ADVISORY COMMITTEE BRIEFING DOCUMENT FOR NAPROXEN

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TABLE OF CONTENTS Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

1. ABBREVIATIONS

ADAPT	Alzheimer's Disease Antiinflammatory Prevention Trial
AMI	Acute myocardial infarction
APC	Adenoma Prevention with Celebrex
CHD	Coronary heart disease
CI	Confidence interval
COX(s)	Cyclooxygenase(s)
COX-1	Cyclooxygenase isozyme 1
COX-2	Cyclooxygenase isozyme 2
CVA(s)	Cerebrovascular accident
GPRD	General Practice Research Database
MI	Myocardial infarction
NDA	New Drug Application
NIA	National Institute on Aging
NSAID	Nonsteroidal antiinflammatory drug
OTC	Over-the-counter
PGHS	Prostaglandin endoperoxide synthase
PGI_2	Prostacyclin
PRR	Proportional reporting ratio
SOC(s)	System organ class(es)
TARGET	Therapeutic Arthritis Research and Gastrointestinal Event Trial
TNF	Tumor necrosis factor
TXA_2	Thromboxane A_2
UK	United Kingdom
US	United States
VIGOR	Vioxx Gastrointestinal Outcomes Research

2. EXECUTIVE SUMMARY

2.1 Background

Naproxen, a nonsteroidal antiinflammatory drug (NSAID), approved in 1976, is currently available in the United States (US) for both prescription use marketed by Hoffman-La Roche Inc. and over-the-counter (OTC) use marketed by Bayer HealthCare LLC, Consumer Care Division. In addition, multiple generic versions of naproxen are currently available.

NSAIDs are a heterogenous set of compounds that have important antiinflammatory, analgesic, and antipyretic properties. NSAIDs consist of several major chemical classes including salicylic acid derivatives, para-aminophenol derivatives, indole and indene acetic acids, heteroaryl acetic acids, arylpropionic acids, anthranilic acids, enolic acids, and alkanones. In addition, the selective cyclooxygenase-2 (COX-2) inhibitors include several additional chemical classes. The major mechanism of action of NSAIDs is based on the inhibition of prostaglandin endoperoxide synthase (PGHS), also named cyclooxygenase (COX), an enzyme that plays a key role in several physiological functions including the process of inflammation.

Naproxen belongs to the chemical class of propionic acid derivatives. This class is widely used and includes ibuprofen, fenoprofen, ketoprofen, flurbiprofen, and oxaprozin. Clinical studies indicate that this class of agents has efficacy comparable to aspirin in the treatment of the signs and symptoms of arthritis. Treatment with these agents results in reduction in pain, joint swelling, and duration of morning stiffness. Treatment also results in improvements in strength and mobility. The major differences between the members of this chemical class are in their potency and pharmacokinetics.

The labeled indications for prescription naproxen include relief of the signs and symptoms of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and juvenile arthritis. Additional indications include relief of the signs and symptoms of tendonitis, bursitis and acute gout, and for the management of pain and of primary dysmenorrhea. In clinical studies in patients with rheumatoid arthritis, osteoarthritis, and juvenile arthritis, naproxen has been shown to be comparable to aspirin and indomethacin in controlling the aforementioned conditions of disease activity, but the frequency and severity of the milder gastrointestinal adverse effects (nausea, dyspepsia, heartburn) and nervous system adverse effects (tinnitus, dizziness, lightheadedness) are less in naproxen-treated patients than in those treated with extended use of moderate to high antiinflammatory doses of aspirin or indomethacin. Indications for OTC use include the temporary relief of minor pain associated with conditions including arthritis, muscle pain, and back ache. The risk/benefit profile of naproxen has been well established over the past 28 years.

The National Institute on Aging (NIA) recently reported a suspension of the Alzheimer's Disease Prevention Trial (ADAPT) in part because of findings reported in a National Cancer Institute trial (Adenoma Prevention with Celebrex [APC]) to test the effectiveness of celecoxib in preventing colon cancer. In addition, however, unadjudicated preliminary findings from the ADAPT trial indicated an apparent increase in cardiovascular and cerebrovascular events among the participants taking naproxen when compared with

those on placebo. Prior to the preliminary findings of the ADAPT study, no detrimental cardiovascular (acute myocardial infarction/myocardial infarction [AMI/MI]) or cerebrovascular signal had been detected with naproxen use. In fact, naproxen would not have been expected to have a negative effect on cardiovascular risk based on its mechanism of action and its known clinical pharmacology. In addition, several studies have suggested that naproxen may have a cardioprotective effect.

Roche and Bayer undertook a comprehensive evaluation of the safety data available for naproxen to determine whether a potential cardiovascular (AMI/MI) or cerebrovascular signal exists. This analysis included a review of the mechanism of action of naproxen in relation to COX-1 and COX-2 and a review of available preclinical, clinical, and postmarketing data.

2.2 Results

The main conclusions of the naproxen evaluation with respect to cardiovascular and cerebrovascular events are as follows:

- A review of observational studies of naproxen and cardiovascular outcomes covering the period of 1987 to date and involving over 80,000 patients exposed to naproxen showed no increased cardiovascular risk with naproxen. In fact, several studies have suggested that naproxen may have a cardioprotective effect (see Section 8).
- A review of Roche postmarketing surveillance data showed no signal for AMI/MI or cerebrovascular accident with exposures to prescription naproxen of 113,188,125 patients from June 1, 1995 until December 21, 2004 (see Section 6.1).
- A review of the Bayer OTC postmarketing surveillance data from April 2001 until December 23, 2004 did not identify a signal for AMI/MI or cerebrovascular accident with an estimate of 550,000,000 courses of therapy (see Section 6.3).
- Clinical studies in the prescription and OTC naproxen New Drug Applications did not provide any evidence of an increased risk of cardiovascular events (AMI/MI; see Section 5).
- Postmarketing clinical studies, with the exception of the ADAPT study, did not provide any evidence of an increased risk of cardiovascular events with naproxen (see Section 7).
- Naproxen would not be expected to have an adverse effect on cardiovascular risk based on its known clinical pharmacology which includes its ability to inhibit platelet aggregation through its effects on COX-1 (see Section 4).

2.3 Conclusions

The vast majority of data show that there is no relationship between an increased risk of MI and cerebrovascular accidents and the use of naproxen. Unadjudicated preliminary findings from the ADAPT study are inconsistent with the available clinical data for naproxen as well as the known pharmacologic properties of the propionic acid derivatives. The benefit/risk for prescription and OTC naproxen remains unchanged.

3. INTRODUCTION

Naproxen, a NSAID, is currently available in the United States (US) for both prescription and OTC use. It was approved for prescription use in the US in 1976 and was made available for OTC use as Aleve (naproxen sodium 220 mg) in the US in 1994. Naproxen, as well as other NSAIDs, plays an important role in the chronic and acute treatment of pain and inflammation. The benefit/risk profile has been well established over the past 28 years.

The NIA recently reported a suspension of the ADAPT study, a long-term use study of naproxen and celecoxib versus placebo in Alzheimer's patients in part because of findings reported in a separate trial sponsored by the National Cancer Institute (APC trial) to test the effectiveness of celecoxib in preventing colon cancer. In addition, however, unadjudicated preliminary findings from the ADAPT trial indicated an apparent increase in cardiovascular and cerebrovascular events among the participants taking naproxen when compared with those on placebo. The results of the ADAPT study are not discussed here as the findings have not yet been published or made available for analysis. Prior to the preliminary findings of the ADAPT study, no detrimental cardiovascular signal had been detected with naproxen use. In fact, naproxen would not have been expected to have a negative effect on cardiovascular risk based on its mechanism of action and its known clinical pharmacology. In addition, several studies have suggested that naproxen may have a cardioprotective effect.

Roche and Bayer undertook a comprehensive evaluation of the safety data available for naproxen to determine whether a potential cardiovascular (AMI/MI) or cerebrovascular signal exists. This analysis included a review of the mechanism of action of naproxen in relation to COX-1 and COX-2 and a review of available preclinical, clinical, and postmarketing data.

4. BACKGROUND ON NAPROXEN

4.1 Naproxen Labeling

Naproxen is currently available in the US for both prescription and OTC use. It was originally developed by Syntex and was acquired by Roche in 1994. Table 1 provides the regulatory history of naproxen.

Table 1 Regulatory Chronology for Naproxen

1976	Original prescription approval in the US for the relief of signs and symptoms of rheumatoid arthritis
1980	Additional prescription indications: osteoarthritis, analgesic use and dysmenorrhea
1983	Additional prescription indications: ankylosing spondylitis, tendonitis, bursitis and acute gout
1986	Prescription approval for juvenile arthritis
1994	Approval for OTC use

The current indications for prescription naproxen in the US include relief of the signs and symptoms of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and juvenile arthritis. All forms, except EC-Naprosyn (enteric-coated naproxen), also carry indications for relief of the signs and symptoms of tendonitis, bursitis, and acute gout, and for the management of pain and of primary dysmenorrhea. The current US Package Insert for naproxen is provided in Appendix 1.

OTC naproxen was approved in 1994 for short-term episodic use with labeling that reflects the well established benefit/risk profile. The current OTC label for naproxen is provided in Appendix 2.

4.2 NSAID Clinical Pharmacology

NSAIDs are a heterogenous set of compounds that have important antiinflammatory, analgesic, and antipyretic properties. NSAIDs consist of several major chemical classes including salicyclic acid derivatives, para-aminophenol derivatives, indole and indene acetic acids, heteroaryl acetic acids, arylpropionic acids, anthranilic acids, enolic acids and alkanones. In addition, the selective COX-2 inhibitors include several additional chemical classes. The major mechanism of action of NSAIDs is based on the inhibition of PGHS, also named COX, an enzyme that plays a key role in different physiological functions, but also in the process of inflammation. Each of the compounds inhibit COX by different binding mechanisms. For example, aspirin irreversibly inhibits COX. The vast majority of the remaining NSAIDs are organic acids and act as reversible, competitive inhibitors of COX. As the inhibition is reversible, the duration of action for the nonselective NSAIDs is primarily related to their pharmacokinetic clearance [1].

The major exception is the para-aminophenols (including acetaminophen). While this chemical class has antipyretic and analgesic properties, their antiinflammatory effects are very limited. Para-aminophenols are not organic acids and thus, do not localize to sites of inflammation.

4.3 Pharmacological Properties of Naproxen

Naproxen belongs to the chemical class of propionic acid derivatives. This class is widely used and includes ibuprofen, fenoprofen, ketoprofen, flurbiprofen, and oxaprozin in

addition to naproxen. Clinical studies indicate that this class of agents has efficacy comparable to aspirin in the treatment of the signs and symptoms of arthritis, but with a lower intensity of side effects than seen with extended use of moderate to high antiinflammatory doses of aspirin or indomethacin. Treatment with these agents results in reduction in pain, joint swelling, and duration of morning stiffness. Treatment also results in improvements in strength and mobility. The major differences between the members of this chemical class are potency and pharmacokinetics.

While there are limitations to the data, in comparative studies naproxen was considered the best tolerated of the chemical class followed by ibuprofen and fenoprofen [1]. In addition, patients preferred naproxen for analgesia and relief of morning stiffness. Of note, there is high interpatient variability for both efficacy and tolerability [1]. Naproxen is highly bioavailable orally (95%). Peak concentrations occur within 2 to 4 hours and more rapidly with naproxen sodium. The half-life of naproxen ranges from 12 to 17 hours.

4.4 Major Pharmacological Differences between Naproxen and Specific COX-2 Inhibitors

The major pharmacological difference between naproxen and selective COX-2 inhibitors is a direct consequence of the capacity to inhibit one or both COX isozymes. Naproxen inhibits both the formation of thromboxane A2 (TXA_2) which is COX-1 dependent and the formation of prostacyclin (PGI_2) which is mostly COX-2 dependent. In contrast, selective COX-2 inhibitors decrease the production of PGI_2, but have no effect on TXA_2 production. While this may result in different effects in multiple organ systems, the remainder of this review will focus on the potential effects on cardiovascular events because this is the issue raised by the ADAPT study findings.

4.4.1 Role of COX-1 and COX-2 in Thromboembolic Events

In investigating the role of PGI_2 on cardiovascular response to TXA_2, it has been observed that PGI_2 decreases the response to TXA_2 [2]. Based on this observation, a rationale for a mechanism of action explaining the difference in the incidence of cardiovascular events between classical NSAIDs and selective COX-2 inhibitors has been proposed [3].

TXA_2 and PGI_2 play a key role in the maintenance of vascular homeostasis. TXA_2 production takes place principally in platelets. TXA_2 promotes platelet aggregation, vasoconstriction, and smooth muscle proliferation, whereas PGI_2 inhibits platelet aggregation and smooth muscle cell proliferation and produces vasodilatation [3]. TXA_2 synthesis is COX-1 dependent, while PGI_2 synthesis is COX-2 dependent. Studies in healthy subjects show that treatment with COX-2 selective inhibitors decreases systemic PGI_2 production with no effect on the TXA_2 synthesis [3].

Naproxen and other classical NSAIDs decrease both PGI_2 production and TXA_2 synthesis, thus maintaining the balance of vasculature homeostasis. In contrast, the selective inhibition of PGI_2 synthesis by selective COX-2 inhibitors would lead to an increase in platelet aggregation, smooth muscle cell proliferation, and vasoconstriction.

4.4.2 Direct Effect on COX-1 and COX-2 Isozymes

4.4.2.1 Effect on Platelet Aggregation In Vitro

Naproxen is a potent inhibitor of the secondary phase of human platelet aggregation in vitro [4]. This effect is mediated though the inhibition of platelet COX-1, thereby blocking the formation of TXA_2. The individual action of propionic acid derivatives on platelet function, bleeding time, and clinical bleeding is reversible. These effects depend, at least in part, on the dose, blood concentration, and drug elimination half-life of the NSAID. In comparison, the effects of aspirin on thromboxane-dependent platelet aggregation are irreversible. Therefore, these effects persist for the circulating time of the platelet after aspirin administration.

4.4.2.2 Effect on Platelet Aggregation in Human Subjects

The effect of twice daily administration of 250 mg of naproxen on platelet aggregation and bleeding time was investigated in healthy male subjects in a randomized, double-blind, placebo-controlled, two-week study that included an aspirin comparator arm. Following 2 weeks of administration of either aspirin or naproxen, bleeding times were significantly prolonged. However, 96 hours after treatment interruption, the effect of naproxen treatment was no different from that of placebo while the effect of aspirin treatment was still apparent [5]. This difference is a direct consequence of the type of enzymatic inhibition exerted by these drugs. Naproxen is a reversible inhibitor of platelet COX-1. Thus, the effect of naproxen on bleeding time was vanishing after 96 hours. In contrast, aspirin is an irreversible inhibitor that blocks platelet COX-1 by acetylating the enzyme. Similarly, 500 mg of naproxen administered twice daily during a two-week period significantly decreased platelet aggregation and TXA_2 synthesis and significantly prolonged bleeding time in patients with rheumatoid arthritis [6].

4.5 Summary

Naproxen is a dual COX-1/COX-2 inhibitor. Naproxen is known to inhibit platelet aggregation through its effects on COX-1 and thus, could potentially decrease the risk of cardiovascular events.

5. STUDIES IN THE NAPROXEN NEW DRUG APPLICATIONS

5.1 Prescription New Drug Application

The original New Drug Application (NDA) for chronic use of prescription naproxen included 545 patients with rheumatoid arthritis. The largest study, ICM 303, included 266 patients. The second study, ICM 260, included 279 patients and represents the long-term follow-up to studies 194, 267, 268 and 315. The total population consisted of 142 males and 403 females. The mean age of the study population was 51.1 years. All patients had rheumatoid arthritis. Of these patients, 302 were treated for more than 6 months, 120 for more than one year and 47 continuously for more than 2 years. Patients were treated with a range of naproxen doses of up to 750 mg/day. A total of 76 of the patients had a prior history of cardiovascular disease. During treatment, no AMIs or cerebrovascular accidents (CVAs) were reported.

5.2 OTC New Drug Application

A clinical program was completed by Syntex and Proctor & Gamble to support the OTC switch of Aleve (naproxen sodium 220 mg). Safety data from these trials included a total of 4,608 patients exposed to naproxen; these data did not suggest any cardiovascular (AMI/MI) or cerebrovascular risk.

5.3 Summary

Clinical data did not indicate any evidence of a signal for cardiovascular (AMIs/MIs) or cerebrovascular events. Based on the lack of evidence for an increased cardiovascular risk, no further prospective studies were performed to look at these events.

6. POSTMARKETING SPONTANEOUS CASE REPORTS FOR MIS AND CVAS

6.1 Cases Reported to Roche

A total of 75,584 events (including serious, nonserious and comanifestations) were reported from September 1973 through December 21, 2004 for all naproxen products for all System Organ Classes (SOCs). Of these events, 4,018 events were reported for the SOC of cardiac disorders (896 were serious events).

A total of 71 case reports of AMI/MI were retrieved from Roche's drug safety database using the Medical Dictionary for Drug Regulatory Affairs preferred terms of MI and AMI under the SOC of cardiac disorders. Of the 71 case reports, 33 cases were reported by spontaneous sources (including two literature cases) and 38 cases were reported from clinical trials.

A total of 81 case reports were retrieved from Roche's drug safety database using the MedDRA high-level term of central nervous system hemorrhages and CVA under the SOC of nervous system disorders. Of the 81 case reports, 56 cases were reported by spontaneous sources (including one literature case) and 25 cases were reported from clinical trials.

Total patient exposure to prescription naproxen from September 1973 until May 31, 1995 is not available.

Total patient exposure to prescription naproxen from June 1, 1995 until December 21, 2004 is 34,162,026 for naproxen and 79,026,099 for naproxen sodium for a combined total of 113,188,125 patients.

Given the large exposure to naproxen, the incidence of AMI/MI and stroke are lower than the incidence of these events expected in a general population. This phenomenon is likely due to underreporting. Therefore, an alternative approach to look at the frequency of events is the Proportional Reporting Ratio (PRR).

6.2 PRR Results

PRR has been applied to compare the frequency of the selected adverse events between naproxen and all the other drugs in the Roche safety database. PRR is a numerical

method to generate signals from adverse event reports; it is also referred to as the disproportionality method or disproportionality check [7].

Results of the PRR analysis through December 21, 2004 for naproxen (including all formulations such as naproxen, naproxen sodium prescription and naproxen sodium OTC) are presented in Table 2 and Table 3.

No signal for the detection of an association between naproxen and either AMI/MI and ischemic coronary artery disorders or stroke was generated.

Table 2 PRR Results for AMI/MI and Ischemic Coronary Artery Disorders - Roche

Event	No of Reports	PRR	Significance (p-value)
Ischemic coronary artery disorders (high-level term)	96	0.16	<0.05
AMI/MI (preferred terms)	60	0.18	<0.05

Note: One case may have more events and all of them are counted for PRR analysis. Twenty two cases of ischemic coronary artery disorders and 12 cases of AMI/MI were blinded cases and were excluded from the PRR analysis.

Table 3 PRR Results for Stroke - Roche

Event (high-level term)	No of Reports	PRR	Significance (p-value)
CNS hemorrhages and cerebrovascular events	71	0.16	<0.05

Note: One case may have more events and all of them are counted for PRR analysis. Thirteen cases of CNS hemorrhages and cerebrovascular accidents were blinded cases and were excluded from the PRR analysis

6.3 Spontaneous Cases Reported to Bayer

A total of 12,183 spontaneous adverse event reports for naproxen sodium have been reported to Bayer since April 2001. Of these, there were 7 reports of MI and 9 reports of cerebrovascular events (cerebrovascular hemorrhages, CVA, and transient ischemic attacks). The estimated OTC exposure to naproxen sodium during this time period is 550,000,000 courses of therapy. A course of therapy is defined as two tablets per day for 10 days, which is representative of the episodic nature of OTC use.

6.4 Summary

A review of the Roche naproxen safety database did not show a signal for AMI/MI or cerebrovascular accident. A review of the Bayer OTC dataset confirmed a lack of a signal for these events in the OTC setting.

7. POSTMARKETING CLINICAL STUDIES

7.1 Large, Randomized, General Safety Studies

Two large, randomized, general safety studies, Vioxx Gastrointestinal Outcomes Research (VIGOR) and Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), have been published in which naproxen was administered chronically and the incidence of cardiovascular events was examined.

7.1.1 VIGOR

VIGOR was a large, randomized trial comparing rofecoxib (Vioxx®) to naproxen to assess long-term gastrointestinal safety [8]. The study was designed to continue until the predefined number of gastrointestinal endpoints had been achieved, but, at a minimum, 6 months after the last patient was enrolled. Cardiovascular endpoints were assessed by an adjudication committee, but the study was not designed to independently assess cardiovascular risk. Patients with a history of a CVA within the last 2 years or an AMI within the last year were excluded from the study. In addition, patients on aspirin, ticlodipine or other anticoagulants were excluded from the study.

The study randomized 8,076 patients with rheumatoid arthritis to treatment with either rofecoxib 50 mg twice daily (n=4047) or naproxen 500 mg twice daily (n=4029). Median exposure at the time of publication was 9 months. The rate of death from cardiovascular causes was the same in both groups (0.2%). The rate of ischemic cerebrovascular events was 0.2% in both groups. The rate of MI was four times higher on rofecoxib than naproxen. Further analysis showed that 14.6% of patients treated with rofecoxib had at least one cardiovascular adverse experience versus 9.7% of the patients treated with naproxen.

The overall rate of cardiovascular events reported in association with naproxen in this trial is consistent with what would be expected in this population [9]. However, the absence of a control arm prevents comparison to either a placebo or other NSAIDs.

7.1.2 TARGET

The TARGET study evaluated the safety of lumiracoxib versus naproxen and ibuprofen for 52 weeks of treatment in patients with osteoarthritis [10]. In addition to a gastrointestinal endpoint, the study was designed with a second primary cardiovascular endpoint. The cardiovascular endpoint was based on the Antiplatelet Trialists Collaboration endpoint of nonfatal and silent MI, stroke or cardiovascular death. The study was designed as two separate substudies: 1) lumiracoxib 400 mg once daily versus ibuprofen 800 mg three times daily; and 2) lumiracoxib 400 mg once daily versus naproxen 500 mg twice daily. Patients were stratified on the basis of age and the use of low-dose aspirin. Patients were monitored on the study for 52 weeks of treatment. Safety data including electrocardiograms and blood pressure measurements were prospectively collected during the study. Of note, cardiovascular endpoints were evaluated by a blinded adjudication committee.

The safety analysis population included patients who started treatment. For the naproxen substudy, the safety population included 4,741 patients on lumiracoxib and 4,730 patients

on naproxen. For the ibuprofen substudy, the safety population included 4,376 patients on lumiracoxib and 4,397 on ibuprofen. Overall, the characteristics of the patients in the two substudies were similar, with the exception of cardiovascular risk which was higher in the naproxen substudy. At baseline, a total of 12% of the patients in the naproxen substudy had a history of cardiovascular risk compared to 8% in the ibuprofen substudy. In addition, the number of patients with cerebrovascular disease and angina pectoris was numerically higher in the naproxen substudy compared to the ibuprofen substudy.

The incidence of cardiovascular and cerebrovascular events in the overall study and the two substudies is shown in Table 4.

The TARGET study showed that naproxen had a lower rate of cardiovascular events than lumiracoxib. Using lumiracoxib as the reference point for both studies, the overall rate of cardiovascular events for naproxen was relatively lower than for ibuprofen.

Table 4 Incidence of Confirmed or Probable Cardiovascular and Cerebrovascular Events

	Both substudies		Lumiracoxib vs ibuprofen substudy		Lumiracoxib vs naproxen substudy	
	Lumiracoxib (n=9117)	NSAIDs (n=9127)	Lumiracoxib (n=4376)	Ibuprofen (n=4397)	Lumiracoxib (n=4741)	Naproxen (n=4730)
Patients with confirmed or probable cardiovascular or cerebrovascular events	85 (0·93%)	75 (0·82%)	33 (0·75%)	32 (0·73%)	52 (1·10%)	43 (0·91%)
Patients with confirmed or probable clinical myocardial infarction, silent myocardial infarction, stroke or cardiovascular death (primary endpoint)	59 (0·65%)	50 (0·55%)	19 (0·43%)	23 (0·52%)	40 (0·84%)	27 (0·57%)
Patients with confirmed or probable:						
Cardiovascular death	19 (0·21%)	18 (0·20%)	8 (0·18%)	10 (0·23%)	11 (0·23%)	8 (0·17%)
All myocardial infarctions	23 (0·25%)	17 (0·19%)	5 (0·11%)	7 (0·16%)	18 (0·38%)	10 (0·21%)
Silent	3 (0·03%)	5 (0·05%)	0	2 (0·05%)	3 (0·06%)	3 (0·06%)
Clinical	20 (0·22%)	12 (0·13%)	5 (0·11%)	5 (0·11%)	15 (0·32%)	7 (0·15%)
Fatal	2 (0·02%)	3 (0·03%)	0	2 (0·05%)	2 (0·04%)	1 (0·02%)
Non-fatal	18 (0·20%)	9 (0·10%)	5 (0·11%)	3 (0·07%)	13 (0·27%)	6 (0·13%)
Stroke	24 (0·26%)	21 (0·23%)	8 (0·18%)	9 (0·20%)	16 (0·34%)	12 (0·25%)
Fatal	5 (0·05%)	2 (0·02%)	2 (0·04%)	1 (0·02%)	3 (0·06%)	1 (0·02%)
Non-fatal	19 (0·21%)	19 (0·21%)	6 (0·14%)	8 (0·18%)	13 (0·27%)	11 (0·23%)
Ischaemic stroke	23 (0·25%)	17 (0·19%)	8 (0·18%)	6 (0·14%)	15 (0·32%)	11 (0·23%)
Fatal	4 (0·04%)	0	2 (0·04%)	0	2 (0·04%)	0
Non-fatal	19 (0·21%)	17 (0·19%)	6 (0·14%)	6 (0·14%)	13 (0·27%)	11 (0·23%)
Haemorrhagic stroke	1 (0·01%)	4 (0·04%)	0	3 (0·07%)	1 (0·02%)	1 (0·02%)
Fatal	1 (0·01%)	2 (0·02%)	0	1 (0·02%)	1 (0·02%)	1 (0·02%)
Non-fatal	0	2 (0·02%)	0	2 (0·05%)	0	0
Cardiac arrest	0	0	0	0	0	0
Transient ischaemic attack	7 (0·07%)	6 (0·07%)	5 (0·11%)	1 (0·02%)	2 (0·04%)	5 (0·11%)
Unstable angina	10 (0·11%)	11 (0·12%)	4 (0·09%)	7 (0·16%)	6 (0·13%)	4 (0·08%)
Deep vein thrombosis	6 (0·07%)	7 (0·08%)	4 (0·09%)	3 (0·07%)	2 (0·04%)	4 (0·08%)
Pulmonary embolism	4 (0·04%)	4 (0·04%)	2 (0·04%)	0	2 (0·04%)	4 (0·08%)

Data are number of patients with event (%). NSAIDs=non-steroidal anti-inflammatory drugs.

Table 2: Incidence of confirmed or probable cardiovascular and cerebrovascular events

7.2 Alzheimer's Disease Study

The only completed, published, randomized, placebo-controlled study of naproxen was conducted in patients with Alzheimer's disease [11]. The trial randomized patients with Alzheimer's disease to 1 year of treatment with rofecoxib 25 mg once daily, Aleve

220 mg twice daily, or placebo for 1 year. The primary objective of the study was to determine the effect on progression of the underlying Alzheimer's disease.

A total of 351 patients were randomized: 111 to placebo, 118 to naproxen, and 122 to rofecoxib. Similar to the TARGET study, approximately 25% of patients were on low-dose aspirin. No specific handling of cardiovascular events was performed and safety data was collected as part of the routine monitoring of the trial.

Serious adverse events of stroke/transient ischemic attack were reported in one patient on placebo, three patients on naproxen, and three patients on rofecoxib. Serious adverse events of MI were reported in one patient on placebo, none on naproxen, and three patients on rofecoxib.

Because the number of serious adverse events are small, there is no suggestion of an increased risk of cardiovascular events with naproxen.

7.3 Pooled Analysis of Controlled Studies with Celebrex

In order to determine whether Celebrex (celecoxib) affects cardiovascular thrombotic risk, a pooled analysis of all controlled arthritis trials for Celebrex was recently conducted and published by White et al [12]. The trials were of varied duration, ranging from 4 to 26 weeks. A total of 2,271 patients were randomized to naproxen with an average duration of exposure of only 8 weeks. There were 18,942 patients randomized to Celebrex, 1,794 to placebo, and 12,973 to NSAIDs (i.e., diclofenac, ibuprofen, naproxen). The primary endpoint was that defined by the Antiplatelet Trialists Collaboration, namely cardiovascular, hemorrhagic, and unknown deaths, nonfatal MI, and nonfatal stroke.

Pooled analyses of the trials revealed an incidence rate of 1.02 events per 100 person years on naproxen, 1.51 events per 100 person years for placebo, and 1.05 events per 100 person years for all NSAIDs. The incidence rates on Celebrex ranged from 0.95 to 1.29 events per 100 person years depending on the trial. A direct comparison of naproxen with Celebrex was provided by the authors which yielded a relative risk of 1.18 (95% confidence interval [CI]: 0.41-3.45; p=0.89).

The authors also carried out a subgroup analysis looking at those patients who were not on aspirin. The rates of the primary endpoint among the nonasprin users were 0.87 per 100 person years on naproxen, 1.17 per 100 person years for placebo, and 0.66 per 100 person years for all NSAIDs. For Celebrex, the rates ranged from 0.50 to 0.66 per 100 person years. A direct comparison of naproxen with Celebrex yielded a relative risk of 1.22 (95% CI: 0.27 – 5.56).

Thus, no evidence of an increased risk of cardiovascular, hemorrhagic, and unknown deaths, nonfatal MI, and nonfatal stroke was seen with naproxen in the Celebrex clinical trials program.

7.4 Aleve Clinical Studies

Six randomized, double-blind, placebo-controlled trials with active comparators have been carried out by Bayer since 1997. These studies included a total of 3,277 subjects

with 1,509 subjects exposed to Aleve. Four trials were single-dose studies and two trials were multidose, arthritis studies where a two-day course of therapy was provided. No deaths, AMI/MI or cerebrovascular events (stroke or transient ischemic attacks) were reported in any of these trials.

7.5 Summary of Postmarketing Clinical Studies

A number of postmarketing clinical studies with naproxen have been conducted in which the incidence of cardiovascular events was examined. None of these studies showed evidence of an increased cardiovascular risk in the naproxen treatment groups.

8. OBSERVATIONAL STUDIES

8.1 Background

Although the cardioprotective effect of aspirin is well known, the association between other NSAIDs and the risk of cardiovascular events is not well understood. It is well known that platelet aggregation plays an important role in the pathophysiology of cardiovascular events. It is also well known that the NSAID, naproxen, confers platelet inhibition [24]. Thus, several researchers investigated the possible cardioprotective effects of naproxen.

This section will summarize observational studies investigating the association between naproxen and the risk of cardiovascular events.

8.2 Summary of Observational Studies

Through Medline searches, several large, case-control and cohort studies investigating the association between naproxen exposure and the risk of cardiovascular events were identified. Table 5 summarizes these studies.

8.2.1 Solomon: New Jersey Medicaid Study

In a large, retrospective, case-control study, frequency matched on age, Solomon et al [13] studied whether NSAIDs have a similar effect on the risk of AMI. They investigated patients from the New Jersey Medicaid or Medicare and Pharmaceutical Assistance for the Aged and Disabled programs. They identified 4,425 AMI cases applying an algorithm developed in another study with a positive predictive value of 96.9%. They used 17,700 control subjects who did not experience an AMI during the study period. Exposure of interest was prescription of NSAIDS in the 6 months prior to diagnosis of MI for cases or in the 6 months prior to the index date for the controls. Analyses were controlled for clinical, sociodemographic, and health care use characteristics, age, sex, ethnicity, insurance statement, medical history of hypertension, diabetes mellitus, and congestive heart failure.

Overall, users of nonaspirin NSAIDs had the same risk as nonusers of NSAIDs. However, naproxen use within the previous 6 months was associated with a significant reduction in the risk of AMI (odds ratio, 0.84 [95% CI: 0.72-0.98]) compared with nonusers of NSAIDs. Comparison of naproxen with ibuprofen revealed a similar benefit in favor of naproxen. The authors reported an apparent 16% to 20% risk reduction on naproxen. This pattern persisted in different subgroups of naproxen users and in patients using different doses and treatment durations.

The authors commented on only one potential limitation in the study, namely OTC use of NSAIDS. However, as the study was conducted in low-to-moderate income patients who

qualify for subsidized or free prescriptions, it is unlikely that OTC use would be widespread enough to have any major influence on the overall interpretation. Other potential confounders such as lipids and smoking histories were also not available. However, the prescription of naproxen is unlikely to be influenced by these. In addition, in order to minimize the potential confounding effect of OTC aspirin use, the authors excluded patients with conditions likely to be managed with aspirin, such as coronary artery disease, cerebrovascular disease, and other similar conditions.

After the availability of COX-2 inhibitors, the authors carried out further, but similar, analyses utilizing two state-sponsored (NJ and PA) pharmaceutical benefits programs. This study investigated the association between rofecoxib and celecoxib and the risk of AMI [14]. As a secondary objective, and with a limited number of patients exposed to naproxen (331 patients), the authors compared rofecoxib and celecoxib with naproxen. Odds ratios of 1.06 (95% CI: 0.83-1.35; p=0.7) comparing naproxen with celecoxib, and 0.85 (95% CI: 0.66-1.11; p=0.2) comparing naproxen with rofecoxib were reported. Thus, compared with the COX-2 inhibitors, the data provided no evidence of an increased risk of AMI among users of naproxen.

8.2.2 Watson: General Practice Research Database Study

A retrospective study from the United Kingdom (UK) General Practice Research Database (GPRD) examined the risk of acute thromboembolic cardiovascular events (MI, sudden death, and stroke) in rheumatoid arthritis patients receiving naproxen [15]. The study included patients aged 40 to 79 years and excluded those with a previous thromboembolic cardiovascular event, and those with medical conditions that might confound the association of interest, including cancer, vasculitis, coagulopathy, renal disease, liver failure, or alcohol or drug abuse at any time prior to study start. In addition, patients with a prescription for flurbiprofen or anticoagulants and/or antiplatelet agents during the year prior to study start and/or 30 days or less prior to their index date were excluded. A total of 809 cases (435 MI, 27 sudden death, 347 cerebrovascular events) were matched with up to four controls with rheumatoid arthritis by sex, age within 5 years, and medical practice. Twenty-six of the case patients were current naproxen users, defined as a prescription with a start date 30 days or less prior to the index date. Past naproxen use was defined as a prescription with an end date more than 30 days, but 365 days or less prior to the index date. No naproxen use was defined as no prescription with an end date more than 365 days prior to the index date. The authors controlled for the calendar year the patient started the study, smoking, prescription for disease-modifying antirheumatic drug use, systemic corticosteroids, or estrogen 90 days or less (but >30 days) prior to the index date, diagnosed or treated diabetes, and medical or surgical condition $\leq$ 6 months, but < 30 days prior to the index date.

The study revealed that current users of naproxen had a reduced risk of acute thromboembolic cardiovascular events compared with nonusers of naproxen with an odds ratio of 0.61 (95% CI: 0.39-0.94). This model considered all thromboembolic events and was adjusted for calendar year of patient start, systemic corticosteroid use, diabetes, and comorbidity. The respective odds ratio for past naproxen use was 0.87 (95% CI: 0.65-1.16). In addition, the study revealed a nonsignificant reduced risk of MI for current users of naproxen compared with nonusers with an odds ratio of 0.57

(95% CI:0.31-1.06). Conversely, no protective effect was seen for any other nonaspirin NSAIDs.

This is a well conducted study in which the authors examined whether or not the baseline characteristics of naproxen users versus nonusers were different. However, they did not find any major differences between the naproxen users and the nonusers. Nonetheless, a possibility of residual confounding due to unmeasured variables cannot be ruled out completely. The authors validated approximately 80% of the cases.

8.2.3 Rahme: Quebec Study

A retrospective, case-control study from Quebec investigated the association between naproxen use and the risk of AMI in patients over 65 years of age [16]. The study compared over 14,000 hospitalized MI cases with the same number of controls. The authors used the RAMQ and Med-Echo databases in Quebec. They restricted their investigations to patients aged 65 years or older. Cases were patients with a hospital discharge summary containing a diagnosis of AMI (ICD-9 code 410) and a discharge diagnosis date between January 1, 1992 and December 21, 1994. Patients with a prior AMI within 4 years of hospitalization were excluded. Additionally, all patients with a diagnosis of an "old" MI during the year before their index date were excluded. Controls were selected from a random sample of the databases and matched by sex and age (within 2 years), one control per case. Concurrent-chronic exposure was defined as prescriptions filled at least twice and with 60 or more consecutive days of prescription duration that covered or overlapped with the index date.

Concurrent-chronic users of naproxen had a lower incidence of AMI than concurrent-chronic users of other NSAIDs (Odds ratio=0.64, 95% CI: 0.48-0.86). That is, concurrent-chronic use of naproxen conferred a 14%-52% reduced risk of AMI compared with users of other NSAIDs. Similarly, concurrent use of naproxen was associated with a small, but statistically significant reduction in the risk of AMI compared with concurrent users of other NSAID (odds ratio 0.79 [95%CI: 0.63-0.99]). The authors concluded that concurrent exposure to naproxen, compared with other NSAIDs, had a protective effect against AMI.

This study has the advantage that the two comparison groups (naproxen users and other NSAID users) are probably quite similar, thus reducing the potential for confounding. The study had several limitations. Neither the indication for NSAID use nor important risk factors, such as cigarette smoking and obesity, could be assessed. These factors could have been differentially distributed in naproxen users versus other NSAID users. However, the authors commented that naproxen and other NSAID users should not differ in AMI risk susceptibility. Concurrent use of OTC drugs, aspirin, naproxen, and ibuprofen, could not be evaluated, but is unlikely to have had a major impact on the overall conclusions.

8.2.4 Schlienger: General Practice Research Database Study

Two further retrospective, case-control studies within the UK GPRD were recently conducted. The first study compared over 3,300 cases of first time AMIs with over

13,000 controls [19]. This study includes data on a relatively large number of elderly patients up to 75 years of age; the authors excluded patients older than 75 years.

As the authors acknowledge, they were not able to adjust for socioeconomic status or lifestyle habits such as physical activity or dietary information because this information is not routinely recorded in the GPRD. Also, data on smoking status or body mass index were absent in 20-30% of cases and controls.

The authors selected first-time AMI patients, free of preexisting diagnosed cardiovascular or metabolic diseases. This was done because the effects of drugs can best be studied in subjects free of clinical risk factors for the disease. However, one may assume that information on previous history is incomplete because events may have occurred before patients were registered in GPRD practices. In addition, risk factors, such as hypertension, may unknowingly have been present prior to the MI.

The authors found the strongest association between MI and NSAID use in the group that had at least 30 prescriptions. However, in the case group, these represent less than 5% of NSAID recipients. This is likely to have been a highly selected group with possibly different risk factors for MI. Also, because of the limited time span covered by GPRD for most patients, many users of 30+ prescriptions are likely to have been misclassified to groups with less use since their history is incompletely covered by GPRD.

As in all observational studies, there is the issue of comparability of baseline characteristics of the recipients of various drugs. In particular, OTC NSAIDs were not captured. However, only ibuprofen was available OTC, so one would expect very little misclassification of overall NSAID exposure. Furthermore, the misclassification would tend to be nondifferential between cases and controls, and have little or no effect on the overall conclusions. The authors further reveal that it was unlikely that elderly patients would take aspirin for cardiovascular protection without a prescription.

When comparing different NSAIDs, the authors had an issue of statistical power. Results are only available in the article for current users of various NSAIDs. Overall, there was no significant protective effect with NSAID exposure. For naproxen, however, there was a trend towards a reduced risk with current use compared with nonusers (odds ratio 0.68 [95% CI: 0.42-1.13]). The authors comment that there was a suggestion of a reduced risk of AMI in naproxen users, but this difference was not statistically significant.

8.2.5 Rodriguez: General Practice Research Database Study

Another recent study that utilized the GPRD compared nearly 4,800 cases of first time MI with 20,000 controls [23]. The study was similar to the previous study [19] except patients with history of coronary heart disease (CHD) weren't excluded.

Overall, the authors could not detect any risk reduction with NSAIDs. For naproxen there was again a trend towards a reduced risk (odds ratio 0.89 [95% CI: 0.64-1.24]) compared with nonusers of NSAIDS [23]. While these findings are entirely consistent with the hypothesis that naproxen confers protection against MI [7, 13, 15, 21], the nonsignificance here is possibly explained by the fact that naproxen exposure was quite

low, with only 19 cases and 105 controls exposed to naproxen in the first study, and 49 cases and 206 controls in the second.

8.2.6 Graham: Kaiser Permanente

A recent presentation at the International Society for Pharmacoepidemiology conference utilized the Kaiser Permanente database. The authors compared over 8,000 cases of AMI or sudden cardiac death with nearly 33,000 controls in a nested case-control study with emphasis on the possible cardiac hazards of rofecoxib. Overall, there was a slight increased risk with recent use (i.e., within the last 60 days) of NSAIDs compared with remote use (i.e., more then 60 days ago) (odds ratio of 1.14 [95% CI: 1.06-1.22]). The authors also presented the risk associated with current use of specific NSAIDs and COX-2 inhibitors. Apart from a rofecoxib dose over 25 mg, which had a substantially increased risk, the risk of cardiac events associated with other NSAIDs and COX-2 inhibitors was small and of similar magnitude (odds ratios 1.09 [95% CI: 0.99-1.21]) for ibuprofen; 1.18 [95% CI: 1.04-1.35]) for naproxen, and 1.16 [95% CI: 1.04-1.30]) for other NSAIDs) [20].

Patients with a history of cardiovascular disease were not excluded; adjustments based on a cardiovascular risk score were made in this analysis. However, this is a very heterogeneous group, many with strong determinants for cardiac events. Consequently, confounding is likely to have occurred, since risk factors such as smoking are incompletely described. As for the cardiovascular risk factors described, these differed between various groups of NSAIDs (not provided for naproxen).

There is no analysis relating outcome with duration of use. This is probably because of limited follow-up (average time of approximately 1.5 years). A comparison was made not with nonNSAID use, but with 'remote use' (> 60 days since last use of an NSAID), which makes interpretation difficult.

Data were not available on smoking behavior and OTC aspirin use; however, a telephone survey was done with a limited number of patients. Results of this suggested that there were no marked differences between NSAIDs. No review of medical records was done.

8.2.7 Kimmel: Philadelphia Study

A recent hospital-based, case-control study in the Philadelphia area compared some 1,150 cases of nonfatal MI with over 4,000 controls [21]. The study was different from others in this review in that exposure information was ascertained directly from the subjects via interviews. A clear advantage here is that exposure to OTC NSAIDs can be collected directly from the subjects. An objective of the study was to investigate any interactions between aspirin use and other NSAIDs with respect to the risk of MI.

In the absence of aspirin use, the authors reported a significant reduction in the risk with other NSAIDs. In particular, for naproxen an odds ratio of 0.48 (95% CI: 0.28-0.82) was reported. In other words, among those patients not taking aspirin, current use of naproxen was associated with approximately a 20%-70% reduction in the risk of MI compared with nonusers of NSAIDs. Among those patients already taking aspirin, there was no significant benefit of NSAIDs.

The authors discuss a potential recall bias. However, such a bias would tend to show a positive association between exposure and being a case. In fact, cases were less likely to be exposed to naproxen than controls suggesting a possible underestimate of the true protective effect of naproxen.

Furthermore, the authors carried out several subgroup analyses to test recall bias, such as including only those patients who had all medication containers during interview, or only those patients who were interviewed within 90 days of the index date. None of these analyses materially altered the overall findings suggesting little or no impact of recall bias. The overall conclusion was that nonaspirin NSAIDs may reduce the risk of MI.

8.2.8 Ray: Tennessee Medicaid Database Study

A cohort study based within the Tennessee Medicaid database followed patients exposed to several NSAIDs and COX-2 inhibitors [17]. The study identified over 70,000 subjects exposed to naproxen and over 200,000 subjects not exposed to any NSAIDS or COX-2 inhibitors. Apart from the high dose of rofecoxib (i.e., over 25 mg) which had a 93% increased risk of serious CHD compared with nonusers, the authors concluded that there was no evidence of an increased risk for any other NSAIDs. In particular, for current users of naproxen, a relative risk of 0.93 (95% CI: 0.82-1.06) was reported compared with nonusers of NSAIDs.

The authors also conducted more refined analyses investigating only new users of NSAIDS and COX-2 inhibitors. Again, for the new users of naproxen, a relative risk of 0.92 (95% CI: 0.73-1.16) was reported compared with nonusers of NSAIDs. The incidence of serious CHD was the lowest for new naproxen users compared with other NSAIDs and COX-2 inhibitors as follows: 11.1 per 1000 patient-yrs (naproxen), 12.0 per 1000 patient-yrs (ibuprofen), 12.2 per 1000 patient-yrs (celecoxib), 13.7 per 1000 patient-yrs (rofecoxib < 25 mg) and 24.0 per 1000 patient-yrs (rofecoxib > 25 mg). Patients were eligible if they were between 50 and 80 years of age.

Patients with preexisting cardiovascular metabolic diseases were not excluded. In fact, over 70% had been treated for cardiovascular disease in the past year. This makes the associations with NSAIDs more likely to be subjected to confounding. Also, as the authors acknowledge, individuals taking rofecoxib or another NSAID could have differed from nonusers with respect to unmeasured factors that affected the risk of serious CHD. Indeed, they show that the distribution of some measured characteristics (e.g., age, sex) differed between recipients of COX-2 inhibitors and ibuprofen or naproxen.

Mean duration of follow-up is not provided in the article. However, the cohorts of users and nonusers had slightly more members than follow-up years, so mean follow-up is less than a year. This is rather short and explains why it was not attempted to relate duration of use of the various drugs with outcome.

The analysis uses events per person-years. However, higher doses of rofecoxib are not recommended for long-term use (> 5 days use). This is likely to result in different use patterns of low versus high doses of rofecoxib. Risk of serious CHD did not increase among high-dose users of celecoxib, naproxen, or ibuprofen.

This rather short report suggests a cardiovascular risk associated with higher-dose users of rofecoxib. No clear positive or negative effects of naproxen are shown. The study has its limitations, notably the mean duration of follow-up appears to be short and no attempt has been made to relate duration of use with outcome.

A previous analysis of the same data gave very similar results (relative risk of 0.95 (0.82-1.09) comparing naproxen with control nonusers of NSAIDs [18]. The authors, however, found a statistically significant protective effect of naproxen compared with ibuprofen (relative risk 0.83 [0.69-0.98]).

8.2.9 Mamdani: Ontario Healthcare Database Study

A similar cohort study was also conducted within the administrative healthcare database in Ontario. The main objective was to investigate an association between COX-2 inhibitors and naproxen on the risk of AMI in elderly NSAIDs-naïve patients [22]. Explicitly, they compared users of celecoxib, rofecoxib, naproxen, and nonnaproxen NSAIDs with a random sample of 100,000 controls dispensed none of these medications. For the four drug cohorts, the initial prescription following the 66th birthday served as an index date. To create the NSAIDS-naïve subject population, anyone prescribed any of the study medications within 12 months prior to the index date was excluded. Subjects receiving more then one study medication were excluded. Only subjects receiving at least two successive prescriptions and who received enough drug for at least 30 days of observation were included.

The database identified nearly 6,000 subjects exposed to naproxen, 12,000 to rofecoxib, 15,000 to celecoxib, 33,000 to nonnaproxen, nonselective NSAIDs, and 100,000 nonexposed controls. The average age was approximately 75 years and the follow-up was up to 1 year. Time–to-event analyses were conducted for AMI and Cox Proportional Hazards models with the control group as reference. The analyses accounted for potential confounders which included hospitalizations in the previous year, malignancies, AMI, stroke, congestive heart failure, coronary disease, and cardiac procedures within the previous 5 years as well as other drug use.

The authors estimated incidence rates of hospitalization for AMI to be 8.2 per 1000 patient-yrs in the controls, 9.6 per 1000 patient-yrs (naproxen), 10.7 per 1000 patient-yrs (celecoxib), and 12.1 per 1000 patient-yrs (rofecoxib). Compared to the control (nonexposed) group, the adjusted relative risk associated with naproxen use was 1.0 (95% CI: 0.6-1.7). The authors reported similar nonsignificant relative risks for other exposed cohorts compared with the control group: celecoxib (0.9), rofecoxib (1.0), and nonnaproxen NSAIDs (1.2). The authors concluded that there was no increase in the short-term risk of AMI among users of these drugs.

The authors carried out several sensitivity analyses such as, matching exposed patients with control patients on age and gender; separate analyses for men and for women; excluding those with a previous history of AMI; accounting for study period since naproxen was available well before celecoxib and rofecoxib. The authors did not reveal any modifications in the overall interpretation based on any of these sensitivity analyses. Furthermore, the authors did not believe that unmeasured potential confounders such as smoking, obesity, and alcohol would explain their findings. As with other database

studies, there was some concern about OTC use of NSAIDs. Only ibuprofen is available OTC in Canada and because the subjects were elderly, they had strong financial incentives to obtain the drugs through prescription. Thus, it is unlikely that OTC use of ibuprofen would have a major impact on the interpretations of the study.

8.2.10 Juni Review

An independent review of published observational studies was recently published by Juni et al [25]. The authors summarize their findings in a forest plot (Figure 1). Apart from one study by Jick [26], a rather small case-control study in the GPRD with only 6 cases of MI exposed to naproxen reported and a reported odds ratio of 1.0 (95%CI: 0.3-3.3), the authors of the meta analysis included all studies cited in this review and no additional studies.

Their overall findings were that the relative risk of MI associated with naproxen exposure was 0.84 (95% CI: 0.75-0.99) compared with both nonusers of NSAIDs and with users of other NSAIDs. Thus, there is a small, but significant, cardioprotective effect of naproxen. The results of this meta analysis are again summarized by Eric Topol in a commentary [27]. He concluded that naproxen was the only NSAID with some cardioprotective effect with an estimated 14% reduction in the risk of MI.

Figure 1 Meta-Analysis of Naproxen and the Risk of MI

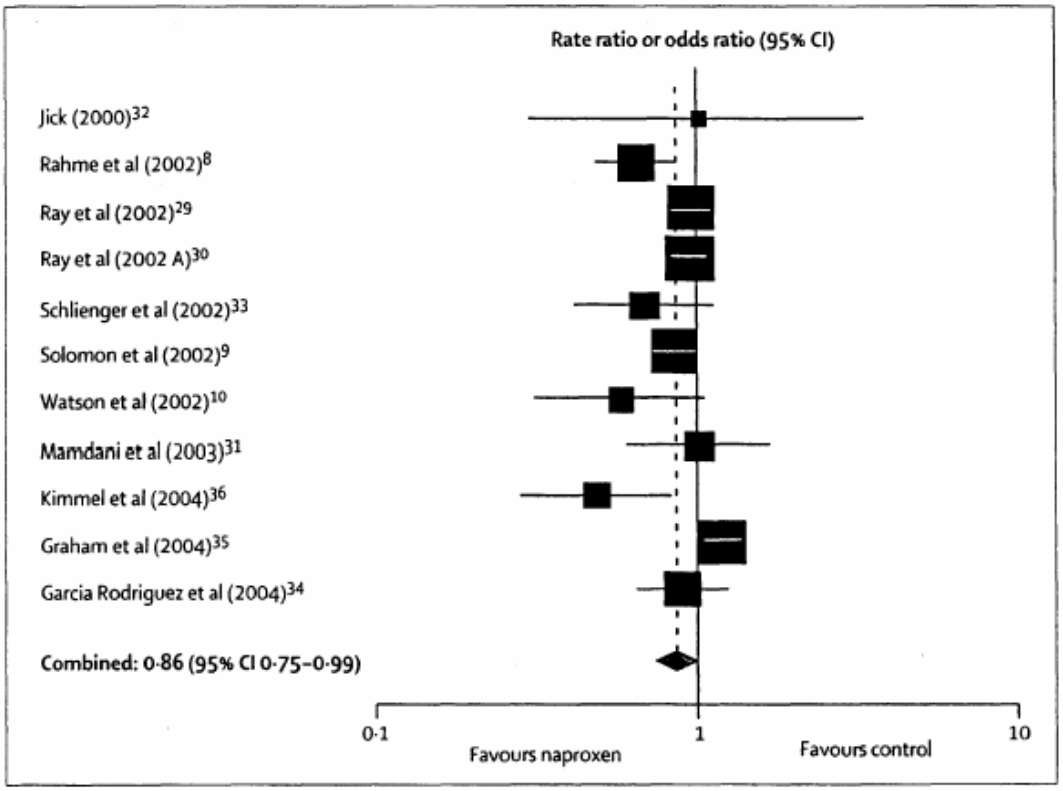

Figure 4: **Meta-analysis of observational studies of naproxen and risk of myocardial infarction**

8.3 Summary of Postmarketing Observational Studies

Because of the lack of large placebo-controlled trials, we have attempted to summarize all major published observational studies investigating an association between exposure to naproxen and the risk of cardiovascular events. The studies were all large and were conducted in different regions of North America and the UK. The studies were fairly consistent in estimating the effect of naproxen on cardiovascular events. Several studies provided statistically significant evidence of a cardiovascular risk reduction with naproxen compared with either nonusers of NSAIDs or users of other NSAIDs [13, 15, 16, 21]. Other studies provided evidence of a trend towards a reduced cardiovascular risk on naproxen; however, the confidence intervals included unity, suggesting data compatible with no effect on cardiovascular risk compared with nonusers of NSAIDs [19, 17, 22, 23]. Only one study provided evidence of a small, but statistically significant increased cardiovascular risk for current use of naproxen compared with remote use of NSAIDs [20]. It is also interesting to note that the same study provided a similar increased risk for ibuprofen and for other NSAIDs. While it is difficult to interpret this study, a possible explanation is that if naproxen confers a slight cardioprotective benefit or if it has no association with cardiovascular events, as suggested by other studies, the

small increased risk in this study could be a chance finding in the context of multiple statistical testing.

Overall, the comprehensive review of the observational studies indicates no evidence of an association between cardiovascular risk and the use of naproxen. In contrast, there appears to be a trend towards a protective effect with an estimated 14% reduction in the risk of MI associated with naproxen [25]. It should be noted that the duration of naproxen use is rarely ascertained from these published studies and therefore, the conclusions in the report may not necessarily be generalizable to chronic use of naproxen.

Table 5 Summary of Observational Studies on Naproxen and Cardiovascular Events

Study Author	Design	N	History of CHD	Events of Interest	Odds Ratio or Relative Risk for Naproxen		Comments
Solomon NJ Medicaid [13]	Case-Control	4400 cases	Excluded	AMI	0.84 (0.72-0.98) vs nonusers of NSAIDs	0.82(0.67-1.01) vs ibuprofen	85% aged 65+
Watson GPRD [15]	Case-Control	800 cases	Excluded	Acute thombem. CV. events	0.61 (0.39-0.94) vs nonusers of NSAIDs	0.65(0.34-1.24) vs users of NSAIDS	75% aged 60+
Rahme Quebec [16]	Case-Control	14000 cases	Not Excluded	AMI	0.64(0.48-0.86) vs other NSAIDs		Age 65+ Chronic (60+ days) use
Schlienger GPRD [19]	Case-Control	3300 cases	Excluded	AMI	0.68 (0.42-1.13) vs nonusers of NSAIDs		50% aged 60+
Rodriguez GPRD [23]	Case-Control	4800 cases	Not Excluded	AMI	0.89 (0.64-1.24) vs non users of NSAIDs		Ages 50-84
Graham Kaiser Permanente [20]	Case-Control	8200 cases	Not Excluded	AMI/sudden Cardiac death	1.18(1.04-1.35) vs remote NSAIDs users.		Mean age 67
Kimmel Philadelphia Hospitals [21]	Case-Control	1150 cases	Not Excluded	MI	0.48 (0.28-0.82) vs nonNSAIDs		Mean age 57, No aspirin use
Ray Tennessee Medicaid [17]	Cohort	70000 Naproxen	Not Excluded	Serious CHD	0.93 (0.82-1.06) current users vs nonusers of NSAIDs	0.92(0.73-1.16) new users vs nonusers of NSAIDS	Mean age 60. Rates: 13.0/1000pyrs nonNSAIDS vs 11.6 current naprox
Mamdani Ontario [22]	Cohort	6000 Naproxen	Not Excluded	AMI	1.0 (0.6-1.7) vs non users		Age 65+. Rates: 8.2/1000pyrs non NSAIDS, 9.6 Naprox, 10.7 celecox.

9. SUMMARY

9.1 Pharmacologic Studies

Naproxen is a dual COX-1/COX-2 inhibitor. Naproxen is known to inhibit platelet aggregation through its effects on COX-1 and thus, could potentially decrease the risk of cardiovascular events.

9.2 Clinical Studies in the NDAs

Clinical data did not indicate any evidence of a signal for cardiovascular (AMI/MI) or cerebrovascular events.

9.3 Other Postmarketing Clinical Studies

A number of postmarketing clinical studies with naproxen have been conducted in which the incidence of cardiovascular events was examined. None of these studies showed evidence of an increased cardiovascular risk in the naproxen treatment groups.

9.4 Postmarketing Surveillance

A review of the Roche naproxen safety database did not show a signal for AMI/MI or CVA. A review of the Bayer OTC dataset confirmed a lack of a signal for these events in the OTC setting.

9.5 Postmarketing Observational Studies

A comprehensive review of observational studies indicates no evidence of an association between cardiovascular risk and the use of naproxen. In contrast, there appears to be a trend towards a protective effect with an estimated 14% reduction in the risk of MI associated with naproxen. It should be noted that the duration of naproxen use is rarely ascertained from these published studies.

10. CONCLUSIONS

The NIA recently reported a suspension of the ADAPT study, a long-term study of naproxen and celecoxib in Alzheimer's patients, in part, because of findings reported in a separate trial sponsored by the National Cancer Institute trial (APC trial) which was designed to test the effectiveness of celecoxib in preventing colon cancer. In addition, however, unadjudicated preliminary findings from the ADAPT trial indicated an apparent increase in cardiovascular and cerebrovascular events among the participants taking naproxen when compared with those on placebo. Prior to the preliminary findings of the ADAPT study, no detrimental cardiovascular signal had been detected with naproxen use. In addition, naproxen would not have been expected to have an adverse effect on cardiovascular risk based on its mechanism of action and its known clinical pharmacology. In fact, several studies have suggested that naproxen may have a cardioprotective effect.

Roche and Bayer undertook a comprehensive evaluation of the safety data available for naproxen to determine whether a potential cardiovascular (AMI/MI) or cerebrovascular signal exists. This analysis included a review of the mechanism of action of naproxen in relation to COX-1 and COX-2 and a review of available preclinical, clinical, and postmarketing data.

The vast majority of data in both the long-term and the short-term setting show that there is no relationship between an increased risk of MI and CVA and the use of naproxen. Unadjudicated preliminary findings from the ADAPT study are inconsistent with the available clinical data for naproxen as well as the known pharmacologic properties of propionic acid derivatives. The benefit/risk for prescription and OTC naproxen remains unchanged.

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