≤ 1200mg/d, ketoprofen ≤ 75 mg/d, naproxen ≤ 660 mg/d)	Strengths & Limitations	Comments
72	**Jones et al**. Literature review of GI and CV risks of NSAIDs	Orignial articles published 1995-2006	131 articles on NSAIDs and CV risk	Not applicable	Qualitative review of articles	Conclusions: NSAIDs have CV and GI risks, but coxibs have less GI risk than NSNSAID, H. pylori treatment and PPIs are useful strategies for GI protection, naproxen preferred in pts with CV risk factors	Not applicable	not applicable	not applicable	Not applicable	Strengths: includes some useful summaries of literature Limitations: qualitative, includes little primary data	Qualitative literature review only
73	**Kearney et al**. RCT MA of CV events with NSAIDs	Published and unpublished (sources: FDA AC mtg, Novartis, Pfizer, Merck) data from coxib RCTs	138 RCTs of coxibs at least 4 wks long with tNSAID or pbo comparison arm (total N=145,373)	Rofecoxib, celecoxib, etoricoxib, lumiracoxib, valdecoxib	APTC (vascular death/nonfatal MI or stroke). Trial level MA with Peto "one step" approximation for rate ratios. Indirect comparisons for tNSAIDs vs pbo	Coxib vs pbo 1.42 (1.13-1.78), with increased rates of MI and vascular death but not stroke. Little change with or without ASA use.	Not analyzed	Not analyzed	Coxibs vs naproxen: RR 1.57 (1.21-2.03). Coxibs vs. non-naproxen NSAID: RR 0.88 (0.69-1.12) overall, with lower RR of stroke (0.62, 0.41-0.95). Dose-related trend test statistically significant for celecoxib. RR versus pbo: naproxen 0.92 (0.67-1.26), ibuprofen 1.51 (0.96-2.37), diclofenac 1.63 (1.12-2.37)	Not analyzed	Strengths: randomized data Limitations: trial level data only, no accounting for duration of exposure, no trials directly comparing tNSAIDs and pbo	A project of the Clinical Trial Service Unit at Oxford Univ. which is currently conducting the Coxib and traditional NSAID Trialists' Collaboration (CNT) project (a patient-level MA).
74	**Levesque et al.** Nested case-control study of MI with celecoxib and rofecoxib use by elderly pts	Quebec health care system database 1999-2002	Random sample of Quebec residents 66+ y.o., with no past MI, dispensed an NSAID Jan. 1, 1999-Jun. 30, 2002 (N=125,000)	20 controls selected per case. Nonuser reference group = pts with no NSAID Rx in past year. 3/4 of celecoxib users did not exceed 200 mg/d	Cases=first hospitalization for MI (with fatal or nonfatal outcome). Conditional logistic regression	RR for first-time use: rofecoxib 1.67 (1.21–2.30), celecoxib 1.29 (0.90–1.83).	For rofecoxib, median exposure of cases = 9 d, RR higher for shorter exposure, & RR returned to baseline after 1 wk off drug.	Not analyzed	See results, no association with celecoxib	Not applicable	Strengths: Examined both time to onset and risk after discontinuation. Limitations: no data on OTC use, limited statistical power for celecoxib analysis	Authors note that these data support a rapid onset and offset of risk from rofecoxib
75	**Motsko et al.** Retrospective cohort study to assess CV risks of nsNSAIDs and coxibs by duration of use	Veteran's Administration facilities of central TX, 1999-2001. TX Medicare and vital statistics data also included	Pts 35+ y.o. prescribed a study drug (N=11,930 pts)	New users of celecoxib, rofecoxib, ibuprofen, etodolac, naproxen; grouped by long term (>180 days) or short term (30-180 d) exposure	MI, stroke, MI-related deaths. Cox PH with ibuprofen as reference.	No associations with short term use; for long-term use, celecoxib HR 3.6 (1.4-9.7) and rofecoxib HR 6.6 (2.2-20.3) vs ibuprofen, with no association for long term etodolac and naproxen	See results. Also, when subgrouped by 30 day windows of use, HRs for celecoxib and rofecoxib increased progressively	Age 65+ had higher HRs for long term use (celecoxib 7.4, rofexocib 13.2)	See results	Not analyzed	Strengths: VA data supplemented by Medicare and vital statistics data. Limitations: doses not analyzed, outcomes could be primary or secondary discharge diagnoses, sample >90% male, no untreated reference group	Strongly time dependent risk for rofecoxib and celecoxib
76	Duplicate of 28											
77	Duplicate of 38											
78	**Rahme et al**. 2009 Retrospective cohort study to characterize trends in risk of hospitalized MI among elderly naproxen users	Quebec health care system (RAMQ); two study periods, Study 1 1999-2001 and Study 2 2002-2004	Pts 65+ y.o. prescribed naproxen or acetaminophen. Study 1 N=240,568. Study 2 N=213,802.	Acetaminophen, naproxen, acetaminophen+ASA, naproxen+ASA	Hospitalization for MI. (Also analyzed GI events.)	No association with naproxen in either study period.	Not analyzed	Not analyzed	Not applicable	Not applicable	Strengths: Naproxen not available OTC so good ascertainment of use. Limitations: only one CV outcome examined	No difference between study periods for MI, but naproxen more strongly associated with GI hospitalizations in study period 2
79	Duplicate of 9											

#	Reference, Study Design & Objective	Data source and time frame	Population & Sample Size	Exposure and dose (mg/d) groups	Outcomes & Analysis	Results	Time to event	Vulnerable subgroups (including pts s/p MI)	Risk by compound	Data on OTC use (ibuprofen ≤ 1200mg/d, ketoprofen ≤ 75 mg/d, naproxen ≤ 660 mg/d)	Strengths & Limitations	Comments
80	**Salvo et al.** Systematic review of RCT MAs by SOS project	29 NSAID clinical trial meta-analyses	Not summarized	MAs that included celecoxib, etoricoxib, lumiracoxib, parecoxib, valdecoxib, rofecoxib, etodolac, meloxicam, nabumetone, ASA	Rates of events with specific drugs were calculated from each MA	"Incidence rates of MI ranged from 0.49 to 1.00% PYs for celecoxib...rates of stroke ranged from 0.14 to 0.29% PYs for celecoxib…" (similar descriptions for other compounds)	Not analyzed	Not analyzed	Not applicable, only incidence rates by compound reported without comparisons	Not applicable	Strengths: randomized datasets Limitations: same RCT may have appeared in different MAs, some MAs did not analyze rates per person year, no analytic comparisons made between compounds	Very difficult to interpret since no comparisons were made between compounds
81	Duplicate of 1											
82	Duplicate of 8											
83	**Solomon et al. 2006** Retropsective cohort study to examine CV risks with coxibs and tNSAIDs use in Medicare beneficiaries	Penna. Medicare 1999-2003	New users (within past 6 mos.) of coxibs or tNSAIDs (N=74,838). Reference group new users of thyroid hormone or glaucoma medication (N=23,532). Mean ages near 80 y.o, predominantly female (79-85% across groups)	Celecoxib (hi >200), rofecoxcib (hi >25), valdecoxib (hi >20), diclofenac, ibuprofen, naproxen, other oral NSAIDs. Hi dose tNSAID >75% of max dose	Hospitalized MI or hospitalized ischemic stroke (hemorrhagic strokes excluded). Cox PH	aRR rofecoxib 1.15 (1.06-1.25). aRR naproxen 0.75 (0.62-0.92). No other stat. sig. associations. Results similar for lo vs hi doses	For 60 days exposure vs >60 days, Rofecoxib RRs were equal and RRs for other drugs were similar.	RR similar by high vs low CV risk at baseline but events more frequent in high risk subgroup	See under Results. For secondary analysis with ibuprofen reference group results were similar.	Not analyzed	Strengths: Large numbers of outcomes. Limitations: hemorrhagic strokes excluded	Sponsored, partially funded by Pfizer. Authors speculate absence of risk with celecoxib attributable to doses mainly under 400 mg/d
84	Duplicate of 42											
85	**Suissa et al.** Nested case-control study in cohort of RA pts to assess risk of MI with DMARDs	PharMetrics claims database 1999-2003	Pts with RA (N=107,908). Ten controls randomly selected for each case matched on age, sex, month of cohort entry	Coxibs (rofecoxib, celecoxib), naproxen, all other NSAIDs, DMARDs, glucocorticoids	Cases=pts with AMI. Conditional logistic regression with current exposure defined as within 30 days of index date	No stat sig aRRs for naproxen, other NSAIDs, celecoxib, rofecoxib, combined coxibs. DMARD use protective (aRR 0.80, 0.65-0.98), glucocorticoids pos. risk (aRR 1.32, 1.02-1.72)	Not analyzed	Not analyzed	See results. RR for rofecoxib 1.18 but not stat sig	Not analyzed	Strengths: homogeneous sample (RA pts only). Limitations: probably underpowered to detect CV risk of NSAIDs	Interesting finding regarding glucocorticoids but underpowered for NSAIDs
86	**Vaithianathan et al.** Retrospective cohort study of CV and GI events with NSAIDs	Medical Expenditure Panel Survey data 1999-2003	Adult survey participants filling 2 or more Rxs for rofecoxib (N=515), celecoxib (N=704), or tNSAID (N=1769) in yr 1 & no Rx for a different NSAID in yr 1 or 2	Exposure defined as two or more Rxs in yr 1	In yr 2, AMI, stroke, or GI bleeding as determined by pt response to survey. Multivariate regression (in Stata, "svy: logistic"); unexposed reference group	AMI: rofecoxib OR 3.3 (1.4-7.7), celecoxib 1.4 (0.6-3.7), tNSAID 1.5 (0.8-2.8). Stroke: rofecoxib no events, celecoxib OR 2.4 (1.1-5.6), tNSAID 1.3 (0.4-3.8). All three associated with GI bleeding	Not analyzed	Not analyzed	See results. Projected nationally, estimated excess coxib events in US population 1999-2004: 46,783 MIs, 21,832 strokes, 100,842 GI bleeds, 26,603 deaths. For tNSAIDs, estimated 87,327 excess GI bleeds, 9606 deaths	Not analyzed	Strengths: exposure determined by pharmacy records rather than pt survey responses. Limitations: Time relationship to exposure unknown. Events self-reported. Fatal events undetected in the data, making national projections of fatal events tenuous. Limited number of CV events (41 total), power accordingly limited	One of few studies to attempt to estimated the population burden of NSAID-related adverse events

#	Reference, Study Design & Objective	Data source and time frame	Population & Sample Size	Exposure and dose (mg/d) groups	Outcomes & Analysis	Results	Time to event	Vulnerable subgroups (including pts s/p MI)	Risk by compound	Data on OTC use (ibuprofen ≤ 1200mg/d, ketoprofen ≤ 75 mg/d, naproxen ≤ 660 mg/d)	Strengths & Limitations	Comments
87	**van der Linden et al.** Nested case-control study to assess risk of MI, CV events and GI events with tNSAIDs and coxibs	PHARMO database in The Netherlands, 2001-2004	All pts dispensed a coxib or tNSAID formed the cohort (mostly ibuprofen and diclofenac). 2196 AMIs, 5500 CV events	Coxibs=celecoxib, rofecoxib, valdecoxib, etoricoxib.tNSAIDs=ibuprofen, diclofenac, naproxen, other. Doses subgrouped as ≤ or >DDD. Controls matched to cases 4:1	Cases=AMI, CV events (AMI, angina, CVA, TIA) and GI events. Conditional logistic regression including adjustment for CV risk score. Current use of any NSAID compared to recent (within 1-60d) and remote use (>60d)	Celebrex, ibuprofen, diclofenac, other NSAIDs associated with AMI, but not naproxen (though naproxen point estimate also >1). MI with current use of celecoxib vs remote NSAID use, hi dose, aOR 3.04 (1.31-7.04), lo dose aOR 1.41 (0.62-3.17). OR tended to be higher for AMI than all CV events	Generally, risk with current use>recent use>remote	Not analyzed separately (OR adjusted for CV risk score)	Current use naproxen vs current use celecoxib, AMI: OR .48 (0.26-0.87). Naproxen and diclofenac with greatest GI event risk.	Ibuprofen: current vs remote AMI OR, < 1200 mg/d = 1.66 (0.92-3.00), >1200 mg/d OR = 1.51 (1.06-2.14).	Strengths: completeness of follow-up, clinically heterogeneous sample, OTC NSAID use believed uncommon. Limitations: outcomes not adjudicated, results by dose incompletely presented. Celecoxib could be prescribed only by rheumatologists during part of study period	Sponsored & co-authored by Pfizer.
88	**van Staa et al**. Retrospective cohort study of MI risk with selected tNSAIDs	GPRD 1987-2006	All pts > 40 y.o. with a first tNSAID Rx (N=729,294). Age, sex, & disease risk score-matched controls (N=443,047)	Major NSAIDs used were ibuprofen (31% of users), diclofenac (40%), naproxen (9%).	MI; Poisson regression to calculate aRR	current use vs past NSAID use: aRR any NSAID 1.25 (1.21-1.29), ibuprofen 1.16 (1.11-1.22), diclofenac 1.34(1.28-1.40), naproxen 1.16 (1.06-1.27). Lower aRRs vs nonusers.	Regression modeling: cumulative dose, daily dose, and switching of NSAIDs increased MI. Risk present with initial Rx	Long term-, frequent-, and multiple- NSAID users with higher risks, which persisted after d/c; authors suggest confounding by indication (if enriched with RA pts)	Overall, diclofenac with highest RR; by dose, hi dose ibuprofen and hi dose diclofenac had highest aRRs. When stratified by # of past NSAID Rxs, no difference between compounds--confounding by indication? No clear influence of ASA use though point estimates lower without ASA for naproxen and ibuprofen.	Ibuprofen <1200 aRR current:past use 1.18 (1.01-1.36). Naproxen <1000 aRR current:past 1.12 (0.95-1.31)	Strengths: Completeness of clinical data, examination of patterns of NSAID use. Limitations: "lumped" OA and RA. Some results only described qualitatively in text.	Sponsored by MHRA. Authors concluded, "Most of the differences in MI risk between diclofenac, ibuprofen or naproxen may be explained by their varied use."
89	**Wade et al**. Retrospective cohort study of MI risk with estrogen use and rofecoxib use in perimenopausal women	Medicaid data from CA, FL, NY, OH, PA, Jan 1999-Nov 2002	Rofecoxib users aged 45-65 y.o. (N=184, 169) stratified by estrogen users or nonusers	Rofecoxib, estrogen	Hospitalization for MI. Cox PH with estrogen exposure term	Estrogen protective (HR 0.72, 0.62-0.84). Rofecoxib HR elevated for both estrogen users (HR 1.69) and nonusers (HR 1.45), no stat sig interaction	Not analyzed	Not analyzed	Not applicable	Not analyzed	Strengths: Examines a unique hypothesis; i.e., that estrogen may ameliorate rofecoxib MI risk. Limitations: rofecoxib only compound studied. Authors argue that the results of the WHI with sample aged 50-79 should not apply to their younger sample aged 45-65 but this seems debatable.	Protective effect of estrogen called into question by WHI results
90	Duplicate of 21											

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Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Update to review of epidemiological data on NSAIDs and thrombotic cardiovascular events

Date:	12-31-2013
Reviewer:	Andrew D. Mosholder, MD, MPH Division of Epidemiology II
Team Leader	Elizabeth M. Maloney, M.S., Dr.P.H. Division of Epidemiology II
Division Director	Judy A. Staffa, Ph.D., R.Ph Division of Epidemiology II
Drug Name(s):	Nonsteroidal antinflammatory drugs (NSAIDs)
Subject	Update to 12-4-2012 literature review
OSE RCM #:	2011-45
Tracked Safety Issue #	1230

This review briefly updates the previous literature review of NSAIDs and cardiovascular (CV) risks (DEPI II review dated 12-4-2012) covering primarily the period 8/2006-8/2011. Among 24 additional papers identified in an updated literature review of NSAIDs and CV risk, four papers were judged particularly relevant because they address one of the topics of interest from the previous review (which were, risk in patients status post myocardial infarction and in other vulnerable patient groups, dose response, time course of risk, risk by compound, risk with over-the-counter use, and stroke as an outcome), and provide additional data to areas that previously had sparse data. The table in Appendix A briefly summarizes the design, results, strengths and limitations of these four studies.

I. Cardiovascular risk in vulnerable populations.

New data on the magnitude of cardiovascular risks in vulnerable patients reinforces previous results from the Danish national health care system (Schjerning Olsen et al., 2011). Specifically, analysis of data from a controlled trial of antihypertensive drugs in patients with atherosclerosis and hypertension showed a more than 2-fold increase in cardiovascular mortality with concomitant NSAID use (representing one additional cardiovascular death per 100 person-years of NSAID use) (Bavry et al., 2011). A lower but still consequential excess risk of one cardiovascular death, myocardial infarction or stroke per 244 person-years of NSAID use was observed in a registry of patients ≥45 years of age with stable atherosclerotic disease or multiple risk factors (Kohli et al., 2013).

A third study (Olsen AM, et al., 2013) added a refinement to previous studies using the Danish national healthcare database by specifically measuring cardiovascular death as the outcome, rather than all-cause mortality. In

addition, the 2013 Olsen et al. paper increased the sample size by roughly 17% over the 2011 publication by the same author (Schjerning Olsen et al., 2011).

Study	Sample Size & Population	Outcome	Excess risk (Number needed to harm) with NSAID use
Bavry	22,576 subjects in antihypertensive drug clinical trial, >50 years old, stable atherosclerotic disease; 882 subjects were chronic NSAID users and 21,694 were in the comparison group.	Cardiovascular death	1 per 100 person-years
Kohli	44,095 subjects in registry of outpatients with atherosclerosis, >45 years old, with stable atherosclerotic disease, or risk factors; 4,420 used NSAIDs.	Cardiovascular death, MI, stroke	61 after 4 years (=1 in 244 person-years)
Olsen	97,698 post-MI patients, of whom 43,134 used an NSAID	Cardiovascular death	1 in 48 person years

II. Frequency of NSAID use.

The Nurses' Health Study prospectively followed 70,971 women aged 44-69 years without cardiovascular disease at study entry to address the question of NSAID dose-response associated with cardiovascular events (nonfatal MI, nonfatal stroke, fatal coronary heart disease, fatal stroke) (Chan et al., 2006). The study assessed dose response in terms of days of NSAID use per month and tablets used per week, and reported statistically significantly increased relative risks for the highest frequencies of days of NSAID use. The table below displays the results for one outcome, fatal coronary heart disease, by days of NSAID use per month. Although there were other studies included in our previous review that addressed dose-response, to our knowledge Chan et al. was the only study to measure intermittent use of NSAIDs, which is relevant to how NSAIDs are used by some people.

	Adjusted Relative Risk (95% Confidence Interval) for Fatal Coronary Heart Disease by Frequency of Use (Days/Month), Nurses' Health Study					
Drug	**None**	**1-4 d/mo**	**5-14 d/mo**	**15-21 d/mo**	**≥22 d/mo**	**P for trend**
NSAID	1.0	1.22 (0.75-1.96)	1.23 (0.71-2.11)	1.38 (0.64-2.98)	1.73 (1.22-2.46)	<0.01

In summary, findings from three studies in vulnerable patient populations tend to support previous results from the Danish national healthcare database in post-MI patients; these studies also observed a relatively high frequency of serious or fatal cardiovascular events with NSAID use by high-CV risk patients. Importantly, two of these studies were from sources other than the Danish healthcare database. A fourth study examined dose effects in terms of frequency of use (i.e., with less than daily use), and found that CV risk was associated with the highest category of usage frequency.

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Appendix A. Summary table of four additional studies relevant to Mosholder 12/4/12 review of NSAID use and cardiovascular risk.

First author, Study Design & Objective	Data source and time frame	Population & Sample Size	Exposure and dose (mg/d) groups	Outcomes & Analysis	Results	Time to event	Vulnerable subgroups (including pts s/p MI)	Risk by compound	Data on OTC use (ibuprofen ≤1200mg/d, ketoprofen ≤ 75 mg/d, naproxen ≤ 660 mg/d)	Strengths & Limitations	Comments
Bavry Post-hoc analysis of data from an antihypertensive clinical trial to assess CV risk with concomitant NSAID use	INternational VErapamil Trandolapril STudy (INVEST) Trial enrolled subjects 1997-2003	Pts 50+ y.o. with hypertension and stable coronary artery disease, randomized to atenolol or verapamil. 882 trial subjects were chronic NSAID users and 21,694 intermittent or never users.	At each visit pts were asked if they used an NSAID (y/n) or ASA (y/n). Visits initially every 6 wks, then every 6 mos. Chronic users were those who said yes at each visit, nonchronic were the remaining subjects	Primary outcome = Death from all causes+MI+stroke. Outcomes adjudicated and NDI searched for post-study deaths. Cox regression with secondary analysis using 1:1 PS matching	Chronic NSAID use primary outcome: adjusted HR 1.47 (1.19-1.82). Similar result for PS matching. CV death rate 2.4/100 p-y for chronic NSAID users, vs 1.4/100 p-y nonchronic NSAID users, HR 2.26 (1.70-3.01). No GI bleeding in chronic NSAID group. Post-study all cause mortality was higher for chronic NSAID users	Assessed graphically with Kaplan-Meier curves, which separate from the origin (i.e., no delay)	Higher BP raised risk (statistically significant interaction); however, chronic NSAID users had lower mean systolic BP	Not examined; most common NSAIDs were thought to be naproxen and ibuprofen	not examined	Strengths: vulnerable pt population (stable coronary artery disease + HTN), data collected in clinical trial Limitations: post hoc analysis, exposure self-reported, compounds & doses not analyzed separately	
Chan Prospective cohort study of the risk of CV events with NSAIDs and APAP	Nurses' Health Study 1990-Jun 2002	70,971 female nurses participating in study	Any NSAID, ASA, APAP exposure, by frequency of use (days/month). Exposure determined by biennial questionnaire.	Nonfatal MI or stroke, fatal coronary heart disease, and fatal stroke. Deaths identified by NDI. Events adjudicated by medical records or interview. Cox PH analysis	NSAIDs or APAP but not ASA increased risk for CV events significantly. Risk related to days used/wk for NSAID & APAP, but not ASA	not examined	Smokers had higher risk with NSAIDs than nonsmokers	Low dose ASA reduced CV events. CV risk increased with dose for NSAIDs and APAP but not ASA.	OTC use included but daily dose not examined	Strengths: only study of CV events with APAP, subjects health professionals, analyzed dose effect, events adjudicated Limitations: exposures averaged over long time periods	
Kohli Cohort study of cardiovascular events in stable atherosclerosis patients using NSAIDs	Reduction of Atherothrombosis for Continued Health (REACH) multinational pt. registry. Subjects enrolled Dec 2003-June 2004	Outpatients with stable atherosclerotic disease followed for 4 years, including 39,674 NSAID nonusers and 4,420 NSAID users. Extends sample and follow-up from previous publication (Barthelemy et al.)	Any NSAID use recorded as "yes or no" at baseline and subsequent yearly assessments. NSAID use analyzed as time-dependent covariate.	Broad set of outcomes including CV death, MI, stroke, heart failure, bleeding treated with transfusion. Cox PH	NSAID use increased composite of CV death+MI+stroke+ CV hospitalization, HR 1.12(1.04-1.21), NNH36 (21-109) @ 4 yrs; no association with bleeding. NSAID use also increased heart failure	Analyzed over 4 yrs but only yearly data on exposure	Higher HRs for antiplatelet drug users but not ASA users	Not examined	not examined	Strengths: examined high risk population over long term. Limitations: compounds not differentiated, exposure only determined annually, NSAID users had greater prevalence of risk factors so adjustment had to be fully successful	In this high risk population, NNH modest for CV events with no significant increase in bleeding events
Olsen Retrospective cohort study of cardiovascular outcomes with NSAID use post-MI	Danish national health registry 1997-2009	97,698 patients aged 30+ years admitted with first-time MI during	Rofecoxib, celecoxib, ibuprofen, diclofenac, naproxen, other NSAIDs	Cardiovascular death; coronary death + nonfatal MI; fatal + nonfatal stroke. Cox PH with no use as reference	All compounds increased risk for each outcome (in dose related way). Overall NNH for CV death = 48 p-y	not examined	Entire sample was post-MI	CV death risk estimates highest for diclofenac and rofecoxib	Ibuprofen ≤ 1200 mg/d and naproxen ≤ 500 mg/d not associated with CV death	Strengths: vulnerable population, large sample Limitations: outcomes not adjudicated, possible confounding by indication with nonuser reference group	

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Medical Officer Review

TSI #:	**1230**
Safety Issue:	**Risk of cardiovascular events associated with NSAID use**
Materials Reviewed:	**Literature on clinical controlled studies**
Date of Review:	**July 30, 2013**
Reviewer:	**Robert A. Levin, MD**
Deputy Director for Safety:	**Judy Racoosin, MD, MPH**
Project Manager:	**Katherine Won**

Table of Contents

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AEs	Adverse events
APC	Adenoma Prevention with Celecoxib (Trial)
APPROVe	Adenomatous Polyp Prevention on Vioxx (Trial)
APTC	Antiplatelet Trialists' Collaboration (combined endpoint)
CAD	Coronary artery disease
CHF	Congestive heart failure
COX-2	Cyclo-oxygenase-2
CV	Cardiovascular
CVA	Cerebrovascular accident
DFMO	Difluoromethylornithine
EDGE II	Etoricoxib versus diclofenac sodium gastrointestinal tolerability and effectiveness (trial)
GI	Gastrointestinal
HR	Hazard ratio
LDA	Low-dose aspirin
MEDAL	Multinational Etoricoxib and Diclofenac Arthritis Long-Term (program)
MI	Myocardial infarction
NSAIDs	Non-steroidal anti-inflammatory drugs
PCI	Percutaneous coronary intervention
PreSAP	Prevention of Colorectal Sporadic Adenomatous Polyps (Trial)
PSA	Prostate-specific antigen
RA	Rheumatoid Arthritis
RR	Relative risk
VICTOR	Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime (Trial)

Executive Summary

Following an internal discussion in August 2011 of new literature report[1] on the topic of cardiovascular risk with NSAIDs, the division conducted a literature search dating back five years to identify recently published clinical trials, epidemiological studies, and review articles. This review examines the clinical trials published during that time for information about two specific issues raised by recently published epidemiological studies: 1) Do the cardiovascular risks with NSAIDs begin to accrue immediately or with short-term use?; 2) Is the potential risk for cardiovascular events associated with the use of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) or cyclo-oxygenase-2 (COX-2) selective NSAIDs higher in subjects with a history of prior myocardial infarction (MI) or other cardiovascular risk factors? The conclusions in this review are based solely on the findings from published clinical controlled studies and do not reflect the findings from epidemiologic studies or meta-analysis.

Conclusions

The findings from the clinical controlled studies do not provide sufficient details to adequately assess the time to event or risk of recurrent MI and death in patients with a prior history of MI or other cardiovascular risk factors treated with NSAIDs. There were several limitations in interpreting and extrapolating findings from the clinical studies. These limitations included the small number of NSAIDs studied and insufficient data on the time to event. Several studies were small and limited to specific patient populations (e.g., post stent placement or percutaneous coronary intervention) and used biomarkers or need for revascularization as endpoints.

With regard to the first question above, time to event was often not reported, or there was an insufficient number of events to reach any statistical significance.

With regard to the second question, some of the studies provided relevant data. In some studies, there appeared to be an association between subjects with cardiovascular (CV) risk factors taking NSAIDs and increased CV events, but the findings were not statistically significant. In the APPROVe study described by Baron, rofecoxib had higher relative risks for the APTC composite outcome with some CV risk factors (e.g., patients with diabetes), but this pattern was not observed consistently (e.g. those with hypertension, hypercholesterolemia). The effect of prior MI on CV risk could not be assessed in this study since subjects with a history of MI were excluded.

In the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) Trial, serious cardiovascular events did not differ significantly between the celecoxib 400 mg once daily and placebo groups, and there was no significant difference in relative risk in subjects with and those without a history of previous cardiovascular events. However, in the Adenoma Prevention with Celecoxib (APC) trial, celecoxib 200 mg twice daily and 400 mg twice daily was associated with an increased risk of cardiovascular risk. Solomon reported in Circulation that, when all doses of

[1] Schjerning Olsen AM, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. Circulation 2011;123:2226-35.

celecoxib tested in both the PreSAP and APC trials were combined, there was nearly a 2-fold increased cardiovascular risk. The authors noted that the trend for a dose-related increase in cardiovascular events and blood pressure raises the possibility that lower doses or other dosing intervals may be associated with less cardiovascular risk. The combined analysis did not show a differential effect of celecoxib among patients with and without a history of prior cardiovascular disease or low dose aspirin use.

In the study reported by Zell using DFMO (difluoromethylornithine)/sulindac for the prevention of colorectal adenomas among patients with high baseline CV risk[2], 12% of DFMO/sulindac-treated patients had an adverse CV event compared to 4% patients in the placebo group, whereas among patients with low and moderate risk scores, the risks were similar in the DFMO/sulindac (6%) and placebo (5%) groups. For patients with high CV risk, there was often insufficient information to determine the specific cardiac risk factor for any given patient because a composite list of cardiovascular diagnoses was used. Also, a composite endpoint was often used to assess adverse CV outcomes, so the specific impact on risk of MI could not be determined.

Background

Schjerning Olsen et al, in a nationwide Danish cohort study published in Circulation in 2011, reported an increased risk of death and recurrent MI in patients with prior MI treated with NSAIDs for as short a duration as one week[1]. Following an internal discussion of this paper, a search of the literature published on this topic over the past five years conducted in August 2011 identified 12 clinical trials, as well as many epidemiological studies and review articles. This review examines the 12 clinical trials for information about time to event and the potential role of history of MI or cardiovascular risk factors on the risk of cardiovascular events associated with use of non-selective NSAIDs or selective COX-2 inhibitors. The epidemiological studies are reviewed by Dr. Andrew Mosholder of the Division of Epidemiology 2 in his review dated December 4, 2012.

Search Methods
A search was conducted of Pubmed (8-11-11) and Embase databases (8-29-11) for relevant articles on NSAIDs and cardiovascular events published within the last five years. The search was limited to humans and English language, and included: commentaries, clinical trials, meta-analyses, review articles and epidemiologic studies. Twelve clinical trials were identified and are the subject of this review.

[2] Increased CV risk was defined as myocardial infarction, coronary artery disease, congestive heart failure or cerebrovascular accident, and the number of subjects in each category was not provided.

Overview of Clinical Trials

Rofecoxib

Baron JA, Sandler RS, Bresalier RS, Lanas A, Morton DG, Riddell R, Iverson ER, Demets DL. Cardiovascular events associated with rofecoxib: final analysis of the APPROVe trial. Lancet 2008 Nov 15;372(9651):1756-64.
http://www.ncbi.nlm.nih.gov/pubmed/18922570/sites/entrez?otool=mdufdrlib

Objective: To report the cardiovascular outcomes of long-term follow-up of participants in the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial.

Design: Multicenter, randomized, placebo-controlled, double-blind trial.
Population: 2587 patients with a history of colorectal adenomas were recruited worldwide during 2000 and 2001.

Methods: The Adenomatous Polyp Prevention on Vioxx (APPROVe) study assessed the effect of 3-year treatment with a cyclo-oxygenase-2 inhibitor, rofecoxib (25 mg), on recurrence of neoplastic polyps of the large bowel. Participants were followed for adverse events while on treatment and during the following 14 days. However, after early termination of the study because of cardiovascular toxicity, the authors attempted to follow up all randomized patients for at least 1 year after stopping study treatment. External committees blindly assessed potential serious cardiovascular events. The focus of the analysis was the combined incidence of non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular, hemorrhagic, and unknown causes (Antiplatelet Trialists' Collaboration [APTC] combined endpoint). The authors used Cox proportional hazards regression to calculate endpoint hazard ratios.

Exclusion criteria included uncontrolled hypertension (>165–95 mm Hg); angina or congestive heart failure with symptoms at minimal activity; history of myocardial infarction, coronary angioplasty, or coronary arterial bypass grafting within the past year; and history of stroke or transient ischemic attack within the past 2 years.

Results: Patients received rofecoxib 25mg daily (n = 1287) or placebo (n = 1300). Extended post-treatment cardiovascular follow-up data was obtained from 84% of participants, and extended mortality follow-up from 95%. In total, including the extended follow-up period, 59 individuals had an APTC endpoint in the rofecoxib group and 34 in the placebo group (hazard ratio 1.79, 95% CI 1.17-2.73; p=0.006). Rofecoxib increased the risk of the combined APTC endpoint of myocardial infarction, stroke, and vascular death (Table 1). Participants on rofecoxib had increased risks of myocardial infarction (HR 1.94, log rank p=0.02) and stroke (HR=2.17, p=0.05). Investigation of the time course of the increased risk is limited by the small number of events. However, the HR for the APTC endpoint did not substantially change over time, and the authors report that the data are compatible with an early increase in risk for these events. From the graph (Figure 1) of the cumulative frequency of APTC events, there is no apparent difference in frequency for approximately the first two months, and the difference is not statistically significant until about 32 months. During the first year off treatment, there were more APTC events in the rofecoxib group than in the placebo group, but no difference was evident during the

subsequent follow-up. The authors state that subgroup analyses suggest that individuals with risk factors for cardiovascular disease treated with rofecoxib have higher relative risks for the APTC endpoint than do healthy individuals, but also note that their data are not conclusive on that point (Figure 2). High cardiovascular risk was defined as history of symptomatic atherosclerotic cardiovascular disease, or two or more of the following risk factors: history of hypertension, hypercholesterolaemia, diabetes, or current cigarette smoking.

Table 1. Antiplatelet Trialists' Collaboration (APTC) endpoints and overall mortality

	Participants with events on treatment and during the following 14 days			Participants with events during extended follow-up*		
	Rofecoxib	Placebo	Unadjusted HR (95% CI)	Rofecoxib	Placebo	Unadjusted HR (95% CI)
All APTC events	35	18	2·12 (1·20–3·74)	59	34	1·79 (1·17–2·73)
Myocardial infarction	22	9	2·65 (1·21–5·75)	34	18	1·94 (1·09–3·43)
Stroke	12	8	1·64 (0·67–4·02)	19	9	2·17 (0·98–4·80)
Ischaemic stroke	11	6	..	18	6	..
Haemorrhagic stroke	1	2	..	1	3	..
Vascular death	6	5	1·31 (0·40–4·30)	16	13	1·26 (0·61–2·62)
Overall mortality	6†	6†	1·06 (0·34–3·29)	36	28	1·31 (0·80–2·15)

*Full intention-to-treat analysis. †Four additional patients in each group died more than 14 days after cessation of treatment because of an adverse event that took place on, or within, 14 days of treatment.

Figure 1. Difference of cumulative incidence over time with pointwise confidence limits and simultaneous confidence band

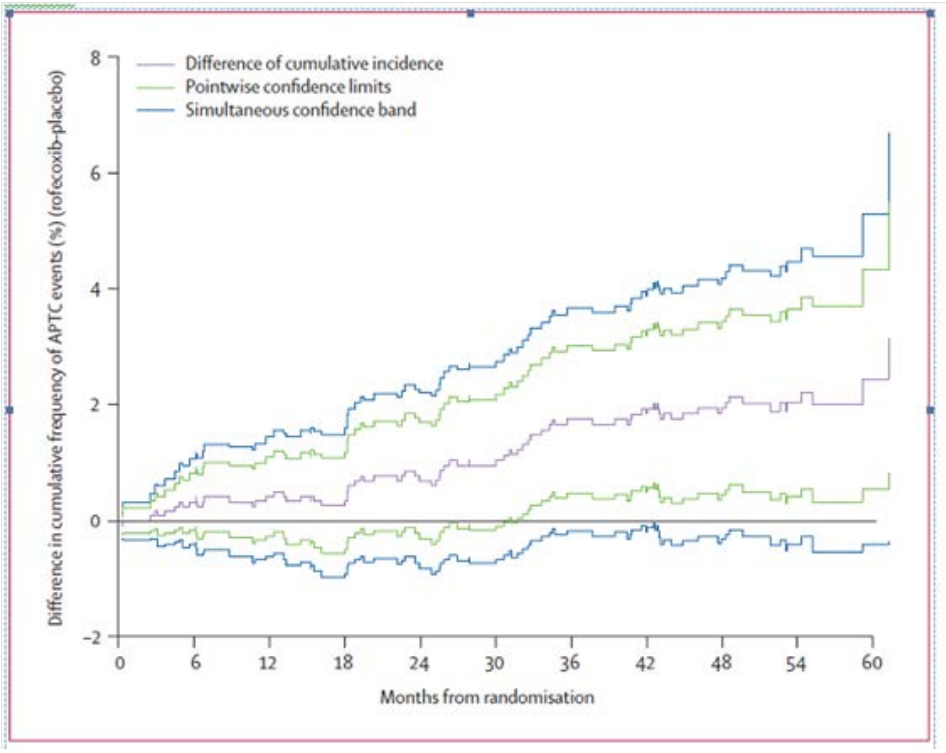
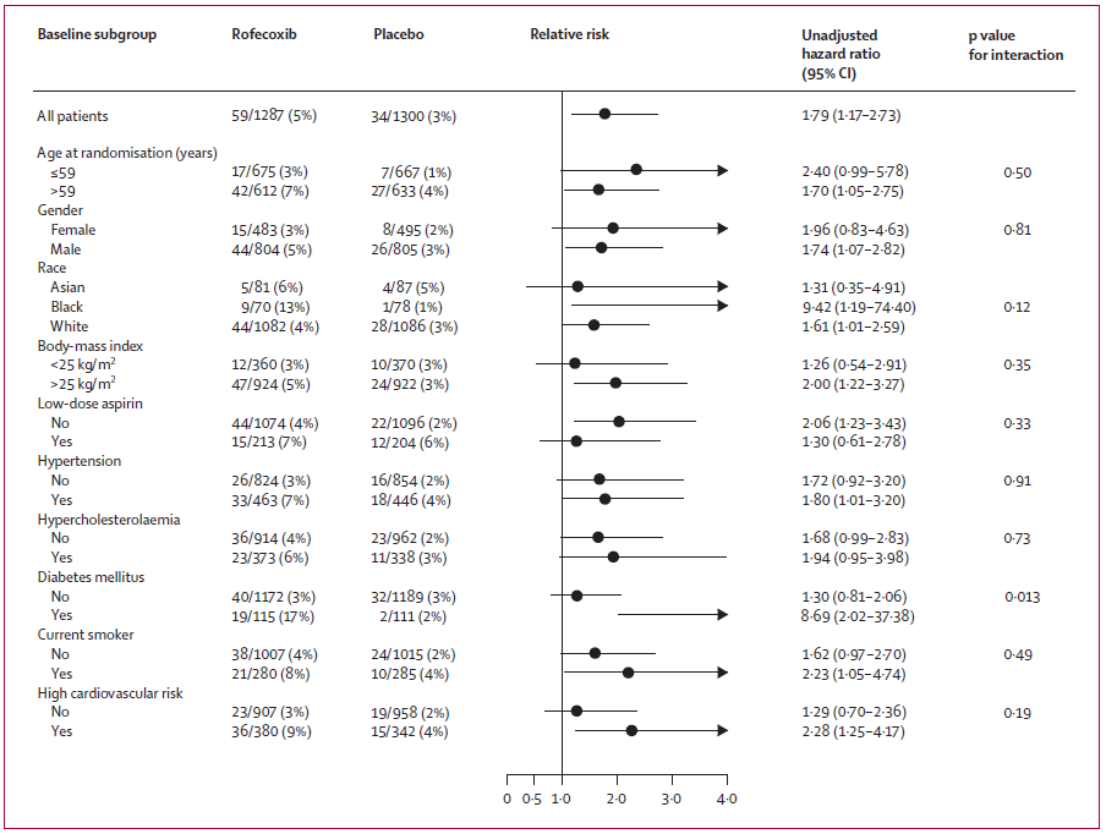


Figure 2. Hazard Ratios for APTC Events by Subgroup



Limitations: Subjects with a history of prior MI were excluded from the study. The only NSAID studied was rofecoxib. There was no adjustment for confounding in any of the analyses. Small numbers prohibit detailed conclusions about when the increased risk begins.

Conclusions: Use of rofecoxib is associated with an increased risk of cardiovascular events (APTC endpoints). The small number of events prohibit any detailed conclusions about when the increased risk begins and ends, but according to the authors, the data are compatible with an early increase in risk that seems to persist for about 1 year after 3 years of treatment. Based on the graph of the cumulative frequency of APTC events, there does not appear to be any increase in risk for the first couple of months. The study provides no information on the association between NSAID use in subjects with prior MI. Rofecoxib-treated patients had higher relative risks for the APTC composite outcome with some CV risk factors (e.g., patients with diabetes), but this pattern was not observed consistently (e.g. those with hypertension, hypercholesterolemia).

Baron JA, Sandler RS, Bresalier RS, Quan H, Riddell R, Lanas A, Bolognese JA, Oxenius B, Horgan K, Loftus S, et al. A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas. Gastroenterology 2006 Dec;131(6):1674 82.
http://www.ncbi.nlm.nih.gov/pubmed/17087947/sites/entrez?otool=mdufdrlib

Objective: To assess whether use of the selective COX-2 inhibitor rofecoxib would reduce the risk of colorectal adenomas in the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial.

Note: A subsequent analysis of the APPROVe trial is summarized above with follow-up extended to one year after discontinuing study drug.

Design: Randomized, placebo-controlled, double-blind trial.

Population: 2587 subjects with a recent history of histologically confirmed colorectal adenomas were enrolled in the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial.

Methods: Subjects with a recent history of histologically confirmed adenomas were randomized to receive daily placebo or 25 mg of rofecoxib. Randomization was stratified by baseline use of cardioprotective aspirin. Colonoscopic follow-up evaluation was planned for 1 and 3 years after randomization. The primary endpoint was all adenomas diagnosed during 3 years of treatment. In a modified intent-to-treat analysis, the relative risk of any adenoma after randomization was computed using Mantel-Haenszel statistics stratified by low-dose aspirin use at baseline.

Results:
In September 2004, 2 months before the anticipated end of the trial, the APPROVe trial was terminated on the advice of the External Safety and Monitoring Board because of a higher rate of cardiovascular events in the rofecoxib group.

Adenomas: Adenoma recurrence was less frequent for rofecoxib subjects than for those randomized to placebo (41% vs 55%; $p < 0.0001$; relative risk [RR], 0.76; 95% confidence interval [CI], 0.69-0.83). Rofecoxib also conferred a reduction in risk of advanced adenomas ($p < 0.01$).

Safety: Rofecoxib was associated with increased risks of significant upper gastrointestinal events and serious thrombotic cardiovascular events. During the treatment period, the rofecoxib group experienced increased risks of thrombotic cardiovascular events (RR, 1.89; 95% CI, 1.18 –3.04) and of upper gastrointestinal perforation, obstruction, symptomatic ulcer, or bleeding (RR, 4.91; 95% CI, 1.98 –14.5).

Limitations: Rofecoxib was the only NSAID studied and the effect of prior MI on cardiovascular adverse events was not analyzed. Subjects with a history of MI within the last year were excluded.

Conclusions: The APPROVe trial with long-term follow-up was reviewed above. Rofecoxib significantly reduced the risk of colorectal adenomas, but was associated with increased rates of serious cardiovascular events. The authors did not provide information on time to event.

Kerr DJ, Dunn JA, Langman MJ, Smith JL, Midgley RS, Stanley A, Stokes JC, Julier P, Iveson C, Duvvuri R, et al. Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. N.Engl.J Med 2007 Jul 26;357(4):360-9.
http://www.ncbi.nlm.nih.gov/pubmed/17652651/sites/entrez?otool=mdufdrlib

Objective: To report cardiovascular adverse events in patients receiving rofecoxib to reduce rates of recurrence of colorectal cancer.

Design: Randomized, placebo-controlled trial.

Population: 2434 patients with stage II or III colorectal cancer after potentially curative tumor resection and chemotherapy or radiotherapy enrolled in the Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime (VICTOR) Trial.

Methods:
Subjects randomized to the rofecoxib group received 25 mg daily. The trial was terminated prematurely due to worldwide withdrawal of rofecoxib. To examine possible persistent risk, all serious cardiovascular thrombotic events reported up to 24 months after the trial was closed were reviewed.

Results: The median duration of active treatment was 7.4 months. The 1167 patients receiving rofecoxib and the 1160 patients receiving placebo were well matched. Of the 23 confirmed cardiovascular thrombotic events, 16 occurred in the rofecoxib group during or within 14 days after the treatment period, resulting in a relative risk of a cardiovascular thrombotic event of 2.66 (95% confidence interval [CI], 1.03 to 6.86) among patients receiving rofecoxib, as compared with those receiving placebo ($p = 0.04$). The relative risk was slightly reduced after adjustment for cardiovascular risk factors (2.41; 95% CI, 0.93 to 6.26; $p = 0.07$). Analysis of the APTC endpoints showed an unadjusted relative risk of 1.60 (95% CI, 0.57 to 4.51; $p = 0.37$) and an adjusted relative risk of 1.42 (95% CI, 0.50 to 4.03; $p = 0.52$).

A further analysis, in which all cardiovascular events that occurred during the treatment period and all those reported within 24 months after trial closure were combined, was performed. The resulting relative risk of a cardiovascular thrombotic event, unadjusted for cardiovascular risk factors, was 1.50 (95% CI, 0.76 to 2.94; $p = 0.24$). Analysis of the APTC endpoints showed an unadjusted relative risk of 1.29 (95% CI, 0.57 to 2.95).

Limitations: Rofecoxib was the only NSAID studied. There was no analysis of whether prior MI increased the risk of cardiovascular adverse events with subjects on rofecoxib.

Conclusions: Rofecoxib therapy was associated with an increased frequency of adverse cardiovascular events among patients with a median study treatment of 7.4 months' duration. The authors report that the statistical power was insufficient for comparisons of risk according to

duration of study treatment. No information on the number of subjects with prior MI or detailed information on time to event was provided.

van Adelsberg J, Gann P, Ko AT, Damber JE, Logothetis C, Marberger M, Schmitz-Drager BJ, Tubaro A, Harms CJ, Roehrborn C. The VIOXX in prostate cancer prevention study: cardiovascular events observed in the rofecoxib 25 mg and placebo treatment groups. Curr Med Res.Opin. 2007 Sep;23(9):2063-70.
http://www.ncbi.nlm.nih.gov/pubmed/17651539/sites/entrez?otool=mdufdrlib

Objective: To report the cardiovascular (CV) safety data collected from a study designed to determine the cumulative incidence of developing prostate cancer over 6 years of treatment with rofecoxib 25 mg per day versus placebo.

Design: Double-blind, randomized, placebo-controlled study.

Population: A total of 4741 men exhibiting prostate-specific antigen levels (PSA) between 2.5 and 10 ng/mL were enrolled.

Methods: Men with PSA levels between 2.5 and 10 ng/mL were stratified by PSA level and use of low-dose aspirin (LDA), and then randomized to rofecoxib 25 mg (n = 2369) or placebo (n = 2372). Before completion, this trial was terminated following the voluntary withdrawal of rofecoxib by Merck on September 30, 2004. All reported thrombotic CV events occurring on-treatment or within 14 days after study drug discontinuation were adjudicated by an independent panel of clinical experts blinded to treatment assignment. Rates per 100 patient-years and relative risk (RR) of thrombotic CV events, rofecoxib vs. placebo, were determined.

Results: Approximately 36% of patients had either a previous history of symptomatic atherosclerotic disease or at least two risk factors for atherosclerotic disease. Median treatment duration was 4.14 (range: 0.03-15.90) months. Twenty-nine patients (14 on rofecoxib, rate 1.27/ 100 patient yrs; 15 on placebo, rate 1.36/ 100 patient yrs) experienced confirmed thrombotic CV events for a RR of 0.94 (95% CI: 0.45, 1.94) for rofecoxib vs. placebo. Four patients (one on rofecoxib; three on placebo) died due to a confirmed thrombotic event. A statistically significantly greater number of patients receiving rofecoxib experienced hypertension-related adverse events versus placebo (n = 20; 0.8% vs. 2; 0.1%, respectively, p = 0.002). There were no cases of congestive heart failure.

Limitations: No conclusions regarding the relative CV safety of rofecoxib 25 mg compared to placebo can be made given the short period of drug exposure, the incomplete enrollment, and the relatively small number of thrombotic CV events observed. Rofecoxib was the only NSAID studied and the effect of prior MI on outcome was not analyzed.

Conclusions: Rofecoxib 25 mg and placebo demonstrated similar risk of thrombotic CV events in this limited dataset. The study was terminated early after a median treatment duration of approximately four months and thrombotic CV events occurring in 29 patients.

Celecoxib

Solomon SD, Pfeffer MA, McMurray JJ, Fowler R, Finn P, Levin B, Eagle C, Hawk E, Lechuga M, Zauber AG, et al. Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. Circulation 2006 Sep 5;114(10):1028-35.
http://www.ncbi.nlm.nih.gov/pubmed/16943394/sites/entrez?otool=mdufdrlib

Objective: To determine the effect of celecoxib on cardiovascular events and blood pressure in two completed trials for the prevention of colorectal adenomas: Adenoma Prevention with Celecoxib (APC) trial and Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial.

Note: The PreSAP trial was previously discussed in the article by Arber et. al.

Design: Randomized placebo-controlled trials.

Population: Patients with a high risk of colorectal adenoma recurrence enrolled in the APC (2035 patients) and PreSAP (1561 patients) trials.

Methods: APC trial studied celecoxib 200 mg twice daily and 400 mg twice daily and the PreSAP trial studied celecoxib 400 mg once daily to test the efficacy and safety of celecoxib against placebo in reducing colorectal adenoma recurrence after polypectomy. Patients were not excluded for preexisting cardiovascular disorders. An independent safety committee for both studies adjudicated and categorized serious cardiovascular events and then combined individual patient data from these long-term trials to improve the estimate of the cardiovascular risk and blood pressure changes associated with celecoxib compared with placebo. Before simultaneous unblinding of the two trials, the Cardiovascular Safety Committee selected the composite endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or heart failure as the primary cardiovascular safety endpoint. Cox regression analysis, stratified by use or nonuse of low-dose aspirin, was used to estimate hazard ratios for each listed hierarchical outcome.

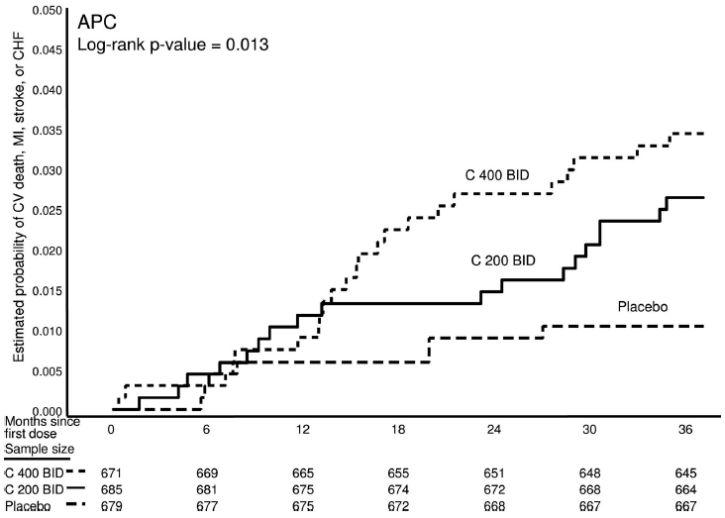
Results: For APC and PreSAP combined, 83 patients experienced cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or heart failure. The hazard ratio for this prespecified composite endpoint was 2.6 (95% (CI), 1.1 to 6.1) in patients taking 200 mg twice daily, 3.4 (95% CI, 1.5 to 7.9) in patients taking 400 mg twice daily in APC, and 1.3 (95% CI, 0.6 to 2.6) in patients taking 400 mg once daily in PreSAP. The combined analysis of APC and PreSAP resulted in an overall hazard ratio for this composite endpoint of 1.9 (95% CI, 1.1 to 3.1). Both dose groups in APC showed significant systolic blood pressure elevations at 1 and 3 years (200 mg twice daily: 1 year, 2.0 mm Hg ($p=0.04$); 3 years, 2.6 mm Hg ($P=0.03$); 400 mg twice daily: 1 year, 2.9 mm Hg ($P=0.005$); 3 years, 5.2 mm Hg ($P<0.001$). In PreSAP there was no difference in blood pressure between placebo and the 400 mg once daily group. The authors report that the combined analysis did not show a differential effect of celecoxib among patients who were or were not taking low-dose aspirin, nor among patients with and without a history of prior cardiovascular disease (Table 2). From the Kaplan-Meier curves (Figure 3) showing time

to cardiovascular endpoints in the APC trial, there does not appear to be a statistically significant increase early on.

Table2. Hazard ratio for cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure in patients who are or are not taking low-dose aspirin and in patients with and without a history of prior cardiovascular disease for the combined APC and PreSAP data.

	Placebo, n/N (%)	Celecoxib, n/N (%)	Hazard Ratio (95% CI)	*P* for Interaction
Low-dose aspirin users				
Yes	7/319 (2.2)	25/570 (4.4)	2.1 (0.9–5.0)	0.8
No	12/988 (1.2)	39/1719 (2.3)	1.8 (1.0–3.5)	
History of cardiovascular events				
Yes	6/167 (3.6)	26/314 (8.3)	2.3 (0.9–5.6)	0.6
No	13/1140 (1.1)	38/1975 (1.9)	1.8 (0.9–3.3)	

Figure 3. Kaplan-Meier Curve Showing Time to Composite End Point



Limitations: Celecoxib was the only NSAID studied. The cardiovascular safety analysis is based on few events and thus has limited statistical power since the studies were originally powered to assess the efficacy of celecoxib in reducing the recurrence of colorectal adenomas.

Conclusions: Celecoxib use was associated with nearly a 2-fold-increased risk for the composite cardiovascular endpoint. The authors note that the trend for a dose-related increase in cardiovascular events and blood pressure raises the possibility that lower doses or other dose intervals may be associated with less cardiovascular risk. The combined analysis did not show a differential effect of celecoxib among patients with and without a history of prior cardiovascular disease.

Arber N, Eagle CJ, Spicak J, Racz I, Dite P, Hajer J, Zavoral M, Lechuga MJ, Gerletti P, Tang J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. N.Engl.J Med 2006 Aug 31;355(9):885-95.
http://www.ncbi.nlm.nih.gov/pubmed/16943401/sites/entrez?otool=mdufdrlib

Objective: To determine whether celecoxib prevents colorectal adenomatous polyps.

Note: A subsequent analysis of this study, combined with the APC trial is reviewed above (Solomon et al.).

Design: Randomized, placebo-controlled, double-blind study.

Population: 1561 subjects with history of colorectal adenomas removed enrolled in the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) Trial.

Methods: Celecoxib was given daily in a single 400 mg dose in the Prevention of Colorectal Sporadic Adenomatous Polyps trial. A total of 1561 subjects were randomized to receive either celecoxib (933 subjects) or placebo (628 subjects) daily, after stratification according to the use or nonuse of low-dose aspirin. The primary outcome was detection of adenomas at either year 1 or year 3 by colonoscopy and was compared among the groups with the use of the Mantel-Cox test.

Results: *Adenomas:* The cumulative rate of adenomas detected through year 3 was 33.6 percent in the celecoxib group and 49.3 percent in the placebo group (relative risk, 0.64; 95 percent confidence interval, 0.56 to 0.75; P<0.001). The cumulative rate of advanced adenomas detected through year 3 was 5.3 percent in the celecoxib group and 10.4 percent in the placebo group (relative risk, 0.49; 95 percent confidence interval, 0.33 to 0.73; P<0.001).

Cardiovascular Events: Thirty-five subjects died of cardiovascular causes or had myocardial infarction, stroke, or congestive heart failure adjudicated by the cardiovascular safety committee; these consisted of 2.5 percent of the celecoxib group (23 of 933) and 1.9 percent of the placebo group (12 of 628) (relative risk, 1.30; 95 percent confidence interval, 0.65 to 2.62), with estimated rates of 9.4 and 7.2 events per 1000 patient-years for celecoxib and placebo, respectively. Of these 35 subjects, 12 came from a subgroup of 198 with a history of cardiovascular or cerebrovascular events (relative risk, 1.55; 95 percent confidence interval, 0.42 to 5.76), and 23 from a subgroup of 1363 without a medical history of cardiovascular or cerebrovascular events (relative risk, 1.14; 95 percent confidence interval, 0.49 to 2.65; the p value for interaction = 0.59), indicating no significant difference in relative risk between subjects with and those without a history of previous cardiovascular events.

A significant increase in adjudicated serious cardiovascular events with the use of celecoxib in the APC trial (an increase in risk by a factor of two or three for a composite endpoint of myocardial infarction, stroke, congestive heart failure, or cardiovascular-related death) prompted suspension of the administration of celecoxib in both the APC trial and this study. As noted above, in this study the relative risk of cardiovascular events with the use of celecoxib as compared with placebo was 1.30 (95 percent confidence interval, 0.65 to 2.62).

Limitations: Celecoxib was the only NSAID studied. The effect of prior MI alone on the outcome of adverse cardiovascular events was not analyzed, but the authors report no significant difference in relative risk between subjects with and those without a history of previous cardiovascular events.

Conclusions: The use of 400 mg of celecoxib once daily significantly reduced the occurrence of colorectal adenomas within three years after polypectomy. Serious cardiovascular events did not differ significantly between the celecoxib and placebo groups, and there was no significant difference in relative risk in subjects with and those without a history of previous cardiovascular events.

Pelliccia F, Pasceri V, Granatelli A, Pristipino C, Speciale G, Roncella A, Cianfrocca C, Mercuro G, Richichi G. Safety and efficacy of short-term celecoxib before elective percutaneous coronary intervention for stable angina pectoris. Am.J Cardiol. 2006 Dec 1;98(11):1461-3.
http://www.ncbi.nlm.nih.gov/pubmed/17126650/sites/entrez?otool=mdufdrlib

Objective: To determine the effects of preprocedural use of celecoxib 200 mg on release of markers of cardiac damage, i.e., creatine kinase (CK), tropinin I and myoglobin after elective percutaneous coronary intervention (PCI).

Design: Randomized, double-blind, placebo-controlled study.

Population: Fifty patients with stable angina pectoris scheduled for PCI.

Methods: Fifty patients were randomized to receive celecoxib (200 mg 2 times daily) or placebo 7 days before percutaneous coronary intervention (PCI). Blood samples were taken before and at 8 and 24 hours after PCI, and measurements of CK-MB, troponin I, and myoglobin were obtained.

Results: The results showed that detection of markers of myocardial injury above the upper limit of normal was significantly lower in the celecoxib than in the placebo group: 12% versus 35% for creatine kinase-MB (CK-MB; $p = 0.001$), 20% versus 48% for troponin I ($p = 0.0004$), and 22% versus 51% for myoglobin ($p = 0.0005$). Myocardial infarction by CK-MB determination was less commonly seen after PCI in the celecoxib group than in the placebo group (5% vs 18%, $p = 0.025$).

Limitations: Celecoxib was administered for only one week in subjects undergoing PCI. Effect of prior MI on cardiac outcome was not analyzed.

Conclusion: Pretreatment with celecoxib for 7 days significantly decreased the incidence of myocardial injury during PCI compared with placebo as measured by the release of markers of myocardial damage. However, the results of this study cannot be generalized to other groups of subjects (e.g. subjects on long-term celecoxib or not undergoing a coronary intervention procedure).

Koo BK, Kim YS, Park KW, Yang HM, Kwon DA, Chung JW, Hahn JY, Lee HY, Park JS, Kang HJ, et al. Effect of celecoxib on restenosis after coronary angioplasty with a Taxus stent (COREA-TAXUS trial): an open-label randomised controlled study. Lancet 2007 Aug 18;370(9587):567-74.
http://www.ncbi.nlm.nih.gov/pubmed/17707751/sites/entrez?otool=mdufdrlib

Objective: To test whether celecoxib can reduce formation of neointima within stents.

Design: Open-label randomized controlled study.

Population: 274 patients with angina pectoris or a positive stress test and native coronary artery lesions for which implantation of paclitaxel-eluting stents was feasible.

Methods: All patients were given aspirin (100 mg daily) and clopidogrel (75 mg daily). A total of 136 patients were randomly assigned to receive celecoxib (400 mg before the intervention, and 200 mg twice daily for 6 months after the procedure). This was an open-label study and a placebo was not used. The primary endpoint was late luminal loss on quantitative coronary angiography at 6 months after the intervention. Secondary endpoints were cardiac death, non-fatal myocardial infarction, and revascularisation of the target lesion. Analysis was done on a modified intention-to-treat basis.

Results: At six months, mean in-stent late luminal loss was lower in the celecoxib group (0.49 mm, SD 0.47) than in the control group (0.75 mm, 0.60) (absolute difference 0.26 mm; 95% CI 0.12-0.40). The frequency of secondary outcomes at six months was also lower in the celecoxib group, mainly because of a reduced need for revascularization of the target lesion. There was no difference in cardiac death and myocardial infarction between the two groups (Table 3).

Table 3. Major adverse cardiac events within six months

	Control (n=137)	Celecoxib (n=130)	Relative risk (95% CI)	p
Target lesion revascularisation	21 (15%)	7 (5%)	0·35 (0·15–0·80)	0·008
Clinically driven target lesion revascularisation	16 (12%)	6 (5%)	0·40 (0·16–0·98)	0·036
Non-fatal myocardial infarction	0 (0%)	1 (1%)	–	0·49
Cardiac death	1 (1%)	0 (0%)	–	1
Total	22 (16%)	7 (5%)	0·34 (0·15–0·76)	0·005

Data are number of patients (%) unless otherwise indicated.

Limitations: Open-label randomized study design in patients receiving coronary artery stent implantation. The only NSAID studied was celecoxib. No information provided on history of prior MI.

Conclusions: The study findings suggest that the adjunctive use of celecoxib for six months after stent implantation in patients with coronary artery disease is safe and can reduce the need for

revascularization of the target lesion. There was no difference in cardiac death and myocardial infarction between the celecoxib group and control group.

Renda G, Tacconelli S, Capone ML, Sacchetta D, Santarelli F, Sciulli MG, Zimarino M, Grana M, D'Amelio E, Zurro M, et al. Celecoxib, ibuprofen, and the antiplatelet effect of aspirin in patients with osteoarthritis and ischemic heart disease. Clin Pharmacol.Ther. 2006 Sep;80(3):264-74.
http://www.ncbi.nlm.nih.gov/pubmed/16952493/sites/entrez?otool=mdufdrlib

Note: This study did not assess clinical cardiovascular outcomes but was designed to measure pharmacodynamic assessments of the antiplatelet effect of aspirin after one week of treatment with celecoxib and ibuprofen.

Objective: To determine whether celecoxib or ibuprofen undermines the functional range of inhibition of platelet cyclooxygenase (COX)-1 activity by aspirin in patients with osteoarthritis and stable ischemic heart disease.

Design: Placebo-controlled, randomized study.

Population: 24 patients undergoing long-term treatment with aspirin for cardioprotection.

Methods: Patients undergoing long-term treatment with aspirin (100 mg daily) for cardioprotection were coadministered celecoxib, 200 mg twice daily, ibuprofen, 600 mg three times daily, or placebo for 7 days.

Results: The coadministration of placebo or celecoxib did not undermine the aspirin-related inhibition of platelet COX-1 activity, as assessed by measurements of serum thromboxane B_2 (TXB_2) levels, as well as platelet function. Ibuprofen did interfere with the inhibition of platelet COX-1 activity and function by aspirin.

Limitations: Study treatment with celecoxib or ibuprofen was only for one week in 24 subjects. The outcome measures were pharmacodynamic assessments (i.e., TXB_2 assay and platelet aggregation) and not clinical outcomes.

Conclusions: Ibuprofen but not celecoxib interfered with the inhibition of platelet COX-1 activity and function by aspirin.

Etoricoxib

Krueger K, Lino L, Dore R, Radominski S, Zhang Y, Kaur A, Simpson R, Curtis S. Gastrointestinal tolerability of etoricoxib in rheumatoid arthritis patients: results of the etoricoxib vs diclofenac sodium gastrointestinal tolerability and effectiveness trial (EDGE-II). Ann.Rheum.Dis. 2008 Mar;67(3):315-22.
http://www.ncbi.nlm.nih.gov/pubmed/17965424/sites/entrez?otool=mdufdrlib

Objective: To compare the gastrointestinal (GI) tolerability, safety, and efficacy of etoricoxib and diclofenac in patients with rheumatoid arthritis (RA).

Design: A randomized, double-blind, active-comparator-controlled study to evaluate the GI tolerability of etoricoxib versus diclofenac in patients with RA

Population: A total of 4086 patients (mean age 60.8 years) diagnosed with RA were enrolled in the EDGE II trial, designed to assess GI tolerability of etoricoxib versus diclofenac in patients with RA. EDGE II was one of three component studies in the MEDAL (Multinational Etoricoxib versus Diclofenac Arthritis Long Term) Program, the first outcomes program designed to evaluate prospectively the thrombotic CV risk of a selective COX-2 inhibitor (i.e., etoricoxib) relative to a the NSAID diclofenac.

Methods: Patients received etoricoxib 90 mg daily (n = 2032) or diclofenac 75 mg twice daily (n = 2054). Use of gastroprotective agents and low-dose aspirin was allowed. The prespecified primary endpoint consisted of the cumulative rate of patient discontinuations due to clinical and laboratory GI adverse experiences (AEs). General safety was also assessed, including adjudicated thrombotic cardiovascular event data. Efficacy was evaluated using the Patient Global Assessment of Disease Status (PGADS; 0-4 point scale). Patients with a history of CV disease were enrolled, with the exception of those with a history of stroke, transient ischemic attack or myocardial infarction within six months.

Results: Mean (SD; maximum) duration of treatment was 19.3 (10.3; 32.9) and 19.1 (10.4; 33.1) months in the etoricoxib and diclofenac groups, respectively. The cumulative discontinuation rate due to GI AEs was significantly lower with etoricoxib than diclofenac (5.2 vs 8.5 events per 100 patient-years, respectively; hazard ratio 0.62 (95% CI: 0.47, 0.81; $p \leq 0.001$)). The incidence of discontinuations with etoricoxib were significantly higher compared with diclofenac for hypertension-related (2.5% and 1.1% respectively) and edema-related (1.5% and 0.4%, respectively) AEs ($p<0.001$ for hypertension and $p<0.01$ for edema). Etoricoxib and diclofenac treatment resulted in similar efficacy (PGADS mean changes from baseline -0.62 vs -0.58, respectively).

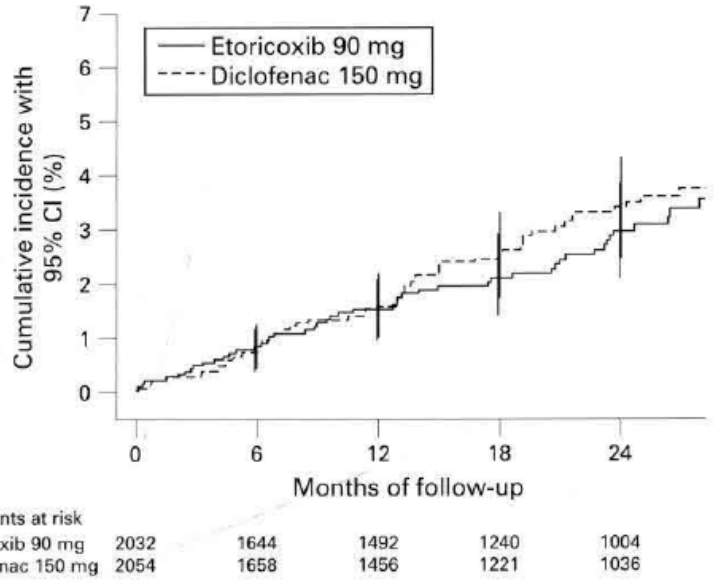
A total of 152 investigator-reported CV events (71 etoricoxib and 81 diclofenac) occurred during the study or within 14 days of discontinuing treatment and were adjudicated, resulting in 103 patients (49 etoricoxib and 54 diclofenac) having 110 confirmed CV events (51 etoricoxib and 59 diclofenac). Confirmed CV event rates are presented in Table 4. Acute myocardial infarctions occurred at a greater rate in diclofenac-treatedc patients as compared to etoricoxib-treated patients, but the authors note that results at the level of individual events should be interpreted cautiously, as the number of events is limited. The cumulative incidence of confirmed CV events was similar over time for etoricoxib as compared with diclofenac (Figure 4).

Table 4. Confirmed cardiovascular events by class: events within 14 days of study end

Confirmed adjudicated event	Etoricoxib 90 mg (n = 2032) 3266 Patient-years		Diclofenac 150 mg (n = 2054) 3251 Patient-years	
	n (%)*	Rate† (95% CI)	n (%)*	Rate† (95% CI)
Total number of patients with end point	49 (2.41)	1.50 (1.11 to 1.98)	54 (2.63)	1.66 (1.25 to 2.17)
Cardiac events	27 (1.33)	0.83 (0.54 to 1.20)	37 (1.80)	1.14 (0.80 to 1.57)
Acute myocardial infarction	14 (0.69)	0.43 (0.23 to 0.72)	22 (1.07)	0.68 (0.42 to 1.02)
Cardiac thrombus	0 (0.00)	0.00 (–)	1 (0.05)	0.03 (0.00 to 0.17)
Fatal acute myocardial infarction	0 (0.00)	0.00 (–)	3 (0.15)	0.09 (0.02 to 0.27)
Sudden cardiac death	7 (0.34)	0.21 (0.09 to 0.44)	4 (0.19)	0.12 (0.03 to 0.32)
Unstable angina pectoris	7 (0.34)	0.21 (0.09 to 0.44)	7 (0.34)	0.22 (0.09 to 0.44)
Cerebrovascular events	14 (0.69)	0.43 (0.23 to 0.72)	14 (0.68)	0.43 (0.24 to 0.72)
Cerebrovascular venous thrombosis	1 (0.05)	0.03 (0.00 to 0.17)	0 (0.00)	0.00 (–)
Ischaemic cerebrovascular stroke	8 (0.39)	0.24 (0.11 to 0.48)	12 (0.58)	0.37 (0.19 to 0.64)
Transient ischaemic attack	5 (0.25)	0.15 (0.05 to 0.36)	2 (0.10)	0.06 (0.01 to 0.22)
Peripheral vascular events	8 (0.39)	0.24 (0.11 to 0.48)	6 (0.29)	0.18 (0.07 to 0.40)
Peripheral arterial thrombosis	1 (0.05)	0.03 (0.00 to 0.17)	1 (0.05)	0.03 (0.00 to 0.17)
Peripheral venous thrombosis	6 (0.30)	0.18 (0.07 to 0.40)	5 (0.24)	0.15 (0.05 to 0.36)
Pulmonary embolism	1 (0.05)	0.03 (0.00 to 0.17)	0 (0.00)	0.00 (–)

*Crude incidence (n/N×100).
†Events per 100 patient-years.
Patients with multiple events may be counted more than once in different terms, but only once in each term.

Figure 4. Kaplan-Meier plot of the cumulative incidence of confirmed cardiovascular events with etoricoxib compared with diclofenac within 14 days of discontinuing therapy in the study



Limitation: This was an active-controlled study between etoricoxib and diclofenac without a placebo control.

Conclusions: Rates of thrombotic CV events were similar between etoricoxib and diclofenac; the cumulative incidence of confirmed thrombotic events was generally constant over time, with no discernible difference between etoricoxib and diclofenac groups at any time. Etoricoxib 90 mg demonstrated a significantly lower risk for discontinuing treatment due to GI AEs compared with diclofenac 150 mg. The authors report that the thrombotic CV safety data from EDGE II have been analyzed as part of the MEDAL Program which was specifically designed to compare the rates of thrombotic CV events of etoricoxib and diclofenac. The authors state that results of the MEDAL Program, which include data from over 34,000 patients with OA or RA, indicate that the risk of thrombotic CV events associated with longer-term treatment with etoricoxib and diclofenac was comparable.

Sulindac

Zell JA, Pelot D, Chen WP, McLaren CE, Gerner EW, Meyskens FL. Risk of cardiovascular events in a randomized placebo-controlled, double-blind trial of difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas. Cancer Prev.Res.(Phila.) 2009 Mar;2(3):209-12.
http://www.ncbi.nlm.nih.gov/pubmed/19258540/sites/entrez?otool=mdufdrlib

Objective: To evaluate the effect of baseline CV risk on adverse CV events in a phase 3 trial of difluoromethylornithine (DFMO) plus the NSAID sulindac versus placebo in preventing colorectal adenomas.

Design: Analysis of patient data from the multicenter colon adenoma prevention trial (randomized, double-blind, placebo-controlled trial).

Population: 375 patients were randomized to receive treatment with either placebo (184) or DFMO/sulindac (191).

Methods: Trial data were analyzed to determine baseline CV risk. High risk included a history of cardiovascular disease defined as myocardial infarction, coronary artery disease, congestive heart failure or cerebrovascular accident but the number of subjects with a specific diagnosis within this group was not provided. CV toxicity outcomes were assessed both overall and excluding high CV-risk patients. A composite endpoint for CV events was used that included myocardial infarction, coronary artery disease, congestive heart failure, cerebrovascular accident and chest pain (only grade 3+ toxicities).

Results: Baseline CV risk scores were similarly distributed within the overall trial population of 184 placebo-treated patients (low risk 27%; moderate risk 34%; high risk 39%) and 191 DFMO/sulindac-treated patients (low risk 30%; moderate risk 29%; high risk 41%). In patients with a high baseline CV risk, the incidence of adverse CV events was greater in the DFMO/sulindac group 9/77 (12%) than among placebo 3/71 (4%) patients. Excluding patients with a high baseline CV risk, the incidence of adverse CV events in patients with low and moderate risk scores were similar in the DFMO/sulindac 7/109 (6%) and placebo 6/110 (5%) groups. The pattern of excess risk in only the DFMO/sulindac group with high baseline CV risk

scores was still observed when patients with chest pain were excluded from the aggregate CV event endpoint.

Limitations: The only NSAID studied was sulindac in combination with DFMO. Cardiovascular risk was based on multiple risk factors with no breakdown provided of which specific risk factors were present (e.g., unknown number of subjects, if any, with prior MI). From the composite endpoint for CV events it is not possible to determine what actual event occurred (i.e., myocardial infarction, coronary artery disease, congestive heart failure, cerebrovascular accident, or chest pain). Due to the small number of events, formal statistical testing for the interaction between baseline CV risk and treatment could not be performed. No information was provided on the time to event.

Conclusion: This study suggests that the risk of an adverse CV event associated with DFMO/sulindac increased with a high, but not with a low/medium baseline CV risk score. However, the study is of limited value because it does not provide details as to the specific risk factors resulting in a high risk score (i.e. MI, CAD, CHF or CVA) or the specific cardiovascular endpoint (i.e., MI, CAD, CHF, CVA or chest pain), and the role of DFMO could not be determined. The study also is of limited value in generalizing to other NSAIDs since only sulindac was studied.

Naproxen

Ozdol C, Gulec S, Rahimov U, Atmaca Y, Turhan S, Erol C. Naproxen treatment prevents periprocedural inflammatory response but not myocardial injury after percutaneous coronary intervention. Thromb.Res. 2007;119(4):453-9.

http://www.ncbi.nlm.nih.gov/pubmed/17157900/sites/entrez?otool=mdufdrlib

Objective: To test whether preprocedural use of naproxen sodium is associated with a reduction in the extent of inflammatory response (C-reactive protein) and myocardial injury after percutaneous coronary intervention (PCI).

Design: Single-center, open-label, placebo-controlled, randomized study.

Population: A total of 97 patients scheduled for elective PCI.

Methods: Patients scheduled for elective PCI were randomized to either naproxen sodium 500 mg twice daily (N=37) or placebo (N=58). Naproxen was started the day prior to the procedure and continued for one week after the procedure. All patients were troponin negative before the procedure. Blood samples for CRP, Troponin I and CK-MB were collected at baseline and after the procedure.

Results: The characteristics were similar between the two groups. After coronary stenting, the rise in CRP levels was significantly higher in controls than those treated with naproxen (Delta CRP=6.4 mg/L in the placebo group and 0.43 mg/L in the naproxen group, $p<0.0001$). The incidence of any troponin I elevation or CK-MB elevation above upper limit of normal was not

statistically different between groups. During follow up (12±2 months), major cardiac adverse events (death, myocardial infarction, and revascularization of target lesion) were similar between groups.

Limitations: In this open-label study the outcome was primarily a lab marker for inflammatory response following PCI. Naproxen was the only NSAID studied and the sample size was relatively small (97 patients). The effect of prior MI on outcome was not analyzed.

Conclusion: This study is of limited value in assessing clinical cardiovascular outcomes since the primary endpoint was a biomarker of inflammation (C-reactive protein) following PCI. Naproxen pretreatment leads to significant suppression in percutaneous coronary intervention related CRP elevation. However this improvement in CRP levels was not associated with any significant reduction in post-PCI myonecrosis.

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/s/

ROBERT A LEVIN
01/08/2014

JUDITH A RACOOSIN
01/08/2014

Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products

Medical Reviewer Consult

DATE:	Desired Completion date: 31 Oct 2011 Date of review: 25 Oct 2011
FROM:	Preston M. Dunnmon, M.D., Medical Officer Division of Cardiovascular and Renal Products, HFD-110
THROUGH:	Norman Stockbridge, M.D., Ph.D., Division Director Division of Cardiovascular and Renal Products, HFD-110
SUBJECT:	Literature Review – CV risk of NSAIDs as a function of duration of therapy
Requestor:	Katherine Won, SRPM, for Bob Rappaport, M.D., Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), HFD-170
Requested Completion:	October 31, 2011
Consult Completion Date:	October 31, 2011

Assessments:

1. Though a double-blind trial randomizing immediately post-MI patients to escalating doses of NSAIDs has not been reported in the literature that this reviewer is aware of, the results of the post-CABG NSAID-treatment study by Nussmeier et al suggests a biologically plausible mechanism whereby the latency period for the onset of CV events could indeed be shown to be less than one week, if this phenomenon were looked for in an appropriately sized and powered clinical trial.
2. In addition to the potential etiology proposed by Antman and others for NSAID induced CV events as a result of prostanoid imbalance favoring thromboxane production over prostacyclin synthesis in atherosclerotic arteries, pharmacodynamic data from Capone et al and Anzellotti et al demonstrate the potential for naproxen to interfere with the antiplatelet action of aspirin. This interference with aspirin has likewise been shown for ibuprofen. Thus, the potential for inhibition of the antiplatelet properties of aspirin by NSAIDs (shown for non-selective NSAIDS to date) may be an important etiologic factor for post-MI CV events, especially in patients not treated with dual-antiplatelet therapy.
3. The findings of the study by Schjerning Olsen and colleagues titled, "*Duration of Treatment With Nonsteroidal Anti-Inflammatory Drugs and Impact on Risk of Death*

and Recurrent Myocardial Infarction in Patients With Prior Myocardial Infarction, A Nationwide Cohort Study," are clinically relevant for scenarios in which chronic/pre-existing NSAID therapy is continued during the immediate post-MI time period, or started de novo in the CCU (e.g. pain control for post-MI pericarditis).

Background

Observational evidence continues to accumulate suggesting an increased CV risk in individuals taking NSAIDs for pain relief, and it is thought that this risk is likely greatest in patients with or at risk for active atherosclerotic processes.[1] Accordingly, all NSAIDs are so labeled, as shown in the black box warning for diclofenac below:

Diclofenac sodium enteric-coated tablets

Tablets of 25 mg, 50 mg, and 75 mg

Rx only

Prescribing information

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS.)

- Voltaren® (diclofenac sodium enteric-coated tablets) is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (See WARNINGS).

[1] Antman, EM, Bennett, JS, Daugherty A, Furberg, C, Roberts H, Taubert, KA. Use of nonsteroidal antiinflammatory drugs, an update for clinicians: a scientific statement from the American Heart Association. *Circulation*. 2007;115: 1634-1642.

Earlier in 2011, Schjerning Olsen et al published an article titled, *Duration of Treatment With Nonsteroidal Anti-Inflammatory Drugs and Impact on Risk of Death and Recurrent Myocardial Infarction in Patients With Prior Myocardial Infarction, A Nationwide Cohort Study*.[2] The Division of Cardiovascular and Renal Products (DCRP) has been consulted by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) to review this article and then to answer the following questions:

1. For patients started on chronic NSAID therapy, cardiovascular events are not typically observed within the first few days or weeks of initiating therapy. Based on other clinical studies, are there any physiologic factors in patients post-MI that would make them susceptible to potential prothrombotic effects of NSAIDs, and if so, is a latency of less than one week biologically plausible?

2. Is the potential for inhibition of antiplatelet properties of aspirin by NSAIDs an important etiologic factor for these events?

3. Are the findings reported in the attached article, in the context of the existing literature, of clinical relevance?

Article Review

Study Rationale:

Though recent studies have associated the use of NSAIDs with increased cardiovascular risk in both healthy patients and those with established CV disease, data regarding CV risk as a function of the duration of NSAID therapy in immediately post-MI patients has been lacking. In their publication titled "*Duration of Treatment With Nonsteroidal Anti-Inflammatory Drugs and Impact on Risk of Death and Recurrent Myocardial Infarction in Patients With Prior Myocardial Infarction, A Nationwide Cohort Study*" (*Circulation, May 24, 2011*), Schjerning Olsen et al examined this topic in a retrospective cohort study of residents of Denmark with a first-time admission for MI from January 1, 1997 to December 31, 2006. Though observational/retrospective, the study's design and execution were strengthened by the following characteristics of the Danish health care system:

- Each resident of Denmark has a unique/permanent identification number that enables individual-level linkage between nationwide registries
- The Danish National Patient Registry keeps records of all hospital admissions in Denmark since 1978

[2] Schjerning Olsen AM, Fosbol EL, Lindhardsen J, Folke F, Charlot M, Selmer C, Lamberts M, Olesen JB, Kober L, Hansen PR,, Torp-Pedersen C, Gislason GH. Duration of Treatment with Nonsteroidal Anti-Inflammatory Drugs and Impact on Risk of Death and Recurrent Myocardial infaction in Patients with Prior Myocardial Infarction: A nationwide Cohort Study. Circulation. 2011; 123: 2226-2235.

- Each hospital admission is registered with 1 main discharge coding diagnosis (ICD 8-10)
- The database was screened to assure that transfers of patients between hospitals are counted as a single admission
- All patients who were alive at discharge after their first MI were included in the study
- The Danish Registry of Medicinal Product Statistics (national prescription registry) tracks all drug prescriptions dispensed from Danish pharmacies since 1995, with each registered according to an international classification (the Anatomical Therapeutic Chemical system), date of dispensing, quantity dispensed, strength, formulation, and affiliation of the prescribing physician
- Because of partial reimbursement of drug expenses by the Danish healthcare system, all pharmacies in Denmark are required to register each drug dispensing in the national prescription registry, ensuring complete registration
- The Central Person Registry registers all deaths within 14 days of occurrence
- The only over-the-counter NSAID available in Denmark is ibuprofen (since 2001), only in low doses (200 mg), and only in limited quantities (100 tablets), thus minimizing the impact of OTC NSAID use on the study outcome.

Study Design:

Patients $\geq$ 30 years admitted with first MI from 1997 to 2006 were analyzed for the occurrence of death and recurrent MI with respect to duration of post-MI NSAID therapy and specific NSAID administered, using multivariable time-stratified Cox proportional-hazard models. Baseline characteristics of the enrolled population by NSAID taken are shown in the following table (Schjerning Olsen et al, Circulation May 24, 2011, p. 2228):

Table. Baseline Characteristics of the Total Study Population and Individual Treatment Groups

Characteristic	Total Population, n (%)	No. NSAIDs, n (%)	Exposure Group, n (%)					
			Rofecoxib	Celecoxib	Ibuprofen	Diclofenac	Naproxen	Other NSAIDs
Total patients	83 677 (100.0)	48 270 (57.7)	3914 (4.7)	4000 (4.8)	19 377 (23.0)	11 181 (13.4)	1816 (2.2)	10 717 (12.8)
Mean±SD age, y	68.0±13.0	70.1±12.9	70.5±12.2	70.6±11.9	65.4±13.0	65.2±12.6	65.9±12.7	68.2±12.6
Women	31 011 (37.0)	17 978 (37.2)	1921 (49.0)	1988 (49.7)	6554 (33.8)	3692 (33.2)	570 (31.4)	4372 (40.8)
Men	52 666 (62.9)	30 292 (62.8)	1993 (50.9)	2012 (50.3)	12 823 (66.2)	7489 (67.0)	1246 (68.6)	6345 (59.2)
Comorbidity								
Cardiac arrhythmias	8903 (10.6)	5872 (12.2)	386 (9.9)	394 (9.9)	1482 (7.7)	860 (7.7)	135 (7.4)	920 (8.6)
Peripheral vascular disease	1480 (1.8)	934 (1.9)	59 (1.5)	77 (1.9)	283 (1.5)	146 (1.3)	25 (1.4)	166 (1.6)
Cerebral vascular disease	4302 (5.1)	2907 (6.0)	187 (4.8)	182 (4.6)	674 (3.5)	368 (3.3)	57 (3.1)	425 (4.0)
Diabetes mellitus with complications	3964 (4.7)	2463 (5.1)	169 (4.3)	173 (4.3)	848 (4.4)	434 (3.9)	70 (3.9)	384 (3.6)
Acute renal failure	820 (0.9)	617 (1.3)	27 (0.7)	19 (0.5)	97 (0.5)	42 (0.4)	7 (0.4)	53 (0.5)
Chronic renal failure	1120 (1.3)	841 (1.7)	30 (0.8)	27 (0.7)	141 (0.7)	62 (0.6)	14 (0.8)	65 (0.6)
Malignancy	495 (0.6)	334 (0.7)	13 (0.3)	18 (0.5)	81 (0.4)	52 (0.5)	6 (0.3)	38 (0.4)
Shock	995 (1.1)	652 (1.4)	40 (1.0)	31 (0.8)	131 (0.7)	90 (0.8)	21 (1.2)	83 (0.8)
COPD	969 (1.2)	650 (1.4)	34 (0.9)	32 (0.8)	152 (0.8)	84 (0.8)	20 (1.1)	110 (1.0)
Gastric ulcer	1461 (1.8)	897 (1.9)	94 (2.4)	90 (2.3)	235 (1.2)	145 (1.3)	26 (1.4)	180 (1.7)
Concomitant medical treatment								
β-blockers	58 141 (69.5)	32 496 (67.3)	2643 (67.5)	2741 (68.5)	14 366 (74.1)	8319 (74.1)	1291 (71.1)	7701 (71.9)
ACE inhibitors	34 890 (41.7)	20 548 (42.6)	1552 (39.7)	1620 (40.5)	7734 (39.9)	4466 (39.9)	718 (39.5)	4265 (39.8)
Statins	44 488 (53.2)	25 622 (53.1)	1594 (40.7)	1675 (41.9)	10 895 (56.2)	6163 (55.1)	901 (49.6)	5312 (49.6)
ASA	41 278 (49.3)	24 591 (50.9)	1503 (38.4)	1566 (39.2)	9340 (48.2)	5209 (46.6)	817 (44.9)	4826 (45.0)
Clopidogrel	29 395 (35.2)	18 532 (38.4)	696 (17.8)	842 (21.1)	6160 (31.8)	3317 (29.7)	449 (24.7)	2910 (27.2)
Spironolactone	7015 (8.4)	4414 (9.1)	320 (8.2)	368 (9.2)	1307 (6.8)	689 (6.2)	122 (6.7)	770 (7.2)
Loop diuretics	33 732 (40.3)	20 290 (42,0)	1820 (46.0)	1836 (45.9)	6798 (35.1)	3778 (33.8)	690 (38.0)	4304 (40.2)
Glucose-lowering drugs	10 155 (12.1)	6042 (12.5)	471 (12.0)	478 (12.0)	2269 (11.7)	1289 (11.5)	213 (11.7)	1228 (11.5)
PCI	22 178 (26.5)	13 618 (28.2)	623 (15.9)	646 (16.2)	4916 (25.4)	2787 (24.9)	409 (22.5)	2307 (21.5)
Socioeconomic factors								
Yearly family income in quintiles								
0	15 147 (18.1)	8392 (17.4)	1021 (26.1)	978 (24.5)	3443 (17.8)	1992 (17.8)	413 (22.7)	2430 (22.7)
1	15 647 (18.1)	9101 (19.9)	948 (24.2)	959 (24.0)	3252 (16.8)	1835 (16.4)	296 (16.3)	2111 (19.7)
2	16 708 (20.0)	10 024 (20.8)	695 (17.8)	733 (18.3)	3585 (18.5)	2066 (18.5)	309 (17.0)	2088 (19.5)
3	17 609 (21.0)	9934 (20.6)	717 (18.3)	760 (19.0)	4415 (22.8)	2631 (23.5)	411 (22.6)	2221 (20.7)
4 (highest)	18 566 (22.2)	10 819 (22.4)	533 (13.6)	570 (14.3)	4682 (24.2)	2657 (23.7)	387 (21.3)	1867 (17.4)

NSAID indicates nonsteroidal antiinflammatory drug; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid; and PCI, percutaneous coronary intervention.

A total of 102,138 patients were admitted with a first MI during the period of 1997 to 2006, of whom 83,677 (81.9%) were discharged alive and included in the study. The population age in years was 68±13.0, and 63% were men. At least 1 prescription claim for NSAID treatment after discharge was identified for 35,405 patients (42.3%) with prior MI. Patients taking nonselective NSAIDs were younger and more often men compared with patients taking selective COX-2 inhibitors. The most commonly used NSAIDs were ibuprofen (23.2%) and diclofenac (13.4%). Rofecoxib (4.7%) and elecoxib (4.8%) were the most commonly used selective COX-2 inhibitors. Of patients taking ibuprofen, diclofenac, and naproxen, there were approximately twice as many men as women.

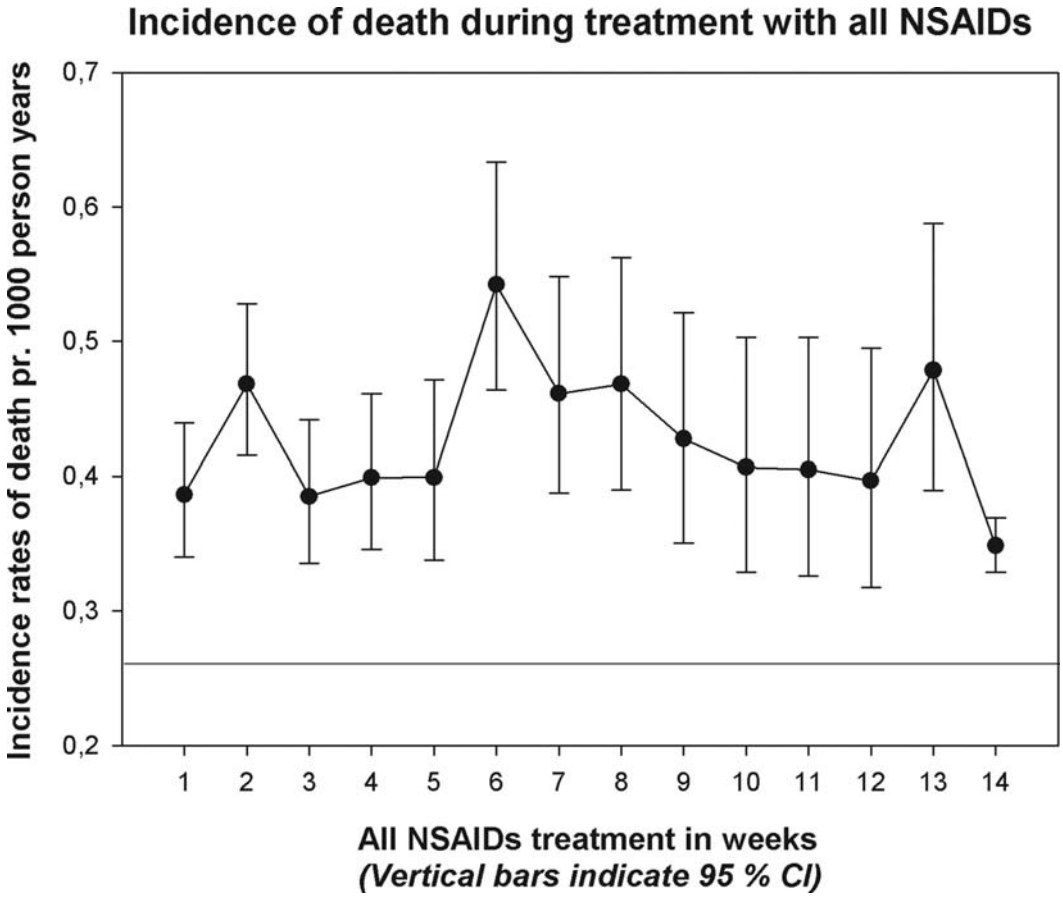
Reviewer's comment: Patients not treated with NSAIDS appear to be sicker at study entry than those who were treated with NSAIDS, as the former group had experienced

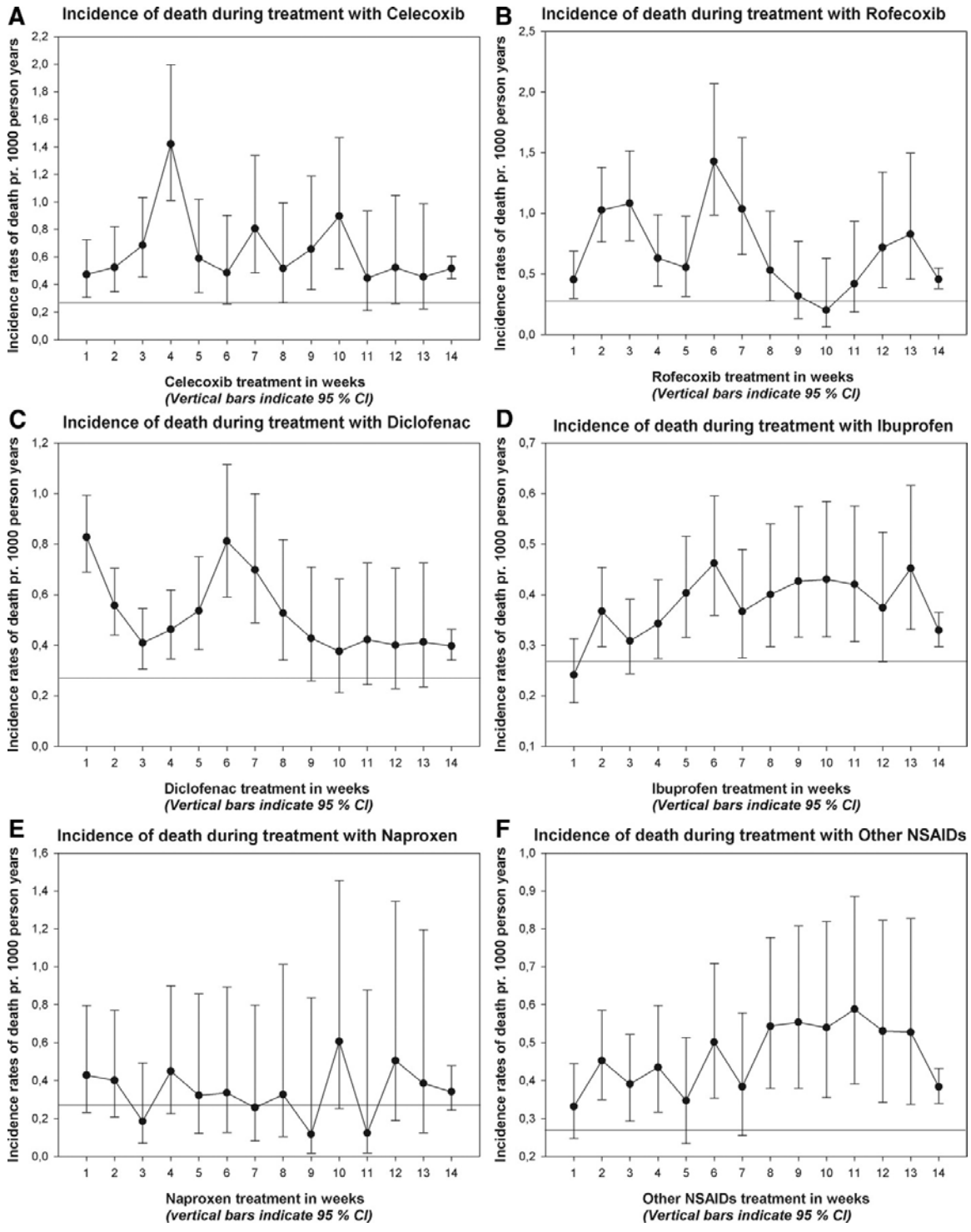
numerically more cardiac arrhythmias, PVD, CVD, DM, ARF, CRF shock, COPD, and, surprisingly, gastric ulcer, than had the entire population, according to baseline characteristics. Likewise, with respect to baseline concomitant therapies, more patients who had not been treated with NSAIDS had experienced a prior PCI (28.2% versus 26.5%), took glucose-lower drugs, loop diuretics, spironolactone, clopidogrel, ASA, and ACE inhibitors. These last two comparative statements had to be made with respect to non-NSAID treated patients versus the entire population, because we do not have numbers for these events in NSAID treated patients (NSAID columns appear not to be exclusive – i.e., a patient could have been on more than one NSAID, so events may have been double counted). Had percentages for clinical outcomes been available for the group who had been treated with NSAIDs overall, the differences would have been even more marked.

Similar percentages of men and women were treated with NSAID therapy. As would be expected, patients taking COX-2 inhibitors appeared to be sicker than those taking non-selective agents, with higher percentages of the former having suffered cardiac arrhythmias, PVD, CVD, and gastric ulcers. Strikingly, though there were more antecedent PVD+CVD+Arrhythmias on COX-2 inhibitors, these patients were less likely to be taking beta blockers, statins, ASA, or clopidogrel, and less likely to have experienced prior PCI as compared to those taking non-selective agents. A higher percentage of the women in the trial were given COX-2 inhibitors (12.6%) as compared to men (7.6%). These differences were not explained by differences in the occurrences of diabetes, acute renal failure, or chronic renal failure between these two groups. These findings raise the possibility that this health system experiences a systematic bias toward less aggressive therapy for CAD in women, thus creating a higher risk group for first events in those taking COX-2 inhibitors as opposed to non-selective agents. It is likewise striking that there is an inverse relationship between family income and the likelihood of taking any NSAID, with lower income patients more likely to receive COX-2 inhibitors.

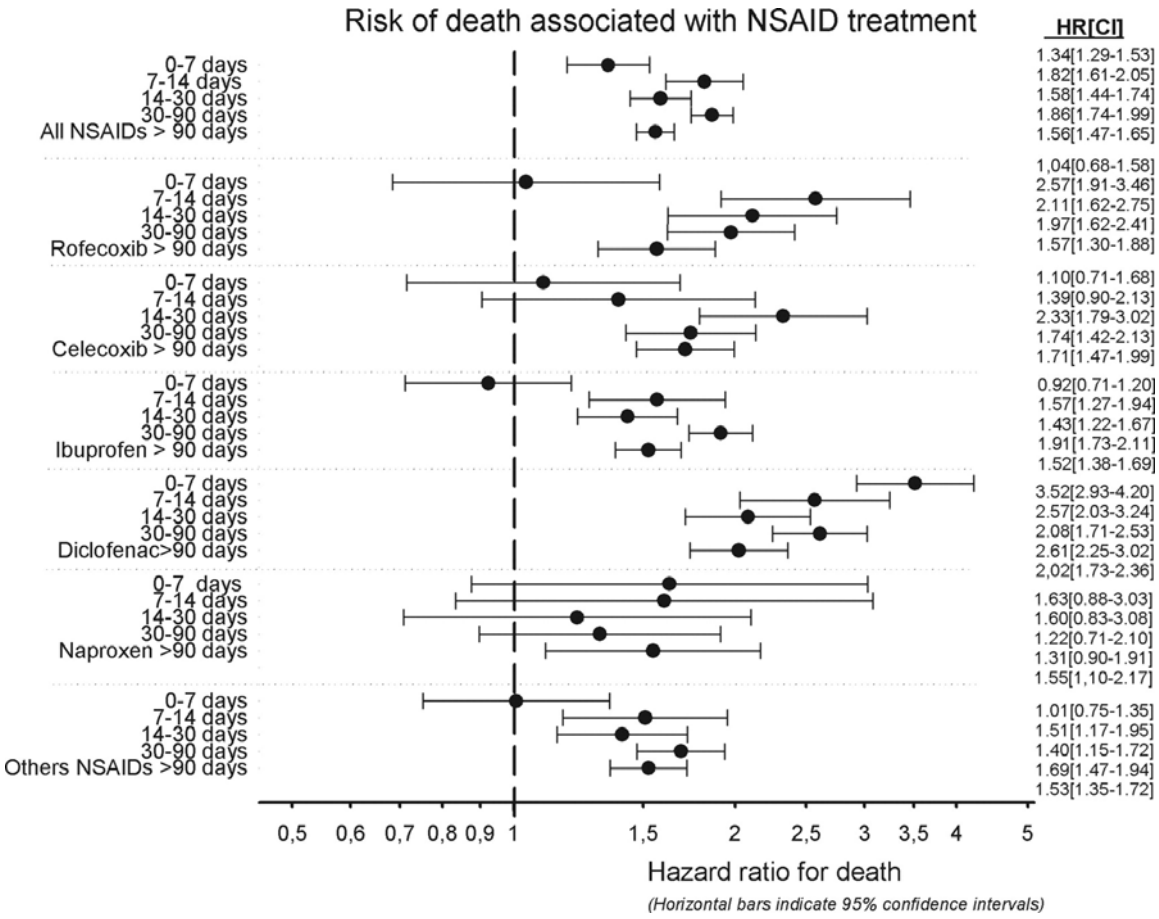
Study Results:

All-cause mortality was calculated per 1000 person years for NSIAD treatment in general, and for the individual NSIADS separately, split out over one week treatment intervals, as compared to the overall incidence rate of death for the entire study population on a horizontal line. These results are shown in the figures below:


Incidence of death during treatment with all NSAIDs
Incidence rates of death pr. 1000 person years
0,7
0,6
0,5
0,4
0,3
0,2
1
2
3
4
5
6
7
8
9
10
11
12
13
14
All NSAIDs treatment in weeks
(Vertical bars indicate 95 % CI)



These analyses supported the results of the time-dependent Cox proportional hazard analyses with an increased risk of death, per the figure below:



Reviewer's comment: outcome trends for the combined endpoint of death and re-MI were similar for all individual drugs and for the overall study population (data presented in manuscript). I would have preferred to have seen a by-week endpoint rate for the no-NSAID control group, with a χ^2 analysis between the No-NSAID group versus the various NSAID groups.

Study Conclusions:

Based on the study results, Schjerning Olsen et al concluded:

> The present results indicate that there is no apparent safe therapeutic window for NSAIDs in patients with prior MI and challenge the current recommendations of low-dose and short-term use of NSAIDs as being safe. Further studies, preferably randomized clinical studies, are warranted to establish the cardiovascular safety of NSAIDs, but given the additional evidence from randomized trials and other observational studies of selective COX-2 inhibitors and nonselective NSAIDs, the accumulating evidence suggests that we must limit NSAID use to the absolute minimum in patients with established cardiovascular disease.

Reviewer's Comment: The authors acknowledge the weaknesses of this study, first and foremost of which is its observational/retrospective design. There is a lack of information about many potentially confounding parameters (BP, BMI, smoking status, lipid levels, and LVEF). However, the authors estimated that a combination of one or more confounders that were present in 20% of the cohort would have to elevate CV risk by 2.2 to 3.3 to explain the study results – an unlikely occurrence. Furthermore, there may have been inadequate control for "confounding by indication" (i.e. the risk that patients taking NSAIDs were more prone to be sick and thus to have a higher baseline CV risk). However, excluding patients with rheumatic diseases apparently did not change the results (text statement, data not shown in manuscript). Furthermore, there was a correlation demonstrated between the degree of COX-2 inhibition and CV risk, as well as between drug dose and CV risk, indicating the importance of the drugs as opposed to the drug indications.

In spite of its weakness, this study by Schjerning Olsen et al raises the level of concern for the use of NSAID overall, but particularly in the vulnerable post-MI population. The relationship between the degree of COX-2 inhibition and CV risk is in alignment with findings and hypotheses put forth by Antman et al in their 2007 AHA position statement on this subject (see below). More concerning for this reviewer, however, is the point that the author raises about there being no apparent safe therapeutic window for NSAIDs in patients with prior MI, and the study results challenge the current recommendations of low-dose and short-term use of NSAIDS as being safe. Supporting the authors' contention here is recent data published in a series of studies by Capone et al and Anzellotti et al on short term/low-dose naproxen therapy, suggesting that for this NSAID that is felt to be the least cardiotoxic of these agents, it may be the low dose, not the high dose, that is associated with CV risk due to potential interference with aspirin (as opposed to a prostanoid imbalance mechanism proposed for COX-2 inhibition).

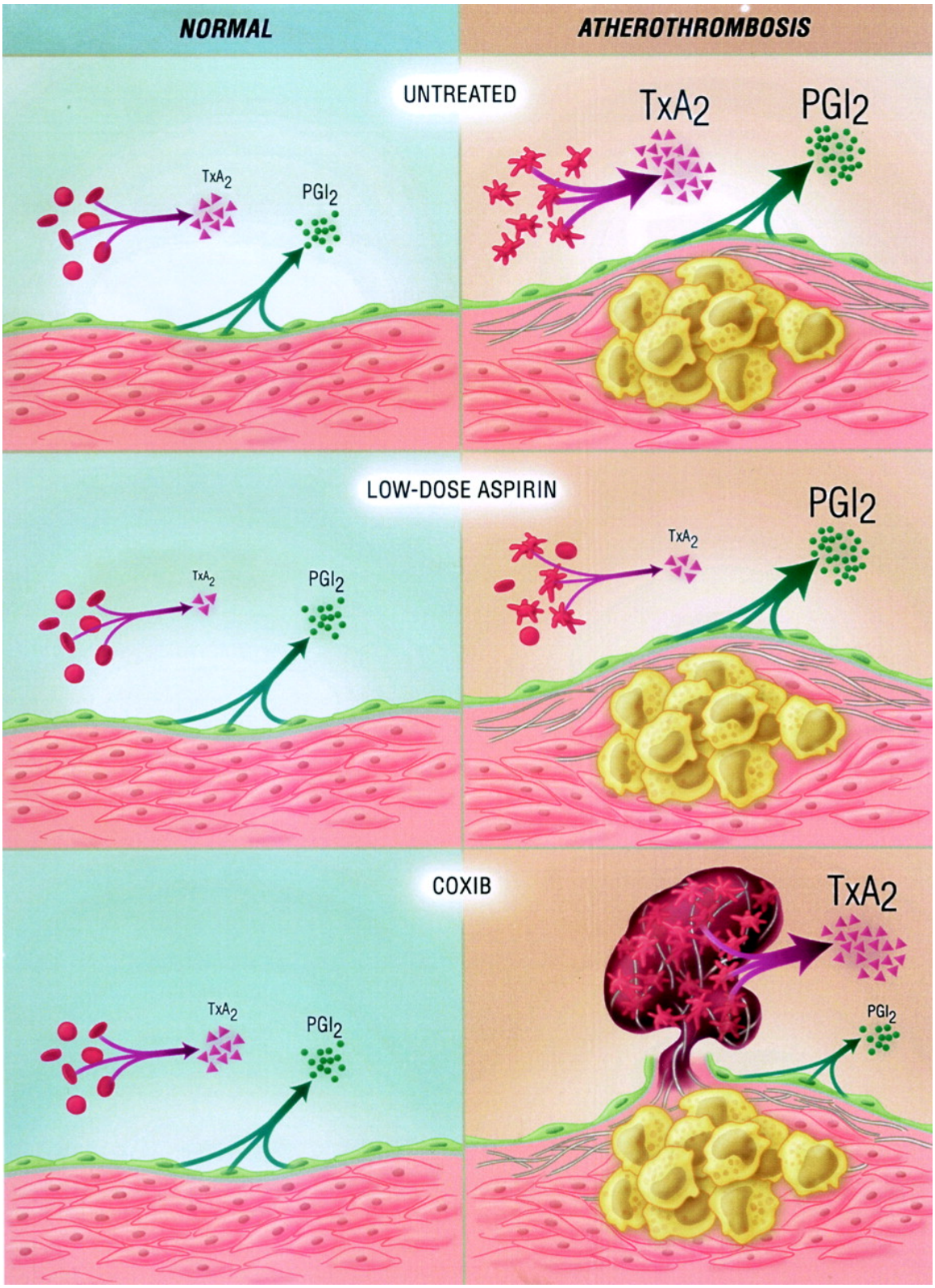
Consult Questions

1. ***For patients started on chronic NSAID therapy, cardiovascular events are not typically observed within the first few days or weeks of initiating therapy. Based on other clinical studies, are there any physiologic factors in patients post-MI that would make them susceptible to potential prothrombotic effects of NSAIDs, and if so, is a latency of less than one week biologically plausible?***

The physiology of prostanoid production in normal coronary arteries as opposed to coronary arteries with established atherosclerotic disease was the subject of an extensive review by Antman and coworkers, and summarized in Figure 1 below (Figure 4 from that publication):[3]

[3] Antman EM, DeMets D, Loscalzo J. Cyclooxygenase inhibition and cardiovascular risk. *Circulation*. 2005;112:759 –770.

Figure 1. Consequences of Cox inhibition for prostacyclin and thromboxane A2 production in normal and atherosclerotic arteries.

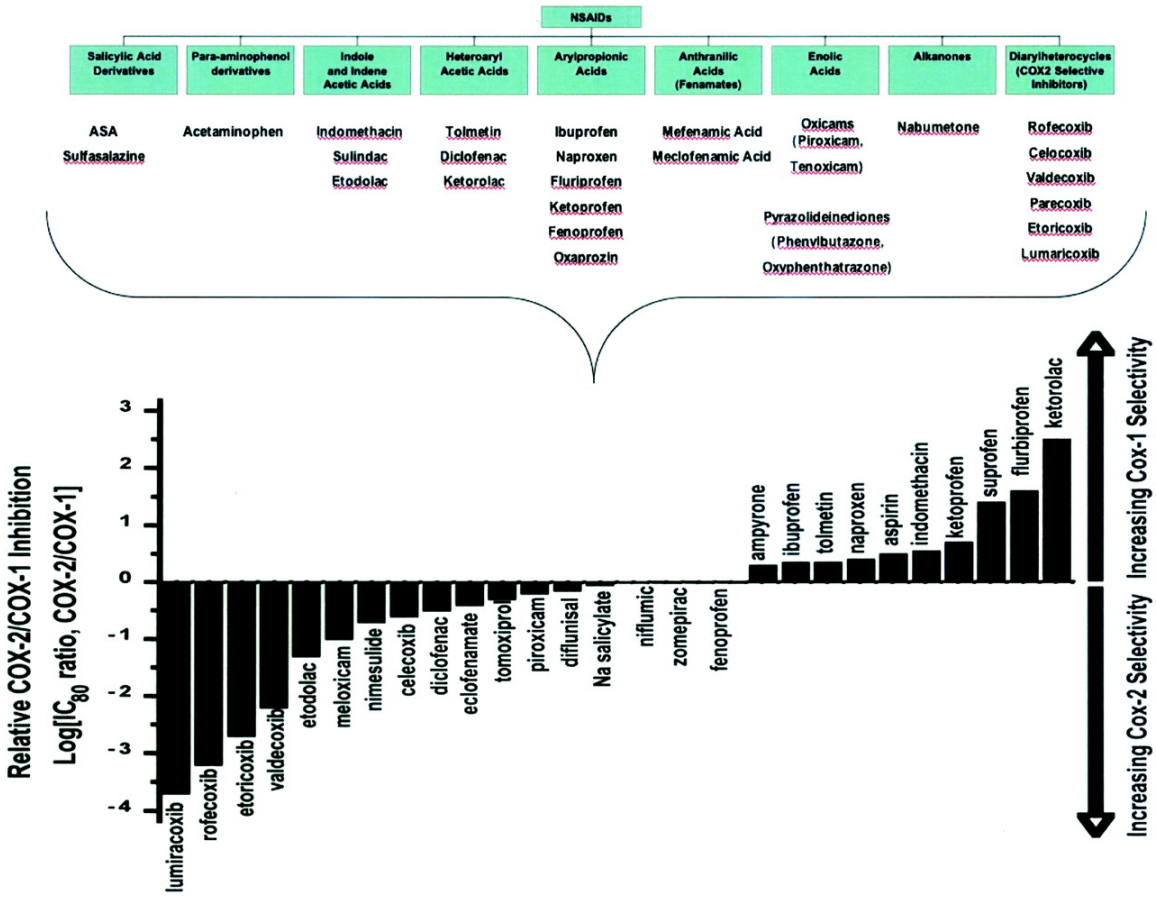


In the excellent accompanying text for this graphic, Antman et al explain the differing physiologies of normal versus atherosclerotic arteries that make the latter more prone to NSAID induced CV events:

> "Endothelial cells are shown as a source of prostacyclin (PGI_2) and platelets as a source of thromboxane A_2 (TxA_2) under untreated conditions (top row) or treated with low-dose aspirin (middle row) or a coxib (bottom row) in the normal (left column) and atherosclerotic artery (right column) for comparison. COX-1 is the only isoenzyme expressed in platelets; endothelial cells express both COX-1 and COX-2. In the normal artery, the balance between PGI_2 and TxA_2 production favors PGI_2 and inhibition of platelet-dependent thrombus formation. In the atherosclerotic artery, both PGI_2 and TxA_2 production is increased, owing in part to increased platelet activation with compensatory PGI_2 formation via both COX-1 and COX-2 in endothelial cell; the net effect is an imbalance favoring TxA_2 production and platelet-dependent thrombus formation. Low-dose aspirin selectively impairs COX-1–mediated TxA_2 production in platelets restoring the net antithrombotic balance. Coxib use suppresses COX-2–dependent PGI_2 production in endothelial cells, which has only a marginal effect on the net antithrombotic balance owing to the importance of COX-1 as a source of PGI_2 in the normal state. In the setting of atherosclerosis, however, COX-2 plays a greater role as a source of PGI_2 and more TxA_2 is produced; thus, inhibiting COX-2 has a more profound effect on prostanoid balance, favoring TxA_2 production and promoting platelet-dependent thrombosis."

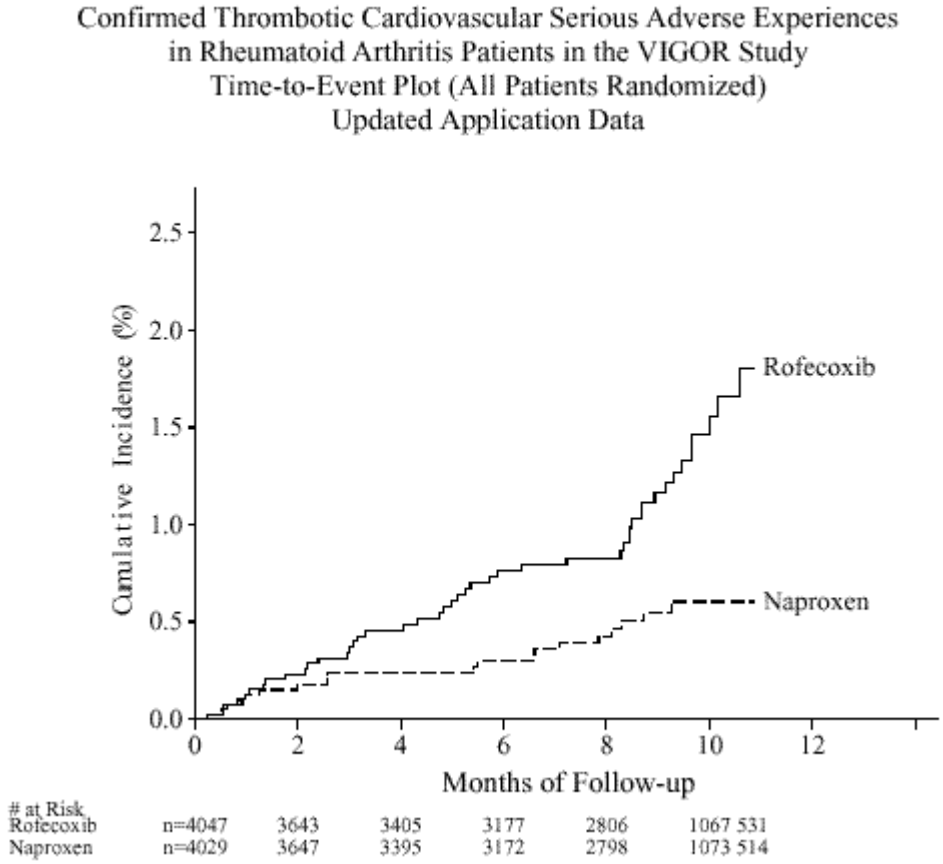
Furthermore, it is proposed that the proclivity for an NSAID to induce excess CV events would be determined by the relative selectivity of an NSAID for COX-2, per Figure 2 below:

Figure 2. NSAID groupings and relative COX-1 vs COX-2 selectivity



There have been no prospective, double blind trials to date that have assessed time to CV event in immediately post-MI patients randomized to NSAID therapy or placebo on top of standard post-MI medical care (i.e. looking for potential NSAID-induced CV events on days 0-7 post-MI). However, there are indicators that NSAID-induced CV risk can and does occur early, reflecting the kinetics of the aforementioned disturbances in the balance of procoagulant/vasoconstrictor prostanoid production (or potential interference with the antiplatelet actions of aspirin as addressed in question 2 below). One of the larger databases showing a relatively early impact of NSAIDs on CV risk came from VIGOR, a study designed to demonstrate the advantage in GI adverse events for selective COX-2 inhibitors. However, the most important finding from VIGOR was the demonstration of excess CV SAEs in RA patients randomized to rofecoxib (selective COX-2 inhibitor) versus naproxen (non-selective COX inhibitor). As demonstrated in Figure 3 below, the KM curves for CV outcomes began separating at about 4 weeks.

Figure 3. Time course of CV events from VIGOR

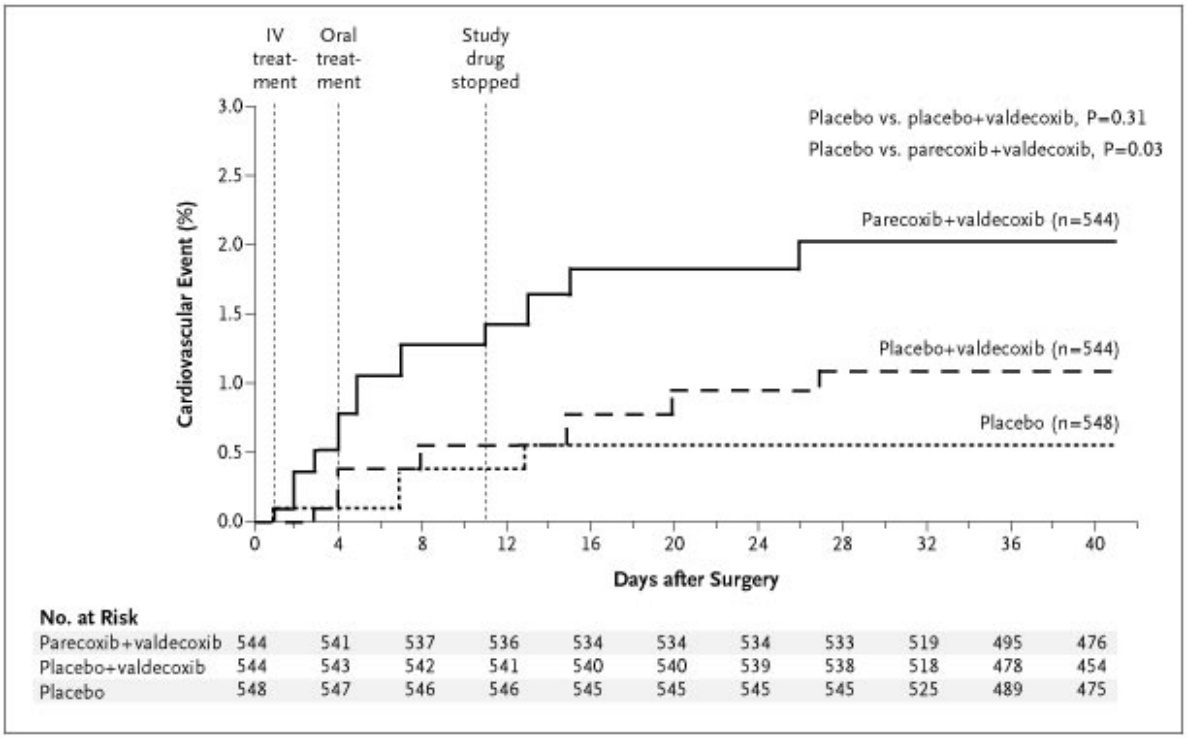


Thus, while VIGOR demonstrates that a differential risk between the NSAIDs can be demonstrated in a matter of weeks, immediately post-MI patient were not enrolled in VIGOR, nor were KM analyses performed, that this reviewer could locate in the FDA review, on CV event rates depending on whether patients had experienced a prior CV event or had important pre-existing risk factors for a CV event. There was no placebo group from which to assess CV risk in no-NSAID versus NSAID treated patients overall.

To try to hone in on the seven to ten day time frame post-MI to assess NSAID-induced CV risk in the more acute setting, there exists another clinical scenario for which there are clinical data that is of interest – specifically, data from patients undergoing CABG surgery. CABG surgery patients typically have clinical indicators of active and sometimes unstable CAD (e.g. unstable angina or symptomatically active coronary anatomy that is not amenable to PCI post-MI). Like ACS patients who experience platelet activation and due to shear forces and plaque rupture, CABG patients experience platelet activation as a consequence of contact between cellular and humoral blood components and the synthetic surfaces of the extracorporeal circuit, possibly predisposing these patients to thrombotic events. In addition, aortic cross-clamping may results in ischemia-reperfusion injury of the myocardium. Inadequate myocardial protection during bypass, coronary embolization, and technical complications with the grafts can exacerbate this potential for ischemic injury. To assess the potential for NSAID-induced

risk of CV events in this setting of vulnerability to ischemia during and immediately post-CABG, Nussmeier et al. randomized 1671 patients in a double-blind study to receive IV parecoxib for at least 3 days, followed by oral valdecoxib; or placebo for 10 days (on top of standard opioid medications as needed). The primary endpoint of the study was the frequency of predefined adverse events, including CV events, renal failure or dysfunction, gastroduodenal ulceration, and wound-healing complications.[4] CV events (MI, cardiac arrest, stroke, and pulmonary embolism) were more frequent among patients given parecoxib and valdecoxib than among those given placebo (2.0% vs. 0.5%; RR 3.7; 95% CI 1.0 – 13.5; P=0.03). KM estimates for time to first CV event are shown in Figure 4 below, and demonstrate separation of the combined IV/PO therapy arm from the placebo arm by day 2.

Figure 4. Time to First CV Event post-CABG



The findings of this study suggest that the more potent and/or rapidly acting the COX-2 inhibition is, the earlier the onset of CV events may be. Therefore, though a double-blind trial randomizing immediately post-MI patients to escalating doses of NSAIDs has not been reported in the literature that this reviewer is aware of, the results of the CABG study by Nussmeier et al suggests a biologically plausible mechanism whereby the latency period for the onset of CV events could indeed be shown to be less than one week, if this phenomenon were looked for in an appropriately designed, sized, and powered clinical trial.

[4] Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoeft A, Parlow JL, Boyce SW, Verburg KM. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med. 2005;352 (11): 1081-1091.

2. ***Is the potential for inhibition of antiplatelet properties of aspirin by NSAIDs an important etiologic factor for these events?***

Per the AHA scientific statement regarding use of nonsteroidal anti-inflammatory drugs (Antman, 2007), evidence indicates that ibuprofen, but not refecoxib, acetaminophen, or diclofenac, interferes with aspirin's ability to irreversibly acetylate the platelet COX-1 enzyme, and this would be expected to reduce the protective effect of aspirin (ASA) on the risk of CV events. The potential for this phenomenon has likewise been demonstrated for naproxen (NAP), and has been the subject of a recent FDA review by Dunnmon and Menon-Andersen, which for convenience is embedded here and linked in DARRTS to this consult:

ASA-Nap Interaction
Review 2011

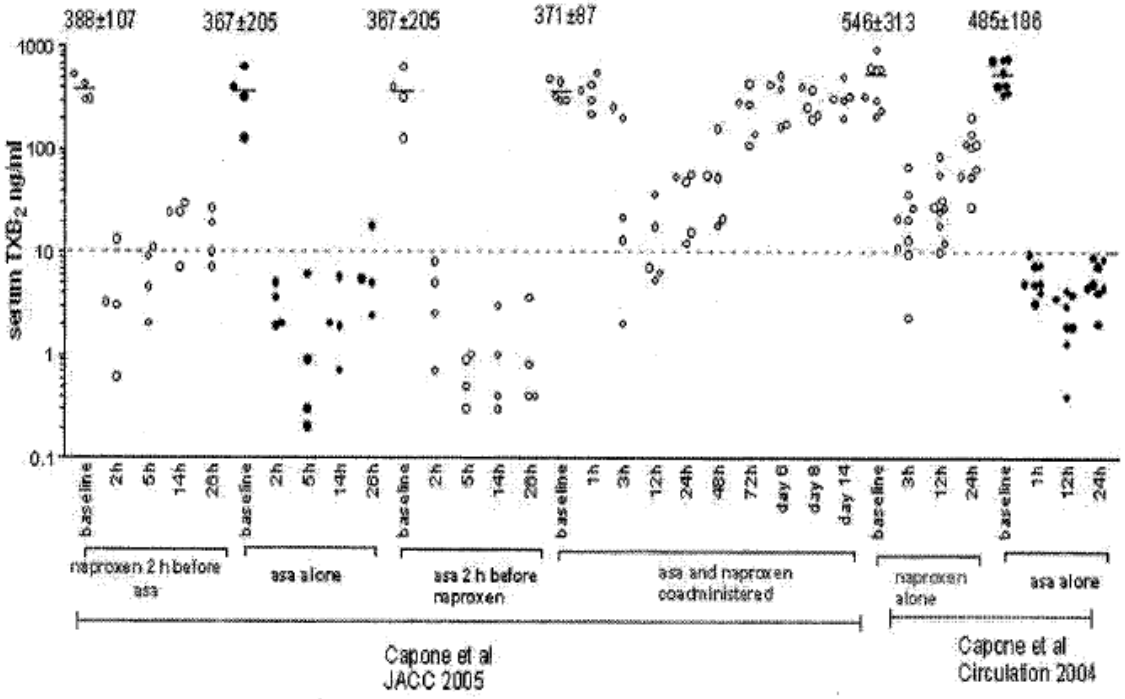
In summary of this review, NAP has intrinsic platelet inhibitory activity as measured by the inhibition of thromboxane B_2 (TXB2) production and subsequent platelet aggregation when used in high split dosing regimens that are typical of the prescription product. However, short intermittent courses of the low dose OTC product may result in NAP washout, leaving unacetylated, activatable platelets in the circulation that could result in negative cardiovascular outcomes. This concern is based on the work of Capone et al. (Table 1) and Patrignani's reanalysis of older Capone studies (Figure 5) as follows:

Table 1. Thromboxane inhibition at time points following final dose after 6 days of dosing with naproxen sodium 220 mg and 440 mg twice daily (from Capone et al., 2007)

Time	% Thromboxane Inhibition ± SD	
	Naproxen sodium 220 mg BID (n=6)	Naproxen sodium 440 mg BID (n=6)
2 h	95.9 ± 5.1	99.2 ± 0.4
5 h	90.8 ± 8.6	98.3 ± 0.5
8 h	88.9 ± 10	96.7 ± 1
12 h	86.6 ± 7.1	92.9 ± 3.1
24 h	69.1 ± 19.9	85.3 ± 5.1

SD= standard deviation, BID=twice daily

Figure 5. Serum TXB2 levels over time compared with drug administered, 100 mg ASA or 500 mg NAP alone, and ASA before or after NAP



Subsequently, Anzellotti et al (Arthritis & Rheumatism, March 2011), demonstrated the potential for an interaction between 100-mg IR QD ASA and 220-mg IR BID NAP in a 3 period cross-over study of 9 healthy subjects. The major findings of this small study include:

- Platelet COX-1 activity ex vivo (reported as the percent of inhibition [% I]), as assessed by the measurement of serum thromboxane B_2 (sTXB2), was decreased at 24 hours (after the first drug was given) when NAP was dosed 2 hours before ASA, but not when ASA was dosed two hours before NAP, as compared to ASA alone (see Figure 1 below from that paper).

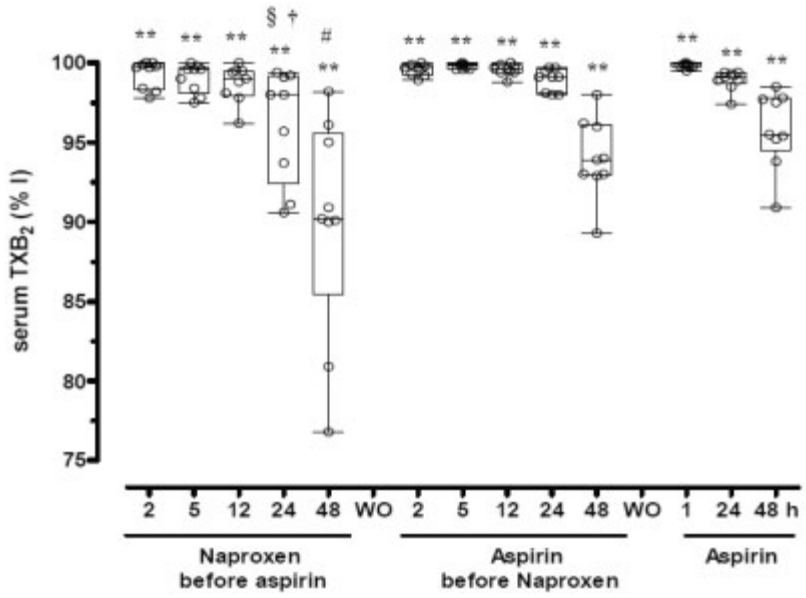


Figure 1. Comparison of the degree and duration of steady-state inhibition of cyclooxygenase 1 (COX-1) activity by administration for 6 days of naproxen sodium (220 mg twice a day) 2 hours before aspirin, naproxen sodium 2 hours after aspirin, or low-dose aspirin alone. Platelet COX-1 activity ex vivo (reported as the percent of inhibition [% I]), as assessed by the measurement of serum thromboxane B_2 (TXB_2), was evaluated in 9 healthy subjects. Data are presented as box plots, where the boxes represent the 25th to 75th percentiles, the lines within the boxes represent the median, and whiskers represent the highest and lowest values. Open symbols represent individual values. At each time point after dosing with the 3 different treatments, serum TXB_2 was significantly reduced compared with predrug values (** = $P = 0.0001$). § = $P = 0.0007$ versus aspirin alone at 24 hours. † = $P = 0.0045$ versus aspirin before naproxen at 24 hours. # = $P = 0.0011$ versus aspirin alone at 48 hours. For this statistical analysis we used mixed-effects model procedures and nonparametric bootstrap resampling technique (35). WO = washout.

- Low-dose aspirin alone caused a significant inhibition of collagen-induced platelet aggregation up to 48 hours after dosing, although heterogeneity of the response was detected. In contrast, collagen-induced platelet aggregation rapidly recovered after the sequential administration of aspirin and naproxen (in both directions; see Figure 2, panel C below from that paper).

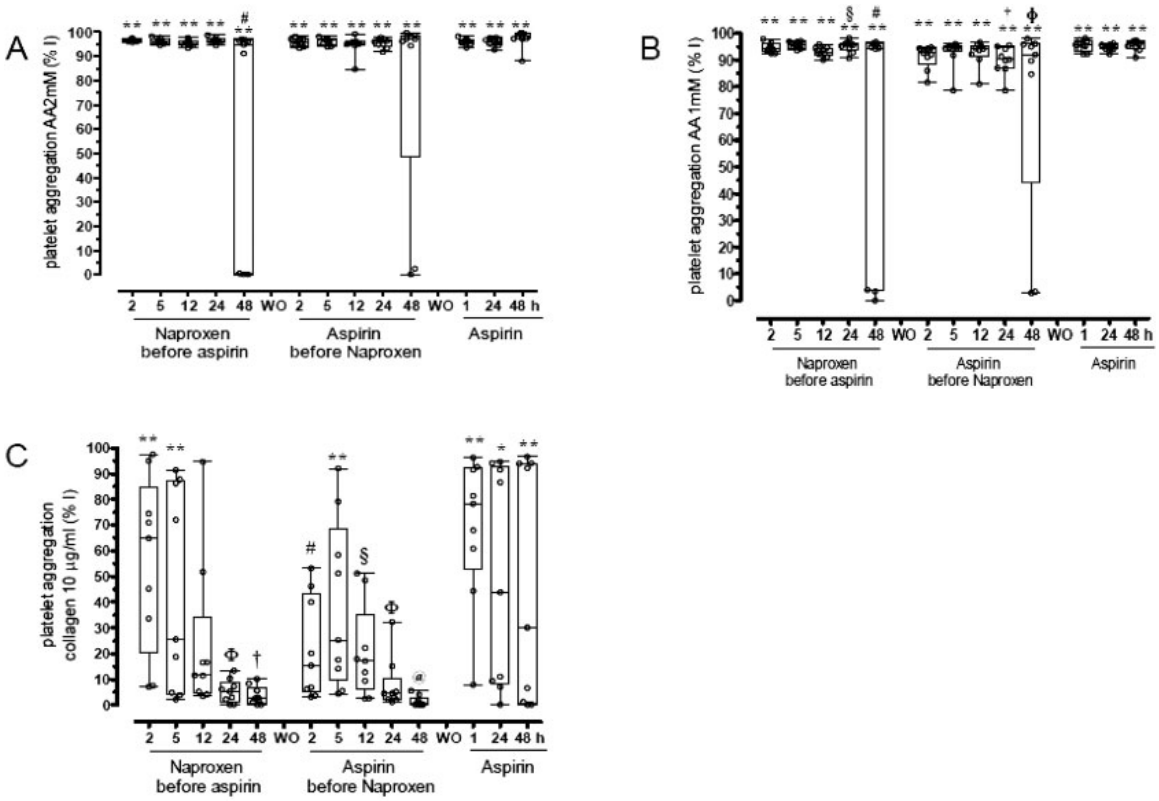


Figure 2. Inhibition of platelet function ex vivo by administration for 6 days of naproxen sodium (220 mg twice a day) 2 hours before aspirin, naproxen sodium 2 hours after aspirin, or low-dose aspirin alone. Platelet aggregation was assessed by measuring the percent of inhibition (% I). Data are presented as box plots, where the boxes represent the 25th to 75th percentiles, the lines within the boxes represent the median, and whiskers represent the highest and lowest values. Open symbols represent individual values. **A,** Platelet aggregation induced by 2 m*M* arachidonic acid (AA). At each time point after dosing with the 3 different treatments, platelet aggregation was significantly reduced compared with predrug values (** = $P = 0.0001$). # = $P = 0.0053$ versus aspirin alone at 48 hours. **B,** Platelet aggregation induced by 1 m*M* AA. At each time point after dosing with the 3 different treatments, platelet aggregation was significantly reduced compared with predrug values (** = $P = 0.0001$). § = $P = 0.0001$ versus aspirin before naproxen at 24 hours. # = $P = 0.016$ versus aspirin alone at 48 hours. † = $P = 0.0003$ versus aspirin alone at 24 hours. Φ = $P = 0.04$ versus aspirin alone at 48 hours. **C,** Platelet aggregation induced by 10 µg/ml collagen. ** = $P = 0.0001$ versus predrug values. Φ = $P = 0.0005$ versus aspirin alone at 24 hours. † = $P = 0.0013$ versus aspirin alone at 48 hours. # = $P = 0.0045$ versus predrug values. § = $P = 0.01$ versus predrug values. @ = $P = 0.0005$ versus aspirin alone at 48 hours. * = $P = 0.0003$ versus predrug values. For this statistical analysis we used mixed-effects model procedures and nonparametric bootstrap resampling technique (35). WO = washout.

Based on this information from Capone et al and Anzellotti et al, DCRP recommended that either NAP be labeled for a potential interaction with ASA, or that a pharmacodynamic study measuring TXB2 inhibition and platelet aggregation be performed, with the following study arms, to rule out this interaction or document its severity and time course:

- Group 1 – ASA and NAP given concomitantly
- Group 2 – NAP 30 min before ASA
- Group 2b – NAP administered 8 – 12 hours before ASA
- Group 3 – ASA alone
- Group 4 – NAP 660 mg ER administered 30 min before ASA.

3. ***Are the findings reported in the attached article, in the context of the existing literature, of clinical relevance?***

Yes. The findings by Schjerning Olsen et al, in the context of the existing literature, are clinically relevant.

Given that opiates and reperfusion therapies are the mainstays for addressing myocardial infarction pain, the argument might be made that NSAID associated CV risk might not be relevant in the post-MI environment. However, there are multiple scenarios where the potential for incremental post-MI CV risk induced by these drugs is of concern. Specifically, recurrent MI can be fatal, or leave a patient with debilitating pump failure and/or arrhythmias, with an increased risk of subsequent sudden cardiac death. Based on the proposed mechanisms of incremental risk (prostanoid imbalance favoring thromboxane-mediated vasoconstriction and platelet aggregation, versus interference with aspirin's antiplatelet activity), recurrent coronary arterial thrombosis following thrombolytic therapy, or stent thrombosis following PCI for MI, are two such scenarios.

If NSAIDs were never used in post-MI patients, this concern would be moot. However, NSAIDs have been used for decades as standard therapy for post-MI pericarditis pain. Furthermore, it is not uncommon for patients with moderate to severe degenerative joint diseases (age related or immune mediated), treated with NSAIDs for DJD pain control, to present with acute myocardial infarctions. In the absence of data to the contrary, it would have to be assumed that resuming or continuing these medications in the immediate post-infarction period would confer the excess risk for CV events that was demonstrated in the observational/retrospective study by Schjerning Olsen et al.

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/s/

PRESTON M DUNNMON
11/02/2011

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11/02/2011

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Assessment of PRECISION protocol, in light of results from a meta-analysis of clinical trial data

Date:	10-17-2013
Reviewer(s):	Andrew D. Mosholder, M.D., M.P.H. Division of Epidemiology II
Team Leader	Elizabeth M. Maloney, M.S., Dr.P.H. Division of Epidemiology II
Division Director	Judy A. Staffa, Ph.D., R.Ph. Division of Epidemiology II
Subject:	PRECISION clinical trial protocol
Drug Name(s):	Celecoxib, naproxen, ibuprofen
Application Type/Number:	IND 48,395 for Celebrex® (celecoxib) Capsules
Serial Number:	1559
Applicant/sponsor:	Pfizer (innovator)
OSE RCM #:	2011-45

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EXECUTIVE SUMMARY

PRECISION is a large, randomized safety trial comparing cardiovascular event rates among patients with high cardiovascular (CV) risk who are randomized to naproxen, ibuprofen, or celecoxib. The sponsor of the study is Pfizer, the manufacturer of celecoxib. Recently available data on nonsteroidal anti-inflammatory drugs (NSAIDs) and CV risks call into question several design features of PRECISION, and also whether it is still reasonable to continue randomization of subjects:

- The analysis will pool 200 mg/day and 400 mg/day dosages of celecoxib, though there is now evidence that these dose levels convey different CV risks.
- Sixty-five percent of the subjects are to be receiving low dose ASA for cardioprotection at baseline. The protocol states that subjects are to take ASA two hours before their study medication, to avoid interference with ASA's antiplatelet activity by ibuprofen and naproxen. If this advice is not followed, subjects receiving ibuprofen or naproxen will have a diminished level of cardioprotection, biasing the trial in favor of celecoxib, which does not interfere with ASA.
- Analyzing ASA users and nonusers in separate subgroups will be necessary to evaluate this potential interaction, but the trial is not statistically powered for these subgroups.
- The ITT analysis is likely to be compromised by misclassification of exposures, to the extent that subjects discontinue treatment or switch drugs. The statistical power for the more easily interpreted modified-ITT analysis will be lower than for the main ITT analysis.
- In general, any factor that biases the trial towards a null result will support the sponsor's goal of declaring celecoxib non-inferior to the other treatments.

A second consideration is whether the results of PRECISION are still necessary to answer the research question. Results from the Oxford University Coxib and traditional NSAID Trialists' Collaboration (CNT) meta-analysis of clinical trial data showed that the CV risk of naproxen is less than that of ibuprofen or celecoxib, in a sample with a minority of ASA users, at doses similar to those in PRECISION. This finding of lower CV risk with naproxen is supported by results from a number of observational studies.

A third consideration is whether the trial can still be considered reasonably safe for the participants. It is generally considered unreasonable from the standpoint of subject welfare to randomize subjects if one of the treatments has been shown to be safer with respect to serious or fatal outcomes. With the recent Oxford CNT analysis there is now credible evidence from randomized trial data that naproxen carries the lower CV risk.

According to 21CFR312.42, grounds for a clinical hold exist when, "Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury." Another basis for a clinical hold under 21CFR312.42 may apply when "The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives."

Sufficient grounds for a clinical hold exist for the reasons stated above. Randomization of subjects is no longer reasonable because of the recently delineated difference in CV risk among the treatments, and significant difficulties with interpretation of the results will compromise the trial's ability to meet its scientific objective.

If a clinical hold is not imposed, subjects should be reconsented so that they can be informed of the findings of the Oxford CNT meta-analysis regarding the PRECISION study drugs, and can

have the option of withdrawing. Subjects and investigators should also be reminded of the instructions for taking low dose ASA.

1 INTRODUCTION

DEPI II has conducted two recent reviews on the topic of ischemic cardiovascular (CV) events with use of nonsteroidal anti-inflammatory drugs (NSAIDs). The first review covered five years of literature articles, primarily describing observational studies of CV events associated with NSAID use. The second review described the recent clinical trial meta-analysis by the Coxib and traditional NSAID Trialists' Collaboration (CNT) of Oxford University. In the course of these reviews, data emerged which are relevant to the design and conduct of an ongoing large international trial comparing the rate of CV events with celecoxib, naproxen and ibuprofen. This trial is known as the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial. As PRECISION was initiated in October 2006, much of the information in the DEPI II reviews was not available when PRECISION was designed. Accordingly, the purpose of this review is to highlight recent data that have implications for the conduct of PRECISION.

2 REVIEW METHODS AND MATERIALS

This review was conducted according to customary epidemiological standards and no special methods were applied. The following materials provided information for this review.

- Protocol for PRECISION (version submitted 8-12-2012)
- PRECISION study summary at www.clinicaltrials.gov[1]
- Article in American Heart Journal by the PRECISION investigators[2]

3 REVIEW RESULTS

The following is a summary of the study design, to provide context for the discussion that follows.

3.1 DESIGN OF PRECISION

Purpose: The purpose of PRECISION is to compare the CV safety of celecoxib to that of naproxen and ibuprofen in arthritis patients at high risk of CV events.

Location: U.S. and international

Design: This is a randomized, double blind, parallel group, three-arm, active controlled study. Patients with osteoarthritis (OA) or rheumatoid arthritis (RA) and CV disease or CV risk factors will be randomized 1:1:1 to celecoxib 200 mg/day, ibuprofen 1800 mg/day, or naproxen 750 mg/day. Randomization will be stratified according to center, a diagnosis of OA versus RA, and use of cardioprotective aspirin (ASA) at baseline. Based on symptoms, investigators may increase dosages to celecoxib 400 mg/day, ibuprofen 2400 mg/day, or naproxen 1000 mg/day. However, in countries where the maximum approved dose for celecoxib in OA is 200 mg/day, 200 mg/day will be the upper limit for OA patients (but not RA patients) randomized to celecoxib. All subjects will receive esomeprazole 20 or 40 mg/day for gastric protection (or another gastroprotective compound if the subject cannot take esomeprazole). The study duration will be 42 months, with subjects to be followed for a minimum of 18 months. Study visits will occur at months 1, 2, 4, 8, 12, and then every 6 months thereafter. Subjects on low dose (no more than 325 mg/day) ASA for cardioprotection may continue it, and investigators are encouraged to recommend initiation of cardioprotective ASA when appropriate for subjects not already

receiving it. The protocol states that ASA "should be administered two hours before the study drug to minimize the potential for an interaction that may reduce the antiplatelet effects of aspirin." The protocol states that "all efforts will be made to keep subjects in the study and on the assigned study treatment…"

Subjects: Participants will be adults with OA or RA requiring chronic NSAID use for arthritis signs and symptoms. Subjects will have elevated CV risk as shown by a history of coronary artery disease, other occlusive arterial disease (including stroke, transient ischemic attack, peripheral artery disease, arterial surgery or angioplasty), diabetes, or at least two of several atherosclerosis risk factors. Subjects will be excluded if they have had a myocardial infarction (MI), stroke, coronary artery bypass surgery, or unstable angina within 3 months. Other exclusionary criteria include significant congestive heart failure, peptic ulcer disease, unstable arrhythmia, active malignancy, and unstable hypertension. Enrollment of non-ASA users will be increased if needed to ensure that at least 35% of the sample is not taking cardioprotective ASA. The targeted sample size is approximately 20,000, but the precise sample size will be determined by a minimum number of study endpoint events.

Endpoints: The study outcome events will be adjudicated by experts blinded to treatment. The primary outcome will be the so-called Antiplatelet Trialists' Collaboration (APTC) endpoint (a composit of CV death, including hemorrhagic death, nonfatal MI, and nonfatal stroke). Secondary endpoints will include the Major Adverse Cardiovascular Events (MACE) (APTC events plus hospitalization for unstable angina or transient ischemic attack, or revascularization). Clinically significant gastrointestinal events (CSGIEs) will also be a secondary outcome and these include GI hemorrhage, GI perforation, and symptomatic peptic ulcer.

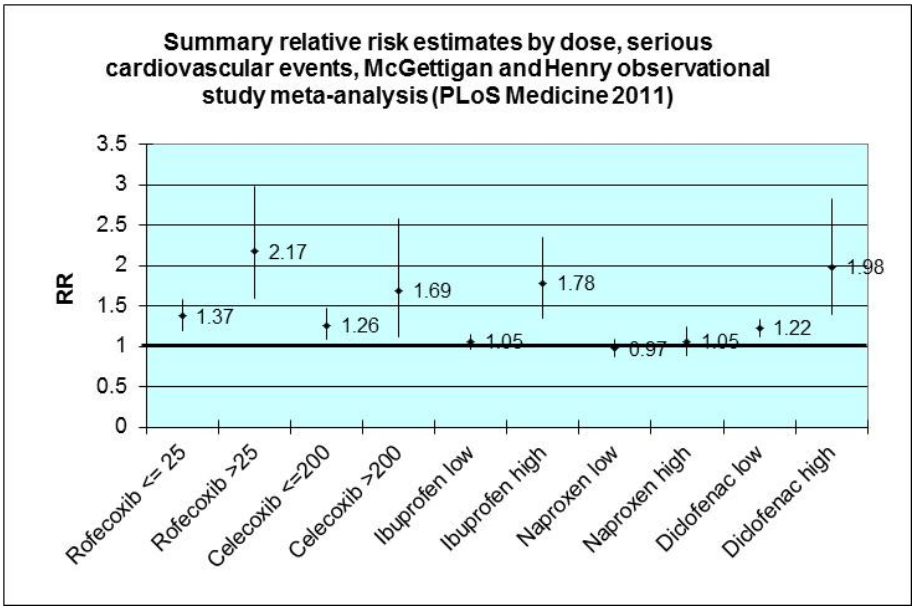
Analysis: The primary analysis will employ a Cox proportional hazards model adjusted for region, OA versus RA diagnosis, and ASA use at baseline to calculate three hazard ratios (HRs) for the primary endpoint (celecoxib:naproxen, ibuprofen:naproxen, celecoxib:ibuprofen). The primary analysis will use the intent-to-treat (ITT) population censored at 30 months (to exclude excessive unexposed person-time). A modified intent-to-treat (MITT) analysis will follow subjects to a maximum of 42 months and will censor subjects 30 days after study drug discontinuation. A compound will be declared non-inferior to the comparator if both the ITT and MITT HRs are less than or equal to 1.12, with upper one-sided 97.5% confidence limits less than 1.33 for the ITT HR and less than 1.40 for the MITT HR.

3.2 ISSUES RAISED BY RECENT FINDINGS

3.2.1 Need to Account for Dose Response

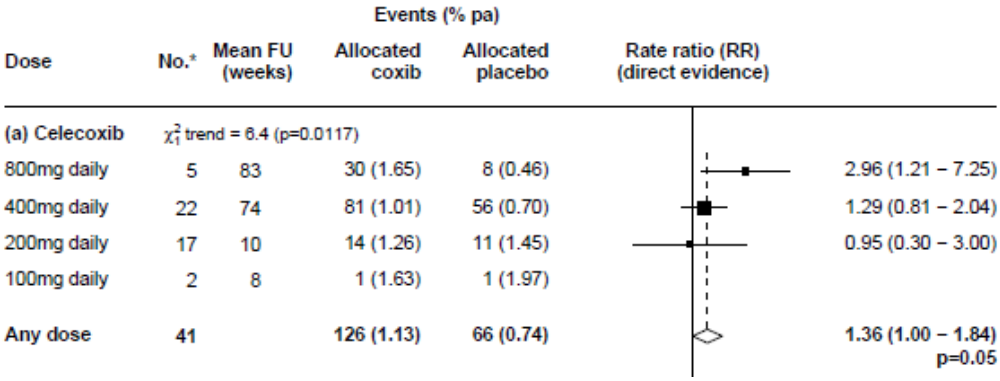
Recent observational studies have indicated a dose-response relationship for thrombotic cardiovascular events and NSAID use. In the meta-analysis of observational studies by McGettigan and Henry,[3] a dose-response was observed for several compounds, excepting naproxen, which was risk neutral at both high and low dosages. The following graph depicts the results of McGettigan and Henry, and shows summary risk estimates from observational studies that analyzed high and low doses separately.

Figure 1.



Of perhaps greater relevance to PRECISION is the examination of dose-response in clinical trials of celecoxib from a recent meta-analysis of NSAID clinical trials by the Oxford University-based Coxib and traditional NSAID Trialists' (CNT) Collaboration.[4] Analyzing fixed doses of 800, 400, 200 and 100 mg/day, they found a statistically significant dose-related trend in the relative risk for major cardiovascular events with celecoxib versus placebo (p-value for dose trend = 0.0117). The following graph is reproduced from the CNT publication and shows the dose-specific rate ratios for major vascular events relative to placebo.

Figure 2, reproduced from Coxib and traditional NSAID Trialists' (CNT) Collaboration.



Only 400 and 200 mg/day dosages of celecoxib will be administered in PRECISION, but these dose levels will be pooled into a single risk estimate for comparison to the other drugs. The dose ranges for naproxen (750-1000 mg/day) and ibuprofen (1800-2400 mg/day) span only a 33% difference, while the dose range for celecoxib spans a 100% difference, thereby complicating interpretation of a single risk estimate for the compound. A dose subgroup analysis could be performed for celecoxib, and would seem warranted based on the findings shown above, but would have reduced statistical power.

3.2.2 Magnitude of cardiovascular risk in vulnerable populations

Since the design and initiation of PRECISION, observational studies in the Danish national healthcare database have examined the magnitude of the cardiovascular risk in absolute terms with NSAID use by high CV risk patients. The following table shows results from a cohort study of 97,698 patients with a past MI.[5] Compared to no use of an NSAID, there was one excess cardiovascular death for every 8 person-years of celecoxib use, 11 person years of ibuprofen use, and 16 person years of naproxen use, at dose levels at or below those in PRECISION. Naproxen showed the lowest absolute risk of the three compounds of interest. These results illustrate the importance of minimizing NSAID use in post-MI patients, but these patients are an important subgroup of the PRECISION sample, and the trial is designed to maintain such subjects on relatively higher NSAID doses for extended periods.

Table 1. Absolute risk of cardiovascular death among post-MI patients administered NSAIDs, Danish national health database (Olsen et al., 2013)

Compound & mg/day	Person-years of exposure producing one excess cardiovascular death (versus no use) (unadjusted)
Celecoxib ≥200	8 (6-11)
Ibuprofen ≥1200	11 (10-12)
Naproxen ≥500	16 (10-38)

Against this concern is the observation that the numbers of cardiovascular events in PRECISION have been fewer than predicted, requiring a protocol amendment to reduce the targeted statistical power. Speculatively, use of low dose ASA may be contributing to the lower-than-expected rate of cardiovascular events. The role of low dose ASA will be discussed in the next section.

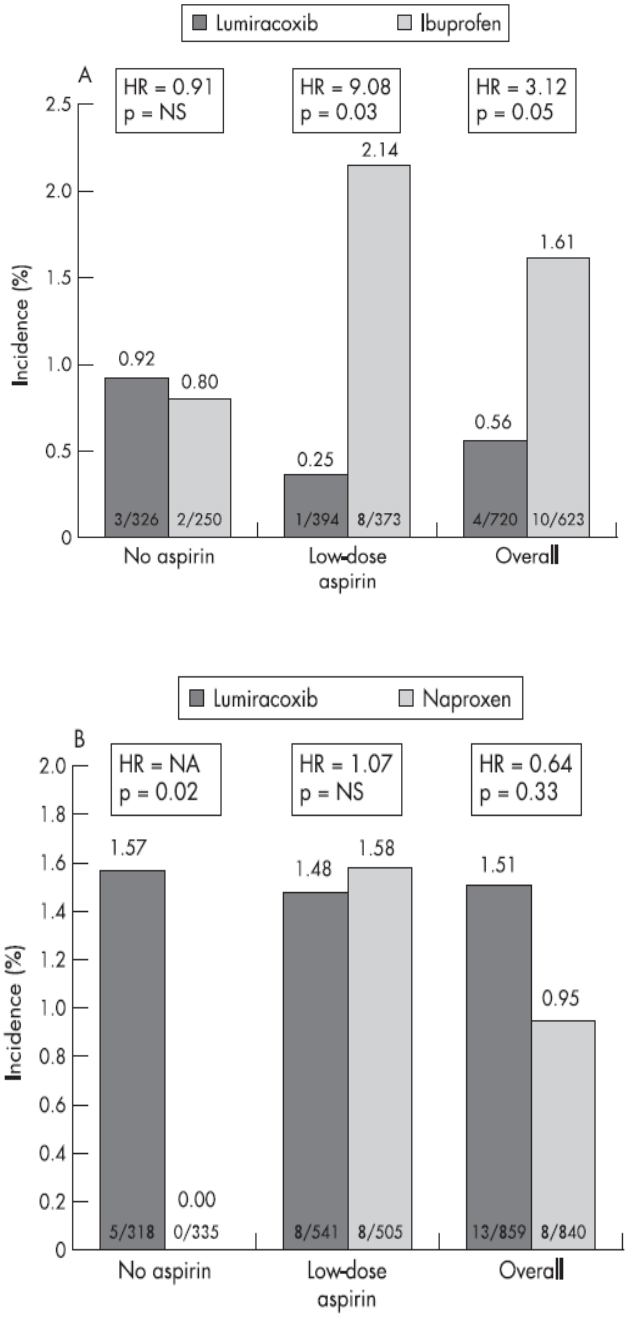
3.2.3 Difficulties presented by concomitant ASA use

Naproxen and ibuprofen, but not celecoxib, are predicted to impair cardioprotection by low dose ASA, via competition for the COX-1 active site (which celecoxib does not block). Interference with ASA's antiplatelet action by nonselective NSAIDs, but not COX-2 selective compounds, has been shown experimentally.[6] Furthermore, in an observational study, MacDonald and Wei found that concomitant ibuprofen elevated cardiovascular mortality among users of low-dose ASA.[7] Additional empirical evidence that this interaction can affect the incidence of cardiovascular outcomes comes from a subgroup analysis of high cardiovascular risk patients in a large clinical trial of lumiracoxib.[8] The so-called TARGET trial included 18,325 subjects, randomized (in separate randomization procedures) to ibuprofen versus lumiracoxib or naproxen versus lumiracoxib. The graph below, reproduced from the paper by Farkouh et al., displays the cardiovascular event incidence in high CV risk patients using or not using ASA.

In the absence of ASA, the incidence of cardiovascular events was similar for lumiracoxib and ibuprofen, and was statistically significantly higher for lumiracoxib than for naproxen. In the presence of ASA, the CV event incidence was statistically significantly higher for ibuprofen versus lumiracoxib, and was similar between lumiracoxib and naproxen. Such a pattern would be consistent with interference with ASA cardioprotection by ibuprofen and naproxen. (There is an unexplained inconsistency in the lumiracoxib event rates compared across the sub-studies,

perhaps owing to the sparseness of the data.) Nonetheless, it can be seen that the pooled event rates (labeled "Overall") do not fully characterize the pattern of cardiovascular events.

Figure 3 (reproduced from Farkouh et al.)



In PRECISION, however, the main analysis will pool ASA users and nonusers, though it can be seen from the example above that a pooled analysis may not adequately show the pattern of cardiovascular risk when there is interference with ASA's antiplatelet effects. Adjusting for ASA use in the Cox Proportional Hazards model, as is planned, would be an appropriate strategy if

ASA use was a simple confounder, but cannot account for an interaction between the study drug and ASA altering the event rate.

The PRECISION protocol specifies a subgroup analysis by concomitant low dose ASA use, which is the appropriate strategy to examine the possible interaction, as in the lumiracoxib example shown. However, given that there are already concerns about statistical power, these subgroups may not have the statistical power desired; the targeted composition for the sample will be 35% not receiving ASA at baseline and 65% receiving ASA at baseline.

Another issue is whether low dose ASA use during the treatment phase of the trial can be analyzed as a time-dependent variable, which would be warranted based on the clinical pharmacology (i.e., we would not expect the effects of ASA to persist for the entire trial if the subject discontinued ASA after baseline). If ASA use is only being documented at baseline, that will be a significant limitation of the analysis.

The protocol states that subjects should be instructed to take low dose ASA two hours before their randomized study drug. This advice, if followed carefully by the subjects, should be sufficient to mitigate the potential interference of ASA's antiplatelet effects by ibuprofen or naproxen (as noted, celecoxib is not expected to generate such interference). Accordingly, the trial should yield meaningful data on the CV risks of the three compounds given either with or without ASA (leaving aside the issue of statistical power for the subgroup analyses). However, it will be critical to assess how strongly the investigators emphasized the advice about separating ASA from the study drug, and how well the subjects followed it during the trial, or there will be serious questions about the interpretability of the results. Specifically, if ASA is taken improperly with ibuprofen or naproxen, loss of ASA antiplatelet activity could result in more CV events. Celecoxib-treated subjects would not be vulnerable to such an interaction, for the reasons noted. The result would be bias favoring celecoxib. The only protection against this bias would be strict adherence on the part of the subjects to the two-hour separation. This interaction would not affect the ASA non-user subgroup, but that will be only 35% of the sample and will have limited statistical power.

3.2.4 Inability to substantiate clinical equipoise with currently available data

Uncertainty with respect to the superiority of one treatment over another in a controlled trial is a prerequisite for randomization of patients to be appropriate; as stated by Joffee and colleagues, "…most authors agree that when the better treatment can be identified with reasonable confidence, it is both unethical and scientifically unnecessary to conduct the trial."[9] Consistent with this principle, the protocol for PRECISION states (pg. 21), "…a key unanswered question is whether there are meaningful CV risk differences among commonly used agents such as celecoxib, naproxen, or ibuprofen…" However, since the PRECISION protocol was drafted in 2006, new information has become available that addresses this previously unanswered question.

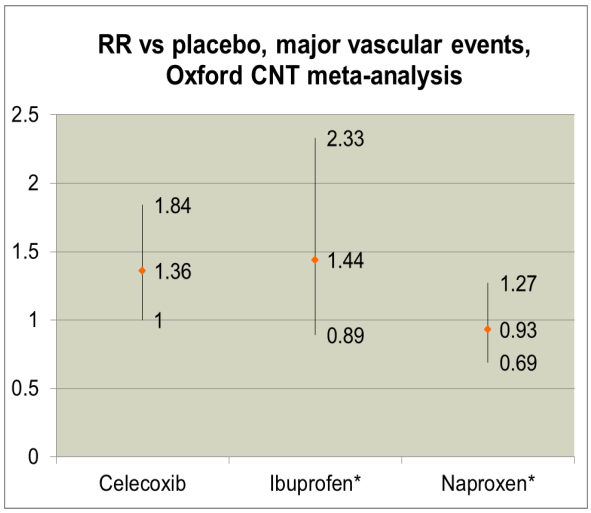
Figure 1 above shows the results of the 2011 meta-analysis of observational studies by McGettigan and Henry. Higher doses of celecoxib and ibuprofen were associated with greater CV risk than either high or low dose naproxen.

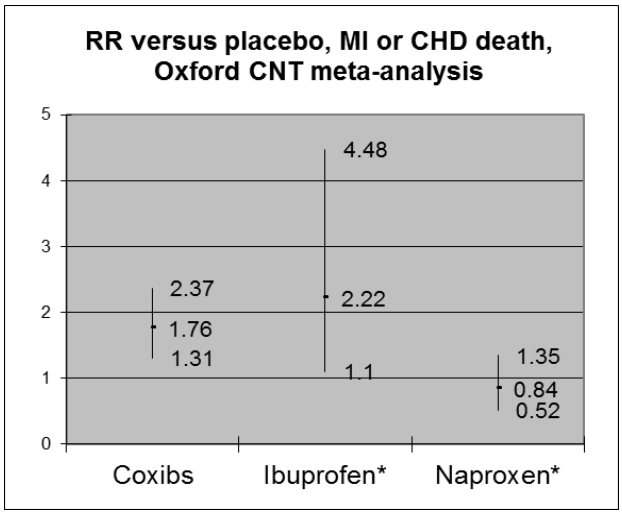
Furthermore, as noted above, the Coxib and traditional NSAID Trialists' (CNT) Collaboration evaluated the CV risk of naproxen, ibuprofen and coxibs (including celecoxib) in randomized controlled trials, in a network meta-analysis. Incidence rate ratios were determined with placebo as the reference. The modal daily doses in the clinical trial data analyzed were 400, 2400, and 1000 mg for celecoxib, ibuprofen and naproxen, respectively (i.e., dosages comparable to those in PRECISION). The graph below displays the results for major vascular events with the three compounds under study in PRECISION in Figure 4. Figure 5 displays results on a secondary

cardiovascular outcome, MI or death from coronary heart disease, albeit for coxibs as a group (data on this secondary outcome for celecoxib separately was not provided in the publication).

Figures 4 and 5. Results from Oxford CNT meta-analysis.

* Rate ratio versus placebo calculated using indirect comparison





Thus, the CNT meta-analysis has provided evidence from randomized controlled trials that naproxen use has a lower CV risk than either ibuprofen or celecoxib, at dosages in a range relevant to PRECISION. With respect to concomitant ASA use, 20% of the CNT meta-analysis subjects were receiving ASA at baseline, so that ASA use is less of a complication in the analysis than it will be in PRECISION, with 65% of PRECISION subjects using ASA at baseline. In light of these results from randomized controlled trial data, reinforced by results from recent observational studies, it is difficult to argue that substantial uncertainty still exists regarding the relative CV risks of the drugs being studied in PRECISION. Accordingly, randomization between celecoxib, naproxen and ibuprofen for a CV outcome study is not supported by the currently available data.

3.2.5 Lack of negative control

PRECISION is an active-comparator study without a placebo (or other negative) control arm. Nonetheless, the goal is to establish non-inferiority of one active treatment over another regarding

CV event rates. This requires an assumption of "assay sensitivity,"[10] in other words, that the trial can detect an increase in CV risk over baseline; without a negative control treatment arm, this cannot be shown, and must be assumed. A finding of non-inferiority for CV risk between two arms in PRECISION could thus be explained by the two treatments having truly equal CV risk, or by a failure of PRECISION to measure CV risk adequately. Variance ("noise") in the trial data will bias the trial towards the null, thereby increasing the likelihood of finding similar CV event rates, and declaring celecoxib non-inferior to the other active treatments. Accordingly, factors that bias the trial towards a null result, such as misdiagnosis of CV events, failure to completely ascertain CV events, or failure to consider an interaction effect of ASA, tend to support rather than impede demonstration of non-inferiority for celecoxib.

3.2.6 Misclassification of exposure with Intent-to-Treat analysis

The protocol stipulates that the primary analysis will be the ITT analysis, in which patients are followed up according to their randomized treatment regardless of how long they actually continue that assigned treatment, until they are censored at 30 months. In a long term trial of this nature, a sizeable number of subjects are expected to discontinue their assigned treatment, and some may even switch to open label use of a different study drug. This is likely to result in misclassification of exposure, in which person time with no drug or a different drug is pooled with person time for the original assigned treatment. To the extent that there are differences in CV risks between drugs, this practice will dilute such differences and thus bias the results toward the null, which in this case is a finding of non-inferiority. The protocol also specifies a modified-ITT (MITT) analysis, in which subjects are censored 30 days after they discontinue their assigned treatment. This MITT analysis should have much greater inferential value than the main ITT analysis, for the reasons stated, though it is a secondary analysis, and will have lower statistical power.

4 DISCUSSION

The design of PRECISION features many strengths; chief among these are the randomization to treatment, large sample size, direct comparison of nonselective NSAIDs to a COX-2 inhibitor, and blinded adjudication of study endpoints. However, the trial was initiated in 2006, prior to the availability of an extensive amount of data on CV risks of NSAIDs, including the Oxford CNT clinical trial meta-analysis. In view of the more recent findings on the topic, it is prudent to consider whether PRECISION is truly capable of providing a meaningful answer to the research question, and whether results from PRECISION are still necessary to address the question. The most recent estimate is that the trial still has three years to go until completion, which provides a practical reason to consider these issues now.

As discussed above, there are several reasons that PRECISION is unlikely to provide readily interpretable data on the CV risks of the three drugs being studied.

- The analysis will pool 200 mg/day and 400 mg/day dosages of celecoxib. There is now evidence that these dose levels convey different CV risks, but dose subgroup analyses are likely to be underpowered.
- Sixty-five percent of the subjects are to be receiving low dose ASA for cardioprotection at baseline. The protocol states that subjects are to take ASA two hours before their study medication, to avoid interference with ASA's antiplatelet activity by ibuprofen and naproxen. If this advice is not followed, subjects receiving ibuprofen or naproxen will have a diminished level of cardioprotection, biasing the trial in favor of celecoxib, which does not interfere with ASA.

- Analyzing ASA users and nonusers in separate subgroups will be necessary to evaluate this potential interaction, but the trial is not statistically powered for these subgroups. In addition, data will be needed on whether subjects initiated or discontinued ASA during the trial, not just whether they were receiving ASA at randomization.
- To interpret data from the subgroup of ASA users properly, data will also be needed regarding how vigorously, and how successfully, those subjects were encouraged to take ASA two hours prior to their study medication.
- The ITT analysis is likely to be compromised by misclassification of exposures, to the extent that subjects discontinue treatment or switch drugs. The statistical power for the more easily interpreted modified-ITT analysis will be lower than for the main ITT analysis.
- In general, any factor that biases the trial towards a null result will support the sponsor's goal of declaring celecoxib non-inferior to the other treatments.

A second consideration is whether the results of PRECISION are still necessary to answer the research question. As noted, results from the CNT meta-analysis of clinical trial data showed that the CV risk of naproxen is less than that of ibuprofen or celecoxib, at doses similar to those in PRECISION, in a sample with a minority of ASA users,. This finding of lower CV risk with naproxen is supported by results from a number of observational studies.

A third consideration is whether the trial can still be considered reasonably safe for the participants. The Danish results showing the high absolute risk of CV death in post-MI patients administered NSAIDs (with numbers-needed-to-harm in tens of person years for fatal CV events) argue against long-term NSAID use by high CV risk patients, yet that is exactly what is encouraged when a high-risk subject enrolls in PRECISION. Against this concern is the lower-than-expected event rate reported thus far in the trial. Moreover, it is generally considered unreasonable from the standpoint of subject welfare to randomize subjects if one of the treatments has been shown to be safer with respect to serious or fatal outcomes. With the recent Oxford CNT analysis, however, there is now credible evidence from randomized trial data that naproxen carries the lower CV risk.

5 CONCLUSION

According to 21CFR312.42, grounds for a clinical hold exist when, "Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury." Such an unreasonable risk can exist in a randomized trial when there is no longer equipoise with respect to the chance of serious or fatal outcomes. While equipoise with respect to CV risk was present several years ago when PRECISION was initiated, now that the results of the Oxford CNT meta-analysis are available, there is credible evidence for superior CV safety of one particular treatment arm (naproxen).

Another basis for a clinical hold under 21CFR312.42 may apply when "The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives." The features of PRECISION discussed above make it likely that the results will be quite difficult to interpret properly with respect to the question of which study treatment has a better CV safety profile. It could be argued that PRECISION will provide data on the CV safety of NSAIDs combined with ASA, since most subjects will be receiving ASA, but to interpret those data properly it must be known whether subjects were instructed to take ASA with an adequate separation of time before their study drug, and even so that subgroup will have limited statistical power.

6 RECOMMENDATIONS

Sufficient grounds for a clinical hold exist for the reasons stated above. Randomization of subjects is no longer reasonable because of the recently delineated difference in CV risk among the treatments, and significant difficulties with interpretation of the results will compromise the trial's ability to meet its scientific objective.

If a clinical hold is not imposed, subjects should be reconsented so that they can be informed of the findings of the Oxford CNT meta-analysis regarding the PRECISION study drugs, and can have the option of withdrawing. Subjects and investigators should also be reminded of the instructions for taking low dose ASA.

7 REFERENCES

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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10/17/2013

ELIZABETH M MALONEY
10/18/2013

JUDY A STAFFA
10/18/2013

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Memorandum to File

DATE:	November 1, 2013
TO:	NDA 20-998; IND 48,395 Celebrex (celecoxib)
FROM:	Judith A. Racoosin, MD, MPH, Deputy Director for Safety, DAAAP
THROUGH:	Bob A. Rappaport, M.D., Director, DAAAP Curtis J. Rosebraugh, MD, MPH, Director, Office of Drug Evaluation 2
RE:	Rationale for allowing the PRECISION trial to continue

Dr. Andy Mosholder, an epidemiology reviewer in Division of Epidemiology 2 (DEPI 2), has been the primary reviewer of the epidemiological studies and meta-analyses addressing the association between NSAIDs and cardiovascular (CV) disease risk. Most recently, he completed a review of a published meta-analysis[1] of 639 randomized controlled trials (RCTs) of NSAIDs that was conducted by the Oxford University Coxib and traditional NSAID Trialists' Collaboration (CNT) to assess the risk of major CV events and gastrointestinal bleeding adverse events. Based on his conclusion from that review, that naproxen does not carry the CV risk that the other NSAIDs carry, he has raised concerns that PRECISION, the postmarket required RCT examining CV risk of celecoxib, using the active controls naproxen and ibuprofen, no longer has equipoise, and has recommended that it be stopped.

[1] Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382: 769-79.

PRECISION, or "Prospective Randomized Evaluation Of Celecoxib Integrated Safety Vs. Ibuprofen Or Naproxen" was initiated in 2006 after the sponsor agreed to conduct the PMC requested by DAAAP. It is a randomized, double-blind, active-controlled, parallel-group study of CV safety in osteoarthritis or rheumatoid arthritis patients with or at high risk for CV disease comparing celecoxib with naproxen and ibuprofen. As summarized on ClinicalTrials.gov, the trial is intended to "answer the question of overall benefit: risk of celecoxib when compared to [the] two most commonly prescribe[d] traditional (non-selective) non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of arthritis pain. For this purpose, patients with osteoarthritis or rheumatoid arthritis with or at risk of developing CV disease will be recruited. The CV, gastrointestinal and renal safety and symptomatic benefit in each treatment group will be assessed accordingly."

Below I will list the main concerns Dr. Mosholder has raised, followed by DAAAP's considerations. Dr. Mosholder's rationale is directly quoted from the executive summary of his review. His concerns fall into two main areas: 1) the ability for the trial as designed to answer the question being studied; 2) that there is no longer equipoise for continuing the trial, now that the Oxford meta-analysis has demonstrated that naproxen has no increased risk of CV adverse events compared to the other marketed NSAIDs, and because equipoise is no longer there, that it is unsafe to continue to randomize patients.

I will address the second concern first, as that is more impactful regarding continuation of the trial. Dr. Mosholder summarized his concerns about equipoise and the safety of randomizing patients as follows:

> A second consideration is whether the results of PRECISION are still necessary to answer the research question. Results from the Oxford University Coxib and traditional NSAID Trialists' Collaboration (CNT) meta-analysis of clinical trial data showed that the CV risk of naproxen is less than that of ibuprofen or celecoxib, in a sample with a minority of ASA users, at doses similar to those in PRECISION. This finding of lower CV risk with naproxen is supported by results from a number of observational studies.
>
> A third consideration is whether the trial can still be considered reasonably safe for the participants. It is generally considered unreasonable from the standpoint of subject welfare to randomize subjects if one of the treatments has been shown to be safer with respect to serious or fatal outcomes. With the recent Oxford CNT analysis there is now credible evidence from randomized trial data that naproxen carries the lower CV risk. According to 21CFR312.42, grounds for a clinical hold exist when, "Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury." Another basis for a clinical hold under 21CFR312.42 may apply when "The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives." Sufficient grounds for a clinical hold exist for the reasons stated above. Randomization of subjects is no longer reasonable because of the recently delineated difference in CV risk among the treatments, and significant difficulties with interpretation of the results will compromise the trial's ability to meet its scientific objective.

Dr. Mosholder's conclusions are based on the premise that the results of a large meta-analysis of randomized controlled trials are enough to convince FDA that we have the "final" answer to the question or have established the "truth". Over time, research and experience have demonstrated that the results of a large meta-analysis of clinical trials do not always produce an answer that ultimately is considered to be the truth. Regarding discrepancies between meta-analyses and subsequent large randomized, controlled trials, an important early recognition of this was a study authored by LeLorier et al[2]. They compared 12 randomized trials to 19 meta-analyses of the same questions. If a later randomized trial had not been performed, the meta-analysis (which they considered to be 'truth') would have led to adoption of an ineffective treatment in 32% of cases and rejection of useful treatment in 33%.

Two specific examples where discrepancies have been noted are the Women's Health Initiative (WHI) study and the tiotropium experience. Regarding the WHI, it is helpful to recall that it was a very controversial trial at the time. Female replacement hormones have a positive effect on all lipid parameters, so there was theoretical plausibility that they did good things regarding heart disease prevention, and all the meta-analyses and observational studies at the time were favorable. The trial itself was delayed as there was great argument over whether it was ethical to conduct because many felt that the answer was already known. Ultimately, the randomized trial demonstrated that estrogen plus progestin resulted in an increased risk of heart attacks, strokes, and blood clots. Estrogen alone increased the risk of strokes and blood clots and is no longer recommended for heart disease prevention.

For tiotropium, a meta-analysis was published by Singh[3] identifying stroke, MI, and death as concerns for a formulation-device marketed in the US. The sponsor, Boehringer Ingelheim (BI), undertook an internal meta-analysis identifying stroke as a concern. A different formulation-device available overseas had a meta-analysis demonstrating an increased risk of death from cardiovascular causes. UPLIFT[4] (Understanding Potential Long-Term Impacts on Function with Tiotropium) was a large randomized controlled trial of the tiotropium "handihaler" that was under way around the time that the meta-analyses were published, and it did not identify an increased risk for the cardiovascular outcomes. This issue was taken to an Advisory Committee for discussion in 2009, and the panel overwhelming said that UPLIFT addressed the potential

[2] LeLorier J, Gregoire G, Benhaddad A, et al. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. NEJM 1997; 337:536-542.

[3] Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA 2008;300: 1439-50. [Erratum, JAMA 2009;301:1227-30.]

[4] Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. NEJM 2008;359: 1543-54.

safety signals. Recently, BI has concluded another large non-inferiority safety trial comparing the two different formulation-device combinations that revealed that the foreign formulation-device was non-inferior for cardiovascular safety. This was briefly discussed at a recent Advisory Committee meeting, and panel members felt this data eliminated the concern with the foreign formulation/device (although it was not the topic of the meeting, it came up and it was discussed).

Finally, there is the example of rosiglitazone. The large randomized open-label trial "Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD)[5]" has disparate results from the meta-analyses that have been conducted[6]. Following readjudication of the RECORD outcomes demonstrating a difference in outcomes from the meta-analyses (discussed at an advisory committee meeting in June 2013), there has been criticism of the Agency by some in the academic community (and as discussed at the Advisory Committee meeting[7]) for putting the TIDE (Thiazolidinedione Intervention With Vitamin D Evaluation) trial on hold, noting that, had the trial been permitted to proceed, FDA would have had a definitive answer about the safety of rosiglitazone by now[8]. The results of the readjudication of RECORD have led CDER to revisit the REMS and labeling and make substantial changes loosening prescribing requirements.

Given these examples of discrepancies between the results of meta-analyses and large clinical trials from the literature and recent CDER experience, DAAAP believes that there is reason to continue with the PRECISION trial. Furthermore, the PRECISION trial has a data safety monitoring board that is regularly evaluating the pattern of occurrence of study endpoints to determine if the stopping rules have been met. DAAAP has not received any communications from Pfizer (sponsor of celecoxib) that such a point has been reached.

Regarding the concerns about study design and study conduct, Dr. Mosholder has articulated these concerns:

- The analysis will pool 200 mg/day and 400 mg/day dosages of celecoxib, though there is now evidence that these dose levels convey different CV risks.

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[5] Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. The Lancet 2009; 373: 2125-2135.

[6] FDA meta-analyses were conducted and discussed at advisory committee meetings in 2007 and 2010.

[7] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM369180.pdf

[8] Hiatt WR, Kaul S, Smith RJ. The cardiovascular safety of diabetes drugs- Insights from the Rosiglitazone Experience. NEJM 2013; 369: 1285-6.

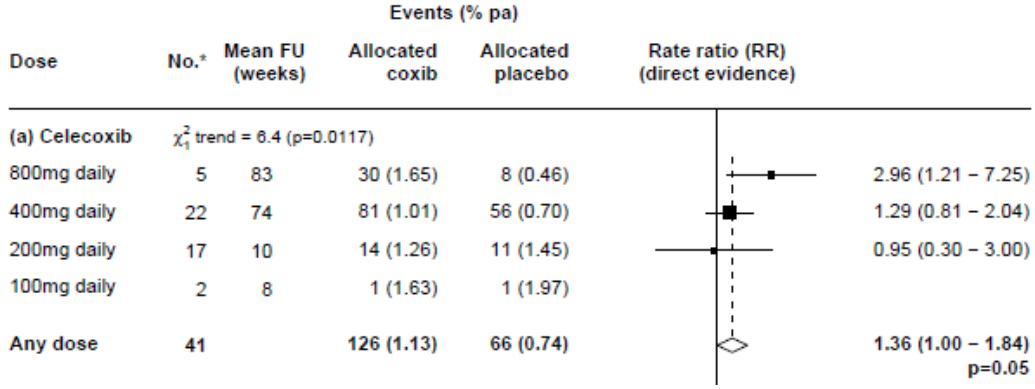
• Sixty-five percent of the subjects are to be receiving low dose ASA for cardioprotection at baseline. The protocol states that subjects are to take ASA two hours before their study medication, to avoid interference with ASA's antiplatelet activity by ibuprofen and naproxen. If this advice is not followed, subjects receiving ibuprofen or naproxen will have a diminished level of cardioprotection, biasing the trial in favor of celecoxib, which does not interfere with ASA.

• Analyzing ASA users and nonusers in separate subgroups will be necessary to evaluate this potential interaction, but the trial is not statistically powered for these subgroups.

• The ITT analysis is likely to be compromised by misclassification of exposures, to the extent that subjects discontinue treatment or switch drugs. The statistical power for the more easily interpreted modified-ITT analysis will be lower than for the main ITT analysis.

• In general, any factor that biases the trial towards a null result will support the sponsor's goal of declaring celecoxib non-inferior to the other treatments.

Regarding the first point above, the Oxford CNT meta-analysis demonstrated a statistically significant dose-response for celecoxib and major vascular events. However, as demonstrated in the figure below, the dose-response finding was driven primarily by the 800 mg dose, with very little difference in point estimate and 95% confidence interval between the 200 mg and 400 mg doses.



With regard to the second point above, at least some patients randomized to naproxen should experience the cardioprotective effect of inhibiting COX-1 even if they do not time their aspirin intake exactly two hours before their naproxen dose, as required by the protocol. Although Capone et al[9] found that naproxen interfered with the irreversible inhibitory effect of aspirin on platelet COX-1 activity in vitro, the "effect was undetectable during the continuous and regular administration of an antiinflammatory dose of naproxen (500 mg BID) and low-dose aspirin because naproxen can mimic the inhibitory effect of aspirin on platelet TXA2 generation." They note, though, that in real world use, such an inhibitory effect might not be reached 100% of the

[9] Capone ML, Sciulli MG, Tacconelli S, et al. Pharmacodynamic Interaction of Naproxen With Low-Dose Aspirin in Healthy Subjects. J Am Coll Cardiol 2005; 45(8): 1295-301.

time because of patient variability and inconsistency in compliance with the twice-daily dosing regimen.

Regarding the trial conduct issues, DAAAP is always concerned whether a trial has been conducted properly, but this cannot be determined until after the trial has been submitted and the study conduct has been reviewed.

On October 8, 2013, DAAAP staff and ODE2 leadership met with DEPI2 staff and the Office of Pharmacovigilance and Epidemiology leadership to discuss Dr. Mosholder's concerns about the PRECISION trial. Many of the points in this memo were discussed during the course of that meeting. At that meeting the decision was made to bring the topic of continuing the PRECISION trial to the upcoming Arthritis/Drug Safety and Risk Management Advisory Committee meeting scheduled for February 10-11, 2014. We will ask the Primary Investigator of the trial to present the status of the study, and there will be a question to the committee about whether there is still equipoise for continuing the trial. Subsequent to this interoffice meeting, we were informed that the Office of Pharmacovigilance and Epidemiology leadership will be drafting a memo that will document the path forward that was agreed at this meeting (as described above).

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/s/

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11/04/2013

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11/04/2013

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	December 20, 2013
From:	Solomon Iyasu MD, MPH Director, Office of Pharmacovigilance and Epidemiology (OPE) Office of Surveillance and Epidemiology (OSE)
To	The File
Drug Name(s):	Nonsteroidal anti-inflammatory drugs (NSAIDs)
Application type/Number	NDA 20,998, IND 48,395
Subject:	Comments on the PRECISION trial

On November 1, 2013, the Division Anesthesia, Analgesia and Addiction Products (DAAP) and the Office of Drug Evaluation-2 (ODE-2) wrote a memorandum[1] documenting a rationale for continuing the PRECISION trial and the agreement on a path forward regarding the PRECISION trial that was reached at a meeting with the Division of Epidemiology and the OPE leadership. The purpose of the OPE memorandum is to provide a written concurrence to the October 8, 2013 agreement and provide comments on our current perspective regarding safety-related meta-analysis of clinical trials.

The Division of Epidemiology-II (DEPI-II),OPE/OSE completed a review of the literature, that most notably included a published meta-analysis of 639 randomized clinical trials of NSAIDs performed by the Oxford University Coxib and traditional NSAID Trialists Collaboration (CNT) that assessed the cardiovascular (CV) safety of NSAIDS. The review, which was completed by Dr. Andy Mosholder, concluded among other things, that naproxen has a lower CV risk relative to ibuprofen or celecoxib. As a result of that conclusion, the review called into question the ethics of continuing an ongoing large postmarketing clinical trial, the "Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen" (PRECISION trial) that was initiated by Pfizer in 2006 at FDA's request. PRECISION is a randomized, double blind, active-controlled, parallel-group study of the cardiovascular (CV) safety of NSAIDs in osteoarthritis or rheumatoid arthritis patients with or at high risk for CV disease. Furthermore, the DEPI-II review also questioned several design features of PRECISION that may limit the ability of the trial to provide interpretable data to discern the comparative CV safety of the three drugs in the trial.

DEPI-II, DAAAP and DB7 have reviewed the CNT meta-analysis and the data from other published observational studies and have been discussing a labeling strategy after concluding that the new evidence

is sufficiently robust and credible. In particular, a statistical review completed by DB7 concluded that the CNT meta-analysis was credible and valid despite some shortcomings outlined in their review. At the center of a conclusion that naproxen confers a lower CV risk than coxibs and ibuprofen is what to do with the ongoing PRECISION trial before implementing any strategy to update the CV safety information in the NSAID labels.

In recent years, there has been an abundance of published meta-analyses of trials of varying quality, implicating some drugs as being associated with serious safety risks. Most have been incompletely documented to enable a full assessment of the methodology and the underlying data behind the meta-analysis. Therefore, such published meta-analyses addressing important and serious safety issues have usually been reviewed by FDA staff, with or without additional independent replication of the analysis.

OPE believes that meta-analyses of clinical trials done for safety may provide important and credible evidence when they are done well, with a protocol and pre-specified analysis plan that employ rigorous and transparent statistical techniques. However, OPE is cognizant of the methodological challenges that limit the rigor and interpretability of data reported in published safety-related meta-analysis of clinical trials for regulatory decision making. One such example of a safety related meta-analysis is the publication by Singh relating to tiotropium safety that is cited in the ODE-2 memorandum. The LeLorier study that found discrepancies between large clinical trials and meta-analyses, and that is also cited in the ODE-2 memorandum, investigated questions of efficacy, and so is not particularly relevant to a safety related meta-analysis. The hormone replacement therapy (HRT) example involved discrepant results between observational studies that showed a cardio-protective effect and a subsequent large randomized clinical trial, the Women's Health Initiative (WHI), which showed cardiovascular harm. Again, these observational studies were focused on evaluating efficacy rather than safety. As such, these examples are not directly relevant to a meta-analysis primarily done to assess harms, as in the case of the CNT or tiotropium experience. The standard for establishing efficacy or clinical benefit based on clinical trials is well established and is not based on meta-analysis. In contrast, best practices for safety related meta-analysis of clinical trials are not well established and the FDA has not issued any Guidance on the subject.

While there are examples where safety-related meta-analysis has provided unreliable results, there are also examples that have provided valid and actionable information alone or in the context of other supporting evidence streams. It is with that context in the background that OPE is eagerly awaiting the development of the Agency Guidance on Meta-analysis, which was the subject of a recent FDA public workshop. Until such time that an FDA Guidance is developed and published, OPE's position is to view published safety-related meta-analyses addressing important potential serious safety risks as hypothesis-generating until a complete and rigorous review, with or without replication, is completed by FDA staff. Upon review, meta-analysis of sufficiently high quality may provide useful and actionable safety information.

On October 8, 2013, the Directors of OPE and ODE-2 and staff of DAAAP and DEPI-II met to discuss the DEPI-II recommendations about the PRECISION trial. During the meeting, a robust discussion of whether or not the new evidence, (primarily the evidence from the CNT analysis that suggested naproxen as having the lowest CV risk) represented a sufficient basis for concluding that there is a lack of clinical equipoise, and to therefore put PRECISION on clinical hold or decide to re-consent subjects already in the trial. It was agreed that a broader discussion of the issues raised by the review, in particular the question about whether or not there is still clinical equipoise to justify the continuation of the PRECISION trial, will take place at the upcoming Arthritic/Drug Safety and Risk Management Advisory Meeting on February 10-11, 2014. Therefore, we will defer taking any further action until after the Advisory Committee meeting.

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1. Racoosin J. "Rationale for allowing the PRECISION trial to continue. November 1, 2013

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/s/

SOLOMON IYASU
12/20/2013

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