Advisory Committee Briefing Document

Celecoxib: Cardiovascular Safety and Overall Benefit/Risk Assessment

In Preparation for a Public Forum on Selective COX-2 Inhibitors

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ABBREVIATIONS

ABPM	Ambulatory Blood Pressure Monitoring
ACE	Angiotensin Converting Enzyme
AMI	Acute myocardial infarction
ADAPT	Alzheimer's Disease Anti-Inflammatory Prevention Trial
AERS	Adverse Event Reporting System
APC	Prevention of Sporadic Colorectal Adenomas with Celecoxib Trial
APPROVe	Adenomatous Polyp Prevention on Vioxx Trial
APTC	Antiplatelet Trialists Collaboration
BID	Twice Daily
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CLASS	Celecoxib Long-Term Arthritis Safety Study
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CRP	C-Reactive Protein
CSC	Cardiovascular Safety Committee
DSMB	Data Safety Monitoring Board
EMEA	European Agency for the Evaluation of Medicinal Products
ERASME	Extractions, Research, Analyses for Economic Medical
EU	European Union
FAP	Familial Adenomatous Polyposis
FDA	Food and Drug Administration
GPRD	General Practice Research Database
ICD	International Classification of Diseases
IRA	Ileorectal Anastomosis
IPAA	Ileal Pouch-Anal Anastomosis
IRG	Independent Research Grant
LDL	Low-Density Lipoprotein
n	Number of Patients With Events
N	Number of Patients Treated
NA	Not Applicable
NCI	National Cancer Institute

ABBREVIATIONS, continued

NDA	New Drug Application
NO	Nitric Oxide
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
PGI_2	Prostaglandin I_2, also known as Prostacyclin
PhRMA	Pharmaceutical Research and Manufacturers of America
PreSAP	Prevention of Colorectal Sporadic Adenomatous Polyps Trial
QD	Once Daily
RA	Rheumatoid Arthritis
SAP	Spontaneous Adenomatous Polyposis
SR	Sustained Release
SUCCESS	Successive Celecoxib Efficacy and Safety Study
TDD	Total Daily Dose
TID	Three Times Daily
TPD	Therapeutic Products Directorate
TXA_2	Thromboxane
TEMC	Treatment Effects Monitoring Committee
UK	United Kingdom
US	United States
USR	Urgent Safety Restriction
VIGOR	Vioxx Intestinal Outcomes Research Trial
WHOART	World Health Organization Adverse Reaction Terminology

1. INTRODUCTION

1.1. Background

Patients seeking relief in chronic painful conditions such as osteoarthritis (OA) and rheumatoid arthritis (RA) or in acute conditions ranging from dysmenorrhea to post-surgical pain can benefit from effective pain relief using any of a variety of non-opiate analgesic and/or anti-inflammatory medications, including acetaminophen, naproxen, diclofenac, ibuprofen, piroxicam, and celecoxib. With any of these medications, benefit/risk considerations may vary according to clinical setting (eg, chronic versus acute pain) and according to patient characteristics such as baseline risk for gastrointestinal or cardiovascular adverse effects. Celecoxib, a diaryl-substituted pyrazole, is a selective inhibitor of the inducible form of the enzyme cyclooxygenase (COX-2), which catalyzes the formation of prostaglandins that act as proinflammatory mediators. As a result of this selective COX-2 inhibitory activity, celecoxib and related medications are believed to provide effective analgesic and anti-inflammatory benefits with less risk of gastrointestinal adverse effects than has been associated with inhibition of both COX-1 and COX-2 using nonselective, non-steroidal anti-inflammatory drugs (NSAIDs). As well as providing effective pain relief, both nonselective NSAIDs and selective COX-2 inhibitors provide a degree of relief from inflammation, making their chronic use necessary for many arthritis sufferers, for whom intermittent use or use of purely analgesic agents like acetaminophen is inadequate. Hence, both nonselective NSAIDs and selective COX-2 inhibitors enjoy extremely widespread use both as prescription arthritis medications and, in the case of some nonselective NSAIDs, as over-the-counter pain relievers.

On 30 September 2004, the selective COX-2 inhibitor rofecoxib (VIOXX®, Merck) was voluntarily withdrawn from worldwide markets after the data safety monitoring board (DSMB) overseeing a long-term, placebo-controlled rofecoxib clinical trial in cancer prevention (the Adenomatous Polyp Prevention on VIOXX [APPROVe] trial; Section 2.3) recommended that the trial be suspended because interim data at 18 months indicated that patients treated with rofecoxib had a significantly increased risk of serious cardiovascular events, including myocardial infarction and stroke, compared to patients treated with placebo. On 17 December 2004, the DSMB for the long-term Prevention of Sporadic Colorectal Adenomas with Celecoxib (APC) trial recommended that use of study medication in this trial should be suspended because interim data at 33 months indicated that patients treated with celecoxib had a significantly increased incidence of serious cardiovascular events, including myocardial infarction, stroke, and death compared to patients treated with placebo (Section 2.3.1). In response, the DSMB for another long-term celecoxib sporadic adenomatous polyposis (SAP) prevention trial, the Prevention of Colorectal Sporadic Adenomatous Polyps Trial (PreSAP), recommended suspension of that trial also. However, no statistically significant increase in cardiovascular risk was observed comparing celecoxib treatment versus placebo treatment in the PreSAP trial at 32 months. Also suspended on 17 December 2004 in response to the finding of

increased cardiovascular risk with celecoxib in the APC trial was treatment with study medication in the long-term Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT); however, no significant increase in cardiovascular risk was observed comparing celecoxib treatment versus placebo treatment in this trial (Section 2.3.2). Rather, interim data at 18 months from the ADAPT trial indicate that overall cardiovascular risk trended higher in patients treated with naproxen 220 mg twice daily (BID) or celecoxib 200 mg BID compared to placebo, with naproxen showing the greater numerical increase.

As a result of the observations described above, significant concern has arisen regarding the cardiovascular safety of both selective COX-2 inhibitors and nonselective NSAIDs. Though the cardioprotective effect of aspirin is well-established in medical practice, this effect is attributable to a biochemical activity in platelets (irreversible acetylation of COX-1) that is not shared with other nonselective NSAIDs.[1] There is little evidence that other nonselective NSAIDs are cardioprotective, and cardiorenal effects including increased blood pressure in NSAID users are well known.[2-12] Moreover, in some settings the cardioprotective antiplatelet effect of COX-1 inhibition with aspirin can be offset by increased risk of cerebrovascular hemorrhage: the use of aspirin for primary cardiovascular prevention in low risk subjects is not recommended due to this increase in risk, as established in an Antiplatelet Trialists' Collaboration (APTC) overview of randomized trials in antiplatelet therapy, because for these subjects the benefit/risk balance is not favorable.[13] Conversely, in post-stroke patients, antiplatelet therapy has minor impact on risk of myocardial infarction (reduction of 2 events per 1000 patients) but a large benefit in reduction of risk for ischemic stroke (reduction of 25 events per 1000 patients).[14]

For the reasons described above, the APTC has recommended that cardiovascular and cerebrovascular risk should be evaluated using a composite endpoint that comprises a variety of serious clinical outcomes including myocardial infarction, stroke, pulmonary embolism, and intracerebral or extracerebral hemorrhage.[14] Thus, studies that use only myocardial infarction as the primary endpoint, as most epidemiology studies of nonselective NSAIDs and selective COX-2 inhibitors have done (Section 2.5.1.1), may characterize cardiovascular safety in a manner that is incomplete. However, because of the very large numbers of patients and cardiovascular events available for analysis, epidemiology studies can be powerful adjuncts to randomized clinical trials in evaluation of the safety of NSAIDs and COX-2 inhibitors. In this document we will review the available epidemiology and clinical trial data on NSAIDs in the medical literature and in comparison with celecoxib. We conclude that not enough is currently known about the relative cardiovascular risks of selective COX-2 inhibitors versus nonselective NSAIDs to make fully informed benefit/risk decisions, because cardiovascular risks with nonselective NSAID use have never been adequately studied, although data presented herein show a comparable risk with celecoxib compared to nonselective NSAIDs. Accordingly, at present the assumption that all nonselective NSAIDs are safer with respect to cardiovascular events than all selective COX-2 inhibitors is not supported by objective data: existing cardiovascular safety data fail to distinguish between nonselective NSAIDs and selective COX-2 inhibitors, with the exception of rofecoxib.

1.2. Regulatory History

In April 1999, celecoxib was approved by the Health Canada's Therapeutic Products Directorate (TPD) to be marketed as CELEBREX® for relief of the signs and symptoms of OA with a recommend dose of 100 mg BID or 200 mg once daily (QD), and for relief of the signs and

symptoms of RA in adults with a recommend dose of 100 mg BID which may be increased to 200 mg BID. Also in May 2002, TPD issued a Notice of Compliance with Conditions for the treatment of familial adenomatous polyposis (FAP) at 800 mg total daily dose (TDD, taken as 400 mg BID) as an adjunct to usual care, and in September 2004, TPD approved CELEBREX for the short-term management of acute pain in adults at a dose of 400 mg TDD on day 1, followed by 200 mg QD on subsequent days up to a maximum of 7 days. In December 2004, for reasons related to safety, a "Dear Healthcare Professional" Letter was sent out to prescribing physicians concerning the suspension of Canadian market authorization (Notice of Compliance with Conditions) for the use of CELEBREX to reduce the number of adenomatous colorectal polyps in patients with FAP.

In December 1998, celecoxib was approved by the United States (US) Food and Drug Administration (FDA) to be marketed as CELEBREX® for relief of the signs and symptoms of OA with a recommend dose of 100 to 200 mg TDD, and for relief of the signs and symptoms of RA in adults with a recommend dose of 200 to 400 mg (200 mg BID) daily. In December 1999, celecoxib was approved for the symptomatic relief of OA and RA in Sweden, which acted as the Reference Member State for a Mutual Recognition procedure in the European Union (EU). Also in December 1999, the FDA approved an additional celecoxib indication at 800 mg TDD (400 mg BID) to reduce the number of adenomatous colorectal polyps in FAP as an adjunct to usual care (eg, endoscopic surveillance and/or surgery), and in October 2001 FDA approved CELEBREX for the management of acute pain in adults and treatment of primary dysmenorrhea at doses of 600 mg TDD day 1, followed by 400 mg TDD thereafter.

In April 2004, the European Medicines Agency (EMEA), in connection with an Article 31 Referral, completed an Article 31/Article 18 of the benefit/risk of the selective COX-2 inhibitor class of medications (celecoxib, etoricoxib, parecoxib sodium, rofecoxib, and valdecoxib). To support this review, Pfizer provided data concerning the benefit/risk profiles of 3 selective COX-2 inhibitor medications (celecoxib, valdecoxib, and parecoxib sodium), with particular emphasis on gastrointestinal and cardiovascular safety and on skin reactions. Following an extensive review of selective COX-2 inhibitor information available at the time (Opinion: November 2003), the scientific committee of the EMEA, the Committee on Medicinal Products for Human Use (CHMP), considered that the overall benefits of selective COX-2 inhibitors outweighed the risk of adverse reactions for the target patient population. In addition, product information for celecoxib was revised following the referral procedure to strengthen warnings. On 18 November 2004, in the context of the 30 September 2004 worldwide withdrawal of rofecoxib, the European Commission requested comprehensive cardiovascular safety information regarding celecoxib, etoricoxib, lumiracoxib, parecoxib sodium, and valdecoxib to support a second Article 31/Article 18 referral, and on 17 February 2005, the CHMP issued an Urgent Safety Restriction (USR), calling for revisions of prescribing information to include a contraindication for selective COX-2 inhibitors in established ischemic heart disease and/or cerebrovascular disease; the requested revisions are currently being finalized.

At a 16-18 February 2005 joint public meeting of the FDA Arthritis and Drug Safety Advisory Committees, extensive data regarding the cardiovascular safety and benefit/risk of selective COX-2 inhibitors including rofecoxib, celecoxib, and valdecoxib were presented and discussed. By majority vote (one vote short of unanimous for celecoxib), the joint Committees recommended that US marketing authorization for rofecoxib, celecoxib and valdecoxib should

not be withdrawn, and that prescribing information for each should be strengthened with Boxed Warnings regarding cardiovascular risks. On 7 April 2005, Pfizer agreed to work with FDA to add an acceptable Boxed Warning to the prescribing information for celecoxib relating to cardiovascular and gastrointestinal safety, along with a contraindication immediately after coronary artery bypass graft surgery. FDA has stated that it will require similar warnings in the prescribing information for nonselective NSAIDs as a precautionary measure, and has asked all sponsors to submit to FDA a comprehensive review of cardiovascular safety data for the respective nonselective NSAID(s).

1.3. Content and Organization of Briefing Document

This Briefing Document presents a critical evaluation of the cardiovascular safety of celecoxib, including comparisons to placebo and, more importantly, to nonselective NSAIDs, the primary therapeutic alternative.

- It will be shown that where celecoxib and nonselective NSAIDs have been studied together in the same setting, including both epidemiology studies and extensive clinical trials up to 1 year in duration in patients with chronic conditions, celecoxib consistently demonstrates no increase in cardiovascular risk compared to nonselective NSAIDs. Where possible, these comparisons are evaluated in terms of the entire spectrum of APTC cardiovascular events.

- While limited, preliminary safety data from long-term (>1 year) celecoxib prevention trials made available recently will also be presented. These data must be understood in the context of what little is known about the cardiovascular risks of nonselective NSAIDs in similar settings.

- The cardiovascular safety of celecoxib will be contrasted with that of rofecoxib, which has shown significant cardiovascular risk in direct comparison to nonselective NSAIDs both in clinical trials and in epidemiology studies.

- The possibility is explored that differences in molecular structure and pharmacology between rofecoxib and celecoxib may explain differences in cardiovascular risk that have been observed with these agents.

Separate executive summaries precede the various sections of this Briefing Document that present data from meta-analysis of results from clinical trials; preliminary results of long-term prevention studies; and reviews of published clinical trials, of published epidemiology studies, and of mechanistic and clinical data regarding the possibility of a class effect for selective COX-2 inhibitors. In addition, a separate summary of overall cardiovascular safety results for celecoxib follows data presentations (Sections 2.7), and benefit/risk considerations for celecoxib in the settings of pain/inflammation and FAP are presented separately at the end of the document (Section 5 and Section 6, respectively).

2. CELECOXIB CARDIOVASCULAR SAFETY

Data presented and reviewed in this evaluation of celecoxib cardiovascular safety include a Pfizer meta-analysis of data from clinical trials of up to 1 year duration in patients with chronic conditions (Section 2.2); recently available results from long-term celecoxib prevention studies (Section 2.3), a review of prospective clinical trials (Section 2.4) and epidemiology studies (Section 2.5) published to date, and an analysis of celecoxib postmarketing safety data (Section 2.6).

2.1. Celecoxib Clinical Development Program

Celecoxib clinical development programs have been conducted for the following indications: symptomatic relief of OA, RA, ankylosing spondylitis, and chronic low back pain (ie, studies in chronic pain indications); acute pain; primary dysmenorrhea; and reduction of intestinal polyps in patients with FAP. Treatment with study medication in long-term trials for SAP prevention (APC and PreSAP) and Alzheimer's disease prevention (ADAPT; not a Pfizer-sponsored clinical development program) has been suspended (efficacy evaluations are ongoing), while other investigational programs in cancer treatment and cancer prevention continue. Patients in completed chronic pain studies, together with patients in a completed 1-year study in patients with Alzheimer's disease, constitute the clinical study population with the greatest celecoxib exposure to date for which comprehensive safety data are available.

Celecoxib acute pain and primary dysmenorrhea studies have included over 3000 patients treated with celecoxib in over 25 studies; few cardiovascular adverse events occurred in these short term studies, and events were balanced across treatment groups. The chronic pain and Alzheimer's disease studies therefore better represent a population with baseline risk for cardiovascular events compared to patients in the acute pain or primary dysmenorrhea studies. In these studies in chronic indications, patients have been treated with daily doses of celecoxib for treatment durations ranging from 2 weeks up to 1 year, at doses ranging from 25 mg BID up to 400 mg BID.

2.2. Meta-Analysis of Data From Studies in Chronic Indications: Summary

To evaluate the cardiovascular safety of celecoxib, 41 completed clinical studies, representing a total of 24,993 patients with chronic conditions treated with celecoxib, were identified for meta-analysis. Patients these studies were treated with celecoxib at doses ranging from 50 to 800 mg TDD for durations ranging from 2 weeks to 12 months; all studies had randomized, parallel-group designs with placebo and/or active comparators (naproxen, diclofenac, ibuprofen, ketoprofen, acetaminophen, loxoprofen [a nonselective NSAID prodrug approved in some countries outside Canada], or rofecoxib). Not included were open label studies, studies with treatment durations <2 weeks, studies that did not have completed study reports as of 31 October 2004, and studies by independent investigators or other sponsors.

Results for all 41 studies that met criteria for meta-analysis either have been published in the medical literature or have been published or otherwise addressed as part of the Pharmaceutical Research and Manufacturers of America (PhRMA) Clinical Study Results Database, available at www.clinicalstudyresults.org.

Endpoints selected for meta-analysis were composites of serious cardiovascular thromboembolic adverse events, myocardial thromboembolic events, cerebrovascular events, peripheral vascular events, and the individual adverse events myocardial infarction and stroke, as well as an endpoint approximating the APTC composite endpoint of cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke.[14] Data were also integrated across studies for summarization and comparison of cardiorenal adverse events defined as follows: hypertension, hypertension aggravated, edema, edema generalized, edema peripheral, cardiac failure, cardiac failure right, and cardiac failure left. Endpoints were derived using World Health Organization Adverse Reaction Terminology (WHOART) medical dictionary terms and were not adjudicated.

The results of this meta-analysis of cardiovascular thromboembolic and cardiorenal adverse events support the following conclusions:

- The risk of serious cardiovascular thromboembolic adverse events and the risk of events comprising the APTC-like composite endpoint in patients with chronic painful conditions treated with celecoxib are similar to those observed in patients treated with nonselective NSAIDs (all nonselective NSAIDs combined, any dose).

- The incidence of myocardial infarction was numerically higher for celecoxib compared to combined nonselective NSAIDs although the confidence interval for this comparison was wide and included 1.0. This increase was offset by a significantly reduced incidence of stroke with celecoxib, including ischemic stroke.

- The overall risk of serious cardiovascular thromboembolic adverse events was similar between celecoxib and nonselective NSAID treatment in analyses stratified according to use or non-use of aspirin, particular celecoxib dose groups, use of particular NSAIDs, age (<65 years or ≥65 years), gender, and presence or absence of history of risk factors such as hypertension, diabetes, hyperlipidemia, or atherosclerotic heart disease, with the

exception of an increased rate of myocardial infarction with celecoxib compared to nonselective NSAID treatment in the presence of a history of atherosclerotic heart disease, and a smaller increase in the risk of the APTC-like endpoint in this subgroup. However, overall cardiovascular thromboembolic adverse events were not increased in this setting, and when patients were stratified by numbers of cardiovascular risk factors at baseline (none, one, or ≥2) no differences in risk compared to nonselective NSAID treatment were observed.

- Because of limited exposure to study medication, small numbers of events, and results driven by a single study in which randomization failed to prevent imbalances between treatment groups in baseline medical history suggesting cardiovascular risk, comparisons between celecoxib and placebo were of very limited value for the statistical evaluation of cardiovascular effects.

2.2.1. Studies in Chronic Indications Included in Meta-Analysis

A full list of all Pfizer-sponsored celecoxib clinical studies was compiled using information from the Pfizer Corporate Clinical Trials Registry and from appropriate legacy Pharmacia sources. Data from studies satisfying the following criteria were included in the meta-analysis:

- Randomized, controlled clinical trial with parallel-group study design;
- Planned duration of treatment ≥2 weeks;
- One or more of the following comparators: placebo, nonselective NSAID(s) (ie, naproxen, ibuprofen, diclofenac, ketoprofen, loxoprofen), or rofecoxib;
- Database, final study report, and supportive documents available as of 31 October 2004.

Open-label studies, pharmacokinetic studies, clinical pharmacology studies, and drug-drug interaction studies were excluded from the meta-analysis, as were studies of celecoxib in the treatment of acute pain. Because the APC, PreSAP and ADAPT trials (ie, SAP and Alzheimer's disease prevention trials) described in Section 1 were ongoing as of 31 October 2004 and throughout the analysis period had only preliminary data available to which Pfizer did not have access, these studies were not included in the meta-analysis. Hence the meta-analysis presented herein represents very limited data for durations of exposure to celecoxib ≥1 year. The full list of 41 celecoxib studies included in the meta-analysis is presented in Table 1; collectively, these studies provide a comprehensive analysis of cardiovascular safety for patients exposed to celecoxib of up to one year of treatment but, as noted above, the meta-analysis does not address cardiovascular safety in patients with durations of exposure to celecoxib >1 year.

Among the studies included in this meta-analysis are Study IQ5-97-02-001 (1-year study in patients with early to moderate Alzheimer's Disease) and its double-blind extension, Study EQ5-98-02-002, which was terminated early when celecoxib did not demonstrate efficacy in Study IQ5-97-02-001. Not included was Study IQ5-98-02-004, a second extension study following Study IQ5-97-02-001, in which patients were treated with open-label celecoxib (as described above, only randomized, controlled trials were included in the meta-analysis).

Table 1. Celecoxib Clinical Studies in Chronic Indications Included in Meta-Analysis

(Page 1 of 2)

Indication Protocol ID	Duration of Treatment	Treatment Groups
Osteoarthritis and/or Rheumatoid Arthritis		
N49-96-02-012	4 weeks	Placebo, Celecoxib 40 mg BID, 200 mg BID, 400 mg BID
N49-96-02-013	2 weeks	Placebo, Celecoxib 40 mg BID, 100 mg BID, 200 mg BID
N49-96-02-020	12 weeks	Placebo, Celecoxib 50 mg BID, 100 mg BID, 200 mg BID, Naproxen 500 mg BID
N49-96-02-021	12 weeks	Placebo, Celecoxib 50 mg BID, 100 mg BID, 200 mg BID, Naproxen 500 mg BID
N49-96-02-022	12 weeks	Placebo, Celecoxib 100 mg BID, 200 mg BID, 400 mg BID, Naproxen 500 mg BID
N49-96-02-023	12 weeks	Placebo, Celecoxib 100 mg BID, 200 mg BID, 400 mg BID, Naproxen 500 mg BID
I49-96-02-041	24 weeks	Celecoxib 200 mg BID, Diclofenac SR 75 mg BID
I49-96-02-042	6 weeks	Celecoxib 100 mg BID, Diclofenac 50 mg BID
N49-96-02-047	4 weeks	Placebo, Celecoxib 25 mg BID, 100 mg BID, 400 mg BID
N49-96-02-054	12 weeks	Placebo, Celecoxib 50 mg BID, 100 mg BID, 200 mg BID, Naproxen 500 mg BID
N49-96-02-060	6 weeks	Placebo, Celecoxib 100 mg BID, 200 mg QD
N49-97-02-062	12 weeks	Celecoxib 200 mg BID, Naproxen 500 mg BID
N49-97-02-071	12 weeks	Celecoxib 200 mg BID, Diclofenac 75 mg BID, Ibuprofen 800 mg TID
N49-98-02-087	6 weeks	Placebo, Celecoxib 100 mg BID, 200 mg QD
I49-98-02-096 (the SUCCESS trial)	12 weeks	Celecoxib 100 mg BID, 200 mg BID, Diclofenac 50 mg BID, Naproxen 500 mg BID
N49-98-02-035/102 (the CLASS trial)	52 weeks	Celecoxib 400 mg BID, Ibuprofen 800 mg TID, diclofenac 75 BID
Osteoarthritis and/or Rheumatoid Arthritis		
I49-98-02-105	12 weeks	Celecoxib 100 mg BID, Diclofenac 50 mg BID
I49-98-02-106	12 weeks	Celecoxib 100 mg BID, Diclofenac 50 mg BID
I49-98-02-107	12 weeks	Celecoxib 100 mg BID, Diclofenac 50 mg BID
N49-98-02-118	6 weeks	Placebo, Celecoxib 100 mg BID, Diclofenac 50 mg TID
N49-99-02-149	6 weeks	Celecoxib 200 mg QD, Rofecoxib 25 mg QD
N49-99-02-152	6 weeks	Placebo, Celecoxib 200 mg QD, rofecoxib 25 mg QD

N = Number of treated patients; QD = Once daily; BID = Twice daily; TID = Three times daily; TDD = Total daily dose.

Table 1. Celecoxib Studies in Chronic Indications Included in Meta-Analysis

(Page 2 of 2)

Indication Protocol ID	Duration of Treatment	Treatment Groups
Osteoarthritis and/or Rheumatoid Arthritis, continued		
N49-00-02-181	6 weeks	Celecoxib 200 mg QD, Rofecoxib 25 mg QD
J49-01-02-216	4 weeks	Placebo, Celecoxib 100 mg BID, Loxoprofen 60 mg TID
635-IFL-0508-002	12 weeks	Celecoxib 200 mg QD, Rofecoxib 25 mg QD, Naproxen 500 mg BID
635-IFL-0508-003	6 weeks	Placebo, Celecoxib 200 mg QD, Rofecoxib 25 mg QD
635-IFL-0508-010	6 weeks	Placebo, Celecoxib 200 mg QD, Paracetamol 1000 QID
A3191006 (the CAESAR trial)	52 weeks	Celecoxib 200 mg QD, Diclofenac 50 mg BID
A3191051	6 weeks	Placebo, Celecoxib 200 mg QD, Naproxen 500 mg BID
A3191052	6 weeks	Placebo, Celecoxib 200 mg QD, Naproxen 500 mg BID
A3191053	6 weeks	Placebo, Celecoxib 200 mg QD, Naproxen 500 mg BID
A3191063	6 weeks	Placebo, Celecoxib 200 mg QD, Ibuprofen 800 mg TID
COXA –0508-249	4 weeks	Placebo, Celecoxib 200 mg QD, Paracetamol 1000 mg QID
Ankylosing Spondylitis		
F49-98-02-137	6 weeks	Placebo, Celecoxib 100 mg BID, Ketoprofen 100 mg BID
N49-01-02-193	12 weeks	Placebo, Celecoxib 200 mg QD, 400 mg QD, Naproxen 500 mg BID
Low Back Pain		
J49-01-02-217	4 weeks	Celecoxib 100 mg BID, Loxoprofen 60 TID
COXA-0508-244	12 weeks	Placebo, Celecoxib 200 mg QD
COXA-0508-245	12 weeks	Placebo, Celecoxib 200 mg QD
COXA-0508-269	12 weeks	Placebo, Celecoxib 200 mg QD, 200 mg BID
Alzheimer's Disease		
IQ5-97-02-001	52 weeks	Placebo, Celecoxib 200 mg BID
EQ5-98-02-002	3 years[a]	Placebo, Celecoxib 200 mg BID

N = Number of treated patients; QD = Once daily; BID = Twice daily; TID = Three times daily; QID = Four times daily; TDD = Total daily dose.

[a] Terminated early when the results of Study IQ5-97-02-001 failed to show attenuation of the symptomatic progression of Alzheimer's disease

2.2.2. Methodology for Meta-Analysis

2.2.2.1. Categorization of Adverse Events

Adverse events identified for analysis were those reported by investigators treating the respective patients in the 41 clinical studies listed in Table 1. Investigator adverse event terms were coded to preferred terms using a Pfizer (Legacy Searle)-modified WHOART dictionary. Adverse events were not independently adjudicated. For analysis, serious adverse events were summarized if they occurred up to 28 days after the last dose of study medication.

The primary endpoint in this meta-analysis is a composite of serious cardiovascular thromboembolic adverse events. However, for this revised meta-analysis, unlike the preliminary Pfizer meta-analysis submitted to EMEA on 7 January 2005 and to the US FDA on 12 January 2005, the composite endpoint was expanded to include fatal myocardial and cerebrovascular events not included in the previous meta-analysis that were identified by subsequent medical review of cases that previously coded as sudden death (this revised meta-analysis has also been submitted to EMEA [02 March 2005] and the US FDA [13 May 2005]). Additionally, all cases of stroke in the previous meta-analysis were reviewed medically and identified as having hemorrhagic, ischemic, or unknown cause; as a result of this review, some events that coded as stroke in the previous meta-analysis were categorized as transient ischemic attack in this revised meta-analysis. Therefore, the serious cardiovascular thromboembolic adverse events category was defined for this revised meta-analysis as shown in Table 2, as were various subcategories of events and individual adverse events shown in bold font.

Table 2. Definition of Serious Cardiovascular Thromboembolic Adverse Events Selected as Endpoints for Meta-Analysis

Cardiovascular Thromboembolic		
Myocardial Thromboembolic	**Cerebrovascular**	**Peripheral Vascular**
Angina pectoris aggravated	Aneurysm, Fatal[a]	Embolism
Cardiac arrest	**Stroke**	Embolism Pulmonary
Circulatory Failure	**Stroke, Hemorrhagic**	Peripheral Ischemia
Myocardial Infarction	Cerebrovascular Accident	Thrombophlebitis Leg
Myocardial Ischemia	Cerebrovascular Disorder	Deep Thrombophlebitis Leg
Myocardial Rupture (Post-Infarction)	Cerebral Hemorrhage	
Tachycardia Ventricular	**Stroke, Ischemic**	
Thrombosis Coronary	**Stroke, Unknown**	
Sudden Death, Death Not Otherwise Specified, and fatal cases of Arteriosclerosis, Atrial Fibrillation, Cardiac Failure, Congestive Heart Failure, Coronary Artery Disorder, and Ventricular Fibrillation[a]	Subarachnoid Hemorrhage	
	Subdural Hematoma	
	Transient Ischemic Attack	

Event categories and adverse events indicated in **bold font** were selected as endpoints.

[a] These events were included together with fatal cases of the other events listed in this table to comprise a composite category, **Cardiovascular Death**, that was also selected as an endpoint for meta-analysis.

Additionally, medical review and categorization of all deaths and all investigator-reported cerebrovascular events allowed for an analysis of the APTC-like composite endpoint of cardiovascular deaths plus nonfatal myocardial infarction plus nonfatal stroke (ischemic,

hemorrhagic, or unknown). In the strict definition of the APTC composite endpoint, events comprising the endpoint are adjudicated by independent, blinded experts;[14] no such adjudication was performed for this meta-analysis (reviewers were three Pfizer physicians who were not blinded to randomized treatment assignments for individual patients; none were cardiologists; all were familiar with celecoxib and NSAID safety).

Cardiorenal adverse events were defined as follows (WHOART terms): hypertension, hypertension aggravated, edema, edema generalized, edema peripheral, cardiac failure, cardiac failure right, and cardiac failure left.

2.2.2.2. Statistical Methods

Separate analyses of serious cardiovascular adverse events and of cardiorenal adverse events were performed using data from studies comparing celecoxib versus placebo and from studies comparing celecoxib versus combined nonselective NSAIDs (naproxen, ibuprofen, diclofenac, ketoprofen, or loxoprofen, any dose). For each of these comparators, analyses included only data from studies in which that comparator was used; ie, analyses comparing celecoxib versus placebo were based on data only from studies that included a placebo treatment group, and analyses comparing celecoxib versus combined nonselective NSAIDs were based on data only from studies that included at least one nonselective NSAID treatment group. Adverse events and serious adverse events with onset >28 days after the last dose of study medication were not included in the meta-analysis, with one exception: in the analysis of time-to-death due to any cause, all deaths were included regardless of time of onset relative to last dose of study medication.

For evaluation of cardiovascular risk associated with celecoxib treatment, the most important analyses are those comparing all patients in the celecoxib ≥200 mg TDD treatment group versus the placebo treatment group or the combined NSAIDs treatment group, since these comparisons involve celecoxib exposure at or above the celecoxib doses indicated for OA or RA, including the 400 mg BID dose indicated for FAP and similar doses used in the very large Celecoxib Long-Term Arthritis Safety Study (the CLASS trial) for gastrointestinal safety. Statistical methods for summarization and analysis were employed as described below; all tests of significance and confidence intervals for statistical comparisons, where provided, were 2-sided with $\alpha = 0.05$, and no adjustments to Type I error were made for multiple comparisons.

- For serious cardiovascular thromboembolic adverse events, the Cochran-Mantel-Haenszel test, stratified by study, was used to analyze differences in incidence rates (numbers of events per patient-year of treatment) between treatment groups. The relative risk of each respective event (categorized as described in Table 2) was expressed as the ratio of celecoxib to comparator; also presented are 95% confidence intervals and p-values for statistical tests of the hypothesis that relative risk = 1.0.

- Kaplan-Meier curves are presented for time-to-event analyses, with log-rank tests used to compare treatment groups; events with onset >364 days were considered as having onset at Day 364.

- Differences in percentages of patients with cardiorenal adverse events, comparing treatment with celecoxib versus treatment with either placebo or combined nonselective NSAIDs, were analyzed using Fisher's Exact Test.

2.2.3. Results: Meta-Analysis of Studies in Chronic Indications

2.2.3.1. Baseline Patient Characteristics and Exposure to Study Medication

Baseline patient characteristics were generally balanced across integrated treatment groups (Table 3). Mean patient age ranged from 58 to 61 years across treatment groups, and women in each treatment group outnumbered men by approximately 2:1. A large majority of patients in each treatment group, ranging from 75% for placebo up to 95% for nonselective NSAIDs, were contributed by OA/RA studies. Use of aspirin for cardioprotection was also balanced across treatment groups (12 to 13% of patients). Baseline characteristics were also balanced across celecoxib dose groups. However, none of these studies were designed to evaluate cardiovascular risk, and randomization was not stratified for cardiovascular risk factors; as a result there were often imbalances in baseline risk factors or aspirin use in individual studies.

Table 3. Baseline Patient Characteristics, Celecoxib Studies in Chronic Indications

	Treatment Group		
Category Characteristic	Placebo N = 4057	Celecoxib (Any Dose) N = 24,933	NSAIDs (Any Dose) N = 13,990
Age (years)			
Mean	58.3	60.8	60.0
≥ 65 years	1447 (35.7)	10,452 (41.9)	5357 (38.3)
≥ 75 years	424 (10.5)	3255 (13.1)	1582 (11.3)
Gender, n (%)			
Male	1450 (35.7)	7505 (30.1)	4201 (30.0)
Female	2607 (64.3)	17,428 (69.9)	9789 (70.0)
Indication			
OA/RA	3040 (74.9)	22915 (91.9)	13303 (95.1)
Chronic Low Back Pain	632 (15.6)	1333 (5.3)	440 (3.1)
Ankylosing Spondylitis	232 (5.7)	377 (1.5)	247 (1.8)
Alzheimer's Disease	153 (3.8)	308 (1.2)	0 (0.0)
Aspirin Use, n (%)	530 (13.1)	3167 (12.7)	1635 (11.7)

OA = osteoarthritis; RA = rheumatoid arthritis; NSAIDs = Non-steroidal anti-inflammatory drugs, namely naproxen, diclofenac, ibuprofen, ketoprofen, and loxoprofen (combined totals).

Altogether, the meta-analysis of data from completed clinical trials comparing celecoxib versus placebo in chronic pain conditions represents a total of 8405 patients treated with celecoxib compared to 4057 patients treated with placebo, and the meta-analysis of data from completed clinical trials comparing celecoxib versus NSAIDs in chronic pain conditions represents a total of 20,463 patients treated with celecoxib compared to 13,990 patients treated with nonselective NSAIDs (any nonselective NSAID, any dose). The actual duration of study drug exposure for subjects included in these meta-analyses is summarized in Table 4.

Table 4. Duration of Exposure, Meta-Analysis of Studies Comparing Celecoxib Versus Placebo or NSAIDs

(Number [%] of Patients)

Comparison Duration of Treatment	Celecoxib (any dose)	Comparator (any dose)
Celecoxib vs Placebo, N	**8405**	**4057**
≥4 Weeks	6654 (79.2)	2758 (68.0)
≥12 Weeks	2584 (30.7)	895 (22.1)
≥24 Weeks	274 (3.3)	131 (3.2)
≥36 Weeks	255 (3.0)	126 (3.1)
≥52 Weeks	199 (2.4)	97 (2.4)
≥60 Weeks	13 (0.2)	6 (0.2)
Celecoxib vs Combined NSAIDs, N[a]	**20463**	**13990**
≥4 Weeks	17974 (87.8)	12312 (88.0)
≥12 Weeks	11206 (54.8)	7426 (53.1)
≥24 Weeks	3029 (14.8)	2847 (20.4)
≥36 Weeks	2472 (12.1)	2340 (16.7)
≥52 Weeks	803 (3.9)	780 (5.6)
≥60 Weeks	82 (0.4)	97 (0.7)
Celecoxib vs Naproxen, N[a]	**6311**	**2953**
≥4 Weeks	5172 (82.0)	2423 (82.1)
≥12 Weeks	2956 (46.8)	1260 (42.7)
≥24 Weeks	2 (0.0)	1 (0.0)
≥36 Weeks	1 (0.0)	0 (0.0)
≥52 Weeks	1 (0.0)	0 (0.0)
≥60 Weeks	0 (0.0)	0 (0.0)
Celecoxib vs Diclofenac, N[a]	**14921**	**7639**
≥4 Weeks	13504 (90.5)	6992 (91.5)
≥12 Weeks	9227 (61.8)	4724 (61.8)
≥24 Weeks	3028 (20.3)	1777 (23.3)
≥36 Weeks	2471 (16.6)	1421 (18.6)
≥52 Weeks	802 (5.4)	330 (4.3)
≥60 Weeks	82 (0.6)	9 (0.1)
Celecoxib vs Ibuprofen, N[a]	**4512**	**2484**
≥4 Weeks	3958 (87.7)	2154 (86.7)
≥12 Weeks	3032 (67.2)	1442 (58.1)
≥24 Weeks	2404 (53.3)	1069 (43.0)
≥36 Weeks	2071 (45.9)	919 (37.0)
≥52 Weeks	536 (11.9)	450 (18.1)
≥60 Weeks	75 (1.7)	88 (3.5)

N = Number of patients treated with study medication; NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely naproxen, diclofenac, ibuprofen, ketoprofen, and loxoprofen.

[a] Because some studies included multiple NSAID treatment groups, summing the Ns for celecoxib-treated patients from comparisons versus individual NSAIDs results in a total that exceeds the N for patients actually treated with celecoxib (any dose) in NSAID-controlled studies.

2.2.3.2. Serious Cardiovascular Thromboembolic Adverse Events: Celecoxib Versus Combined Nonselective NSAIDs

The relative risk of serious cardiovascular thromboembolic adverse events (as defined in Section 2.2.2.1) in studies comparing celecoxib ≥200 mg TDD versus nonselective NSAIDs (any nonselective NSAID, any dose) favored celecoxib in the all patients cohort, among non-users of aspirin, and among aspirin users, although the 95% confidence intervals for all of these relative risk estimates included 1.0 (Table 5).

When normalized for patient exposure to study medication in nonselective NSAID-controlled studies, more serious cardiovascular thromboembolic adverse events occurred among aspirin users (6.0 events per 100 patient-years in the celecoxib ≥200 mg TDD treatment group and 6.0 events per 100 patient-years in the combined nonselective NSAIDs treatment group) compared to non-users of aspirin (1.0 events per 100 patient-years in the celecoxib ≥200 mg TDD treatment group, 1.4 events per 100 patient-years in the combined nonselective NSAIDs treatment group). This difference likely reflects confounding by indication due to differences in baseline cardiovascular risk for aspirin users versus non-users of aspirin.

Table 5. Meta-Analysis of Studies Comparing Celecoxib ≥200 mg TDD Versus Nonselective NSAIDs: Any Serious Cardiovascular Thromboembolic Adverse Event

Population Treatment Group	N	Exposure (pt-years)	n	Relative Risk (95% CI)	p-Value[a]
All Patients					
Celecoxib ≥200 mg TDD	19773	5651	96	0.84 (0.63, 1.13)	0.255
NSAIDs	13990	4386	92	--	--
Non-Users of Aspirin					
Celecoxib ≥200 mg TDD	17599	4889	50	0.76 (0.52, 1.12)	0.171
NSAIDs	12355	3751	54	--	--
Aspirin Users					
Celecoxib ≥200 mg TDD	2174	763	46	0.95 (0.61, 1.48)	0.827
NSAIDs	1635	636	38	--	--

N = Number of patients treated with study medication; n = number of patients with events; CI = Confidence interval; TDD = Total daily dose; NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely naproxen, diclofenac, ibuprofen, ketoprofen, and loxoprofen (combined totals).
[a] Relative risks and p-values for treatment effect are based on Cochran-Mantel-Haenszel test stratified by study.

2.2.3.2.1. Serious Cardiovascular Thromboembolic Event Subcategories and Individual Adverse Events

In studies comparing celecoxib ≥200 mg TDD versus nonselective NSAIDs, relative risks favored treatment with celecoxib ≥200 mg TDD for the serious cardiovascular thromboembolic adverse events composite endpoint, for cardiovascular deaths, and for the APTC-like composite endpoint (non-adjudicated), as well as for the cerebrovascular and peripheral vascular event categories (Table 6). Relative risks favored nonselective NSAIDs over celecoxib ≥200 mg TDD for adverse events in the myocardial thromboembolic category and for myocardial infarction. All of these relative risk estimates had wide confidence intervals that included 1.0, with the

exception of the cerebrovascular event category. The relative risk for stroke significantly favored treatment with celecoxib ≥200 mg TDD over treatment with nonselective NSAIDs, as did the relative risk for ischemic stroke: despite small numbers of events, confidence intervals for these relative risk estimates were relatively narrow, with upper limits <1.0.

Table 6. Meta-Analysis of Studies Comparing Celecoxib ≥200 mg TDD Versus Nonselective NSAIDs: Serious Cardiovascular Thromboembolic Adverse Events

Event Category or Adverse Event	Celecoxib N = 19773	NSAIDs N = 13990	Relative Risk (95%CI)	p-Value[a]
Any Serious Cardiovascular Thromboembolic	**96**	**92**	**0.84 (0.63, 1.13)**	**0.255**
Any Cardiovascular Death	**15**	**19**	**0.72 (0.37, 1.39)**	**0.326**
Any Myocardial Thromboembolic	**62**	**42**	**1.24 (0.83, 1.86)**	**0.298**
Myocardial Infarction	43	22	1.63 (0.95, 2.79)	0.075
Non-Fatal Myocardial Infarction	35	19	1.49 (0.82, 2.70)	0.186
Fatal Myocardial Infarction	8	3	2.51 (0.69, 9.21)	0.164
Any Cerebrovascular	**15**	**33**	**0.33 (0.18, 0.60)**	**<0.001**
Stroke	8	20	0.31 (0.14, 0.68)	0.003
Stroke, Non-Fatal	7	16	0.33 (0.14, 0.78)	0.011
Stroke, Fatal	1	4	0.23 (0.04, 1.50)	0.125
Stroke, Hemorrhagic	1	4	0.16 (0.02, 1.40)	0.097
Stroke, Ischemic	5	14	0.27 (0.10, 0.71)	0.008
Stroke, Unknown	2	2	0.86 (0.14, 5.20)	0.871
Any Peripheral Vascular	**20**	**19**	**0.88 (0.47, 1.63)**	**0.679**
APTC-like Composite Endpoint	**57**	**54**	**0.86 (0.59, 1.26)**	**0.437**
Death Any Cause	**38**	**33**	**1.02 (0.64, 1.62)**	**0.944**

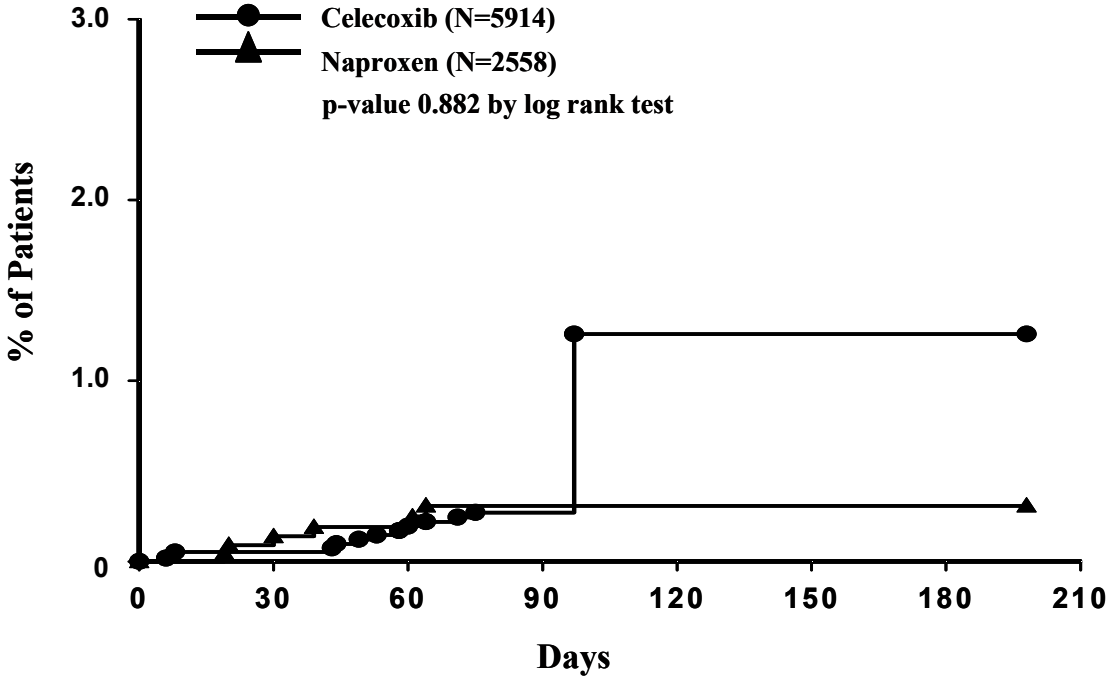
TDD = Total Daily Dose; NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely naproxen, diclofenac, ibuprofen, ketoprofen, and loxoprofen (combined totals); N = Number of patients treated with study medication; CI = Confidence interval; APTC-like = Antiplatelet Trialists' Collaboration composite endpoint (cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke), not adjudicated.

[a] Relative risks and p-values for treatment effect are based on Cochran-Mantel-Haenszel test stratified by study; p-values ≤0.05 are highlighted in gray.

2.2.3.2.2. Time-To-Event Analysis, APTC-Like Composite Endpoint in Studies ≥12 Weeks in Duration: Celecoxib Versus Nonselective NSAIDs

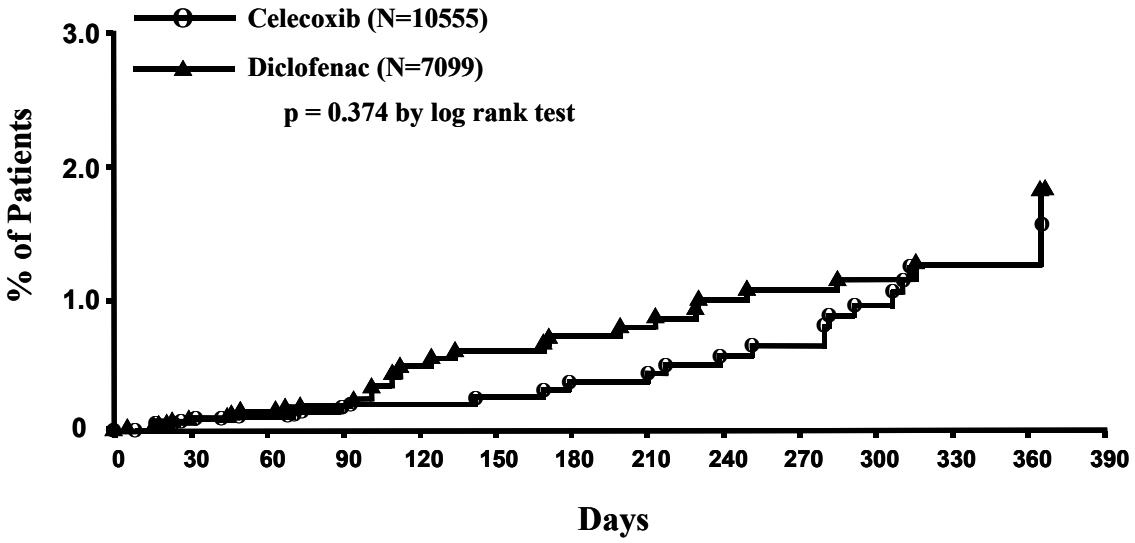
In time-to-event analyses for the APTC-like composite endpoint (cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke, not adjudicated), using data from all studies ≥12 weeks in duration comparing celecoxib (any dose) versus individual nonselective NSAIDs, comparison of event rates resulted in a p-value of 0.882 for celecoxib versus naproxen (Figure 1), a p-value of 0.374 for celecoxib versus diclofenac (Figure 2), and a p-value of 0.729 for celecoxib versus ibuprofen (Figure 3).

Figure 1. Kaplan-Meier Plot for Studies ≥12 Weeks in Duration Comparing Celecoxib (Any Dose) Versus Naproxen: Time to First APTC-Like Composite Endpoint



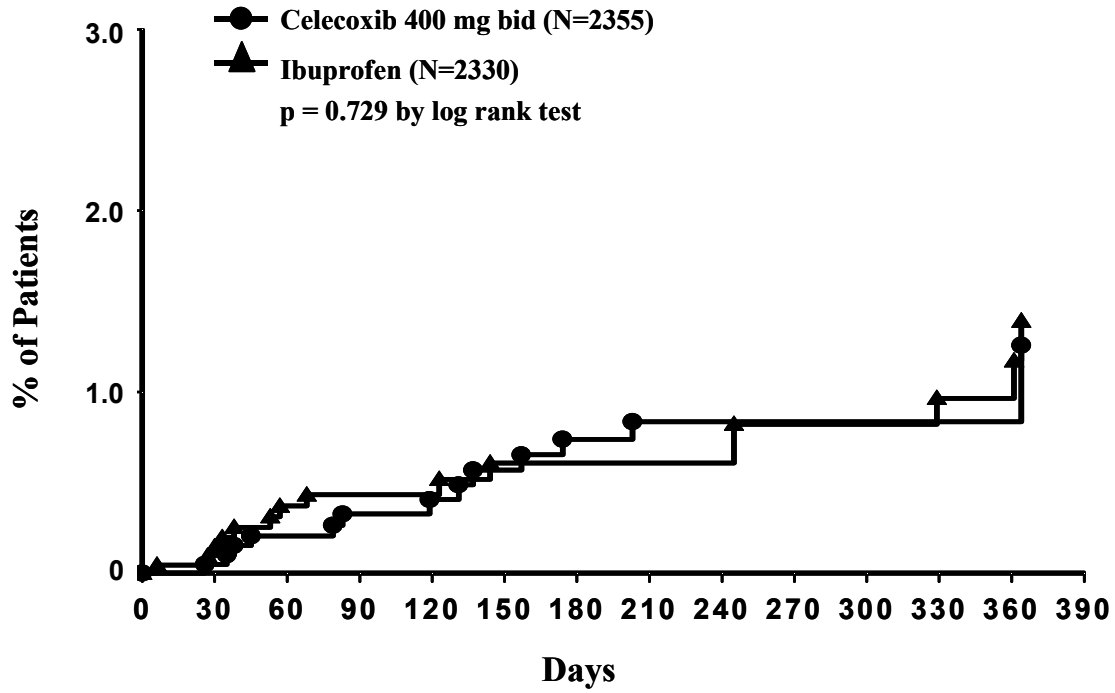
Event rates are based on Kaplan-Meier estimates; events with onset >364 days were taken to occur at Day 364. Includes Studies N49-96-02-020, N49-96-02-021, N49-96-02-022, N49-96-02-023, N49-96-02-054, N49-97-02-062, I49-98-02-096, N49-01-02-193, and 635-IFL-0508-002; celecoxib total daily doses in these studies ranged from 100 mg to 800 mg. APTC-like = Antiplatelet Trialists' Collaboration composite endpoint (cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke, not adjudicated).

Figure 2. Kaplan-Meier Plot for Studies ≥12 Weeks in Duration Comparing Celecoxib (Any Dose) Versus Diclofenac: Time to First APTC-Like Composite Endpoint



Event rates are based on Kaplan-Meier estimates; events with onset >364 days were taken to occur at Day 364. Includes Studies I49-96-02-041, N49-97-02-071, I49-98-02-096, N49-98-02-102, I49-98-02-105, I49-98-02-106, I49-98-02-107, and A3191006; celecoxib total daily doses in these studies ranged from 200 mg to 800 mg. APTC-like = Antiplatelet Trialists' Collaboration composite endpoint (cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke, not adjudicated).

Figure 3. Kaplan-Meier Plot for Studies ≥12 Weeks in Duration Comparing Celecoxib (Any Dose) Versus Ibuprofen: Time to First APTC-Like Composite Endpoint



Event rates are based on Kaplan-Meier estimates; events with onset >364 days were taken to occur at Day 364. Includes Studies N49-98-02-035, and N49-97-02-071; celecoxib total daily doses in these studies ranged from 200 mg to 400 mg. APTC-like = Antiplatelet Trialists' Collaboration composite endpoint (cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke, not adjudicated).

2.2.3.2.3. Patient Subgroups, Cardiovascular Risk Factors, and Blood Pressure: Celecoxib Versus Nonselective NSAIDs

When studies that compared celecoxib ≥200 mg TDD versus nonselective NSAIDs were evaluated according to celecoxib dose (200 mg, 400 mg, or 800 mg TDD), nonselective NSAID comparator (naproxen, diclofenac, or ibuprofen), age (<65 years versus ≥65 years), or gender, no increases in risk of either any serious cardiovascular thromboembolic event or events comprising the APTC-like composite endpoint (nonadjudicated) were observed for celecoxib, with one exception: Risk was somewhat greater within the cohort <65 years of age with celecoxib ≥200 mg TDD compared to combined nonselective NSAIDs; however, the confidence interval for this comparison was very wide and included 1.0, and this increased risk was offset by significantly decreased risk within the cohort ≥65 years of age with celecoxib ≥200 mg TDD compared to combined nonselective NSAIDs for these endpoints. Risks for events in these categories among OA patients were numerically lower with celecoxib compared to nonselective NSAIDs, while risks for events in these categories among RA patients were numerically higher with celecoxib compared to nonselective NSAIDs; relative risk estimates in RA patients were

accompanied by very wide confidence intervals due to small numbers of events and total patients in the RA meta-analysis.

When data from studies comparing celecoxib ≥200 mg TDD versus nonselective NSAIDs were evaluated according to cardiovascular risk factors at baseline (as identified using medical history terms indicating hypertension, atherosclerotic heart disease, diabetes, or hyperlipidemia), no increases in risk of either any serious cardiovascular thromboembolic event or events comprising the APTC-like composite endpoint (nonadjudicated) were observed for celecoxib, with two exceptions: Risks for the APTC-like composite endpoint were somewhat greater among patients with history of atherosclerotic vascular disease and patients with history of diabetes treated with celecoxib ≥200 mg TDD compared to patients in these cohorts treated with nonselective NSAIDs. However, the confidence intervals for these comparison were very wide and included 1.0. Relative risks for these events with celecoxib compared to nonselective NSAIDs did not increase consistently with increasing numbers of cardiovascular risk factors at baseline.

For most patients, blood pressure data were collected only at baseline and the patient's last clinic visit, which usually occurred at the end of treatment. Therefore, no on-treatment blood pressure data are available for patients who terminated the respective studies without this last-visit measurement. Among patients who had events comprising the APTC-like endpoint (not adjudicated), on-treatment blood pressure measurements were not available for 17/57 patients treated with celecoxib ≥200 mg TDD and 17/54 patients treated with nonselective NSAIDs in NSAID-controlled studies. Altogether, a total of 7755/18989 patients (41%) treated with celecoxib ≥200 mg TDD and 5622/13377 patients (42%) treated with nonselective NSAIDs in NSAID-controlled studies had uncontrolled hypertension. Relative risks for the APTC-like endpoint (not adjudicated) were similar comparing celecoxib ≥200 mg TDD to combined nonselective NSAIDs in patients with baseline hypertension (defined as systolic blood pressure ≥140 mmHg) versus patients without baseline hypertension, patients with increased systolic blood pressure on treatment (any increase) versus patients without an increase, and patients with hypertension on treatment versus patients without hypertension on treatment; however, 95% confidence intervals were wide for all of these comparisons. Although the relative risk comparing celecoxib ≥200 mg TDD to combined nonselective NSAIDs in patients with clinically significant changes in blood pressure (defined as systolic blood pressure ≥140 mmHg and systolic blood pressure increased ≥20 mmHg relative to baseline) was much smaller than that observed in patients without clinically significant changes in blood pressure, the relative risk estimate in patients with clinically significant changes in blood pressure was based on very few events and had an extremely wide confidence interval.

Relative risk estimates for the APTC-like endpoint (not adjudicated), comparing celecoxib 200 mg TDD versus combined nonselective NSAIDs, tended to increase with increasing baseline blood pressure, increasing blood pressure at last clinic visit, and increasing values for highest observed blood pressure, except in patients with baseline blood pressure, blood pressure at last clinic visit, or highest observed blood pressure ≥160 mmHg (exposure to study medication was most limited in these cohorts). However, due to small numbers of events, all relative risk estimates comparing celecoxib ≥200 mg TDD versus combined nonselective NSAIDs in cohorts defined by blood pressure were accompanied by very wide confidence intervals, severely limiting the value of these comparisons for hypothesis testing and benefit/risk considerations.

2.2.3.3. Serious Cardiovascular Thromboembolic Adverse Events: Celecoxib Versus Placebo

The relative risk of serious cardiovascular thromboembolic adverse events (as defined in Section 2.2.2.1) in studies comparing celecoxib versus placebo slightly favored treatment with placebo over treatment with celecoxib ≥200 mg TDD in the all patients cohort, although limited exposure to study medication and small numbers of events resulted in wide confidence intervals for this comparison (Table 7). Stratification according to aspirin use showed that this difference in risk was driven primarily by events among aspirin users.

When normalized for patient exposure to study medication in placebo-controlled studies, more serious cardiovascular thromboembolic adverse events occurred among aspirin users (6.3 events per 100 patient-years in the celecoxib ≥200 mg TDD treatment group and 4.4 events per 100 patient-years in the placebo treatment group) compared to non-users of aspirin (1.3 events per 100 patient-years in the celecoxib ≥200 mg TDD treatment group, 1.4 events per 100 patient-years in the placebo treatment group). This difference likely reflects confounding by indication due to differences in baseline cardiovascular risk for aspirin users versus non-users of aspirin.

Table 7. Meta-Analysis of Studies Comparing Celecoxib ≥200 mg TDD Versus Placebo: Any Serious Cardiovascular Thromboembolic Adverse Event

Population Treatment Group	N	Exposure (pt-years)	n	Relative Risk (95% CI)	p-Value[a]
All Patients					
Celecoxib ≥200 mg TDD	7462	1268	28	1.14 (0.57, 2.27)	0.713
Placebo	4057	585	11	--	--
Non-Users of Aspirin					
Celecoxib ≥200 mg TDD	6466	1047	14	0.99 (0.40, 2.45)	0.977
Placebo	3527	494	7	--	--
Aspirin Users					
Celecoxib ≥200 mg TDD	996	221	14	1.29 (0.43, 3.88)	0.649
Placebo	530	91	4	--	--

N = Number of patients treated with study medication; n = number of patients with events; CI = Confidence interval; TDD = Total daily dose.
[a] Relative risks and p-values for treatment effect are based on Cochran-Mantel-Haenszel test stratified by study.

In this meta-analysis, patients in a single, small study (Study IQ5-97-02-001) and its extension (Study EQ5-98-02-002), which together included 308 patients treated with celecoxib ≥200 mg TDD for 273 patient-years of exposure versus 153 patients treated with placebo for 132 patient-years of exposure (Table 8), accounted for much of the difference between treatment with celecoxib and treatment with placebo in serious cardiovascular thromboembolic adverse events as observed in Table 7. Excluding these studies from the meta-analysis would leave 12 serious cardiovascular thromboembolic adverse events for 995 patient-years in the celecoxib ≥200 mg TDD treatment group (1.2 events per 100 patient-years) compared to 6 events for 453 patient-years in the placebo treatment group (1.3 events per 100 patient-years).

Table 8. Meta-Analysis of Celecoxib Studies IQ5-97-02-001 and EQ5-98-02-002: Any Serious Cardiovascular Thromboembolic Adverse Event

COMPARISON Population Treatment Group	N	Exposure (pt-years)	n	Relative Risk (95% CI)	p-Value[a]
CELECOXIB vs PLACEBO					
All Patients					
Celecoxib ≥200 mg TDD	308	273	16	1.56 (0.57, 4.26)	0.383
Placebo	153	132	5	--	--
Non-Users of Aspirin					
Celecoxib ≥200 mg TDD	202	176	9	1.26 (0.39, 4.04)	0.702
Placebo	113	99	4	--	--
Aspirin Users					
Celecoxib ≥200 mg TDD	106	97	7	2.39 (0.31, 18.2)	0.399
Placebo	40	33	1	--	--

N = Number of patients treated with study medication; n = number of patients with events; CI = Confidence interval; TDD = Total daily dose.
[a] Relative risks and p-values for treatment effect are based on Cochran-Mantel-Haenszel test stratified by study.

In Study IQ5-97-02-001, patients ≥50 years of age with early to moderate Alzheimer's disease were treated with placebo (140 patients) or celecoxib 200 mg BID (285 patients) for up to 52 weeks, to assess whether treatment with celecoxib would limit or attenuate the progression of Alzheimer's disease and to evaluate the safety of celecoxib 200 mg BID in this patient population. Interpretation of cardiovascular safety results from Study IQ5-97-02-001 is complicated by imbalances between treatment groups in baseline medical history suggesting increased baseline cardiovascular risk in the celecoxib treatment group (Table 9). Use of concomitant aspirin, a marker of cardiovascular risk, also was unbalanced comparing treatment groups (106/308 patients, 34%, treated with celecoxib versus 40/153 patients, 26%, treated with placebo), suggesting that the celecoxib treatment group had greater cardiovascular risk at baseline than the placebo treatment group.

Table 9. Cardiovascular-Related Medical History Terms That Differ by >2% Between Treatment Groups: Study IQ5-97-02-001

(Number [%] of Patients)

Medical History Term	Placebo N = 140	Celecoxib 200 mg BID N = 285
Hypertension	31 (22.1)	91 (31.9)
Diabetes	10 (7.1)	28 (9.8)
Aortocoronary Bypass Surgery	1 (0.7)	9 (3.2)
Transcerebral Ischemia	4 (2.9)	15 (5.3)
Coronary Artery Disease	1 (0.7)	8 (2.8)

N = Number of patients; BID = Twice daily.

2.2.3.3.1. Serious Cardiovascular Thromboembolic Event Subcategories and Individual Adverse Events

In studies comparing celecoxib ≥200 mg TDD versus placebo, relative risks favored placebo for the serious cardiovascular thromboembolic adverse events composite endpoint, for cardiovascular deaths, for the APTC-like composite endpoint (nonadjudicated), and for deaths due to any cause, as well as for events in the myocardial thromboembolic category but not events in the cerebrovascular and peripheral vascular event categories (Table 10). However, due to limited exposure to study medication and small numbers of events, confidence intervals were very wide for all of these comparisons, and were extremely wide for comparisons using the individual adverse events myocardial infarction, hemorrhagic stroke, and ischemic stroke, all of which numerically favored placebo.

Table 10. Meta-Analysis of Studies Comparing Celecoxib ≥200 mg TDD Versus Placebo: Serious Cardiovascular Thromboembolic Adverse Events

Event Category or Adverse Event	Celecoxib N = 7462	Placebo N = 4057	Relative Risk (95%CI)	p-Value[a]
Any Serious Cardiovascular Thromboembolic	**28**	**11**	**1.14 (0.57, 2.27)**	**0.713**
Any Cardiovascular Death	**11**	**3**	**1.74 (0.49, 6.17)**	**0.392**
Any Myocardial Thromboembolic	**16**	**4**	**1.68 (0.59, 4.81)**	**0.336**
Myocardial Infarction	9	2	1.65 (0.38, 7.21)	0.508
Non-Fatal Myocardial Infarction	7	2	1.24 (0.27, 5.76)	0.786
Fatal Myocardial Infarction	2	0	NA	0.348
Any Cerebrovascular	**11**	**6**	**0.87 (0.32, 2.33)**	**0.780**
Stroke	8	4	0.96 (0.29, 3.17)	0.942
Stroke, Non-Fatal	5	3	0.80 (0.19, 3.31)	0.753
Stroke, Fatal	3	1	1.44 (0.15, 13.68)	0.751
Stroke, Hemorrhagic	2	1	1.02 (0.09, 11.56)	0.985
Stroke, Ischemic	5	1	2.36 (0.29, 19.13)	0.420
Stroke, Unknown	1	2	0.24 (0.03, 2.04)	0.189
Any Peripheral Vascular	**2**	**1**	**0.95 (0.08, 11.38)**	**0.966**
APTC-like Composite Endpoint	**23**	**8**	**1.26 (0.57, 2.80)**	**0.574**
Death Any Cause	**17**	**6**	**1.37 (0.55, 3.46)**	**0.500**

TDD = Total Daily Dose; N = Number of patients treated with study medication; CI = Confidence interval; APTC-like = Antiplatelet Trialists' Collaboration composite endpoint (cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke), not adjudicated.

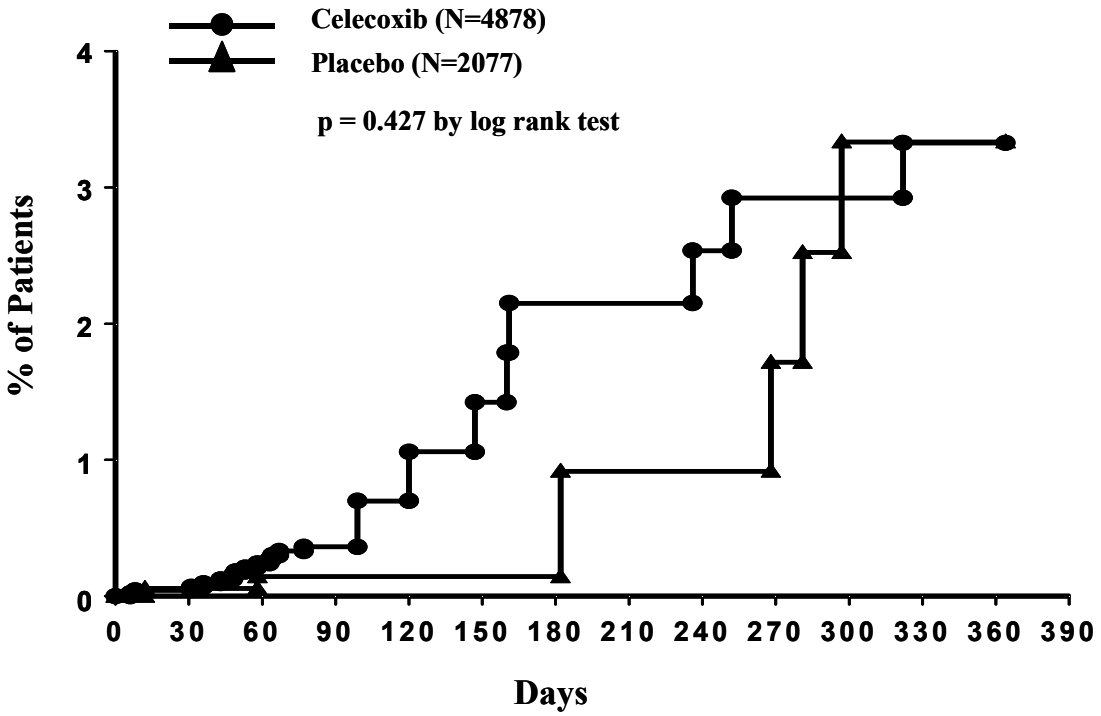
[a] Relative risks and p-values for treatment effect are based on Cochran-Mantel-Haenszel test stratified by study.

2.2.3.3.2. Time-To-Event Analysis, APTC-Like Composite Endpoint in Studies ≥12 Weeks in Duration: Celecoxib Versus Placebo

In a time-to-event analysis for the APTC-like composite endpoint (cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke, not adjudicated; see Figure 4), using data from all studies ≥12 weeks in duration comparing celecoxib (any dose) versus placebo,

comparison of event rates resulted in a p-value of 0.427. The Kaplan-Meier curve for this time-to-event analysis should be interpreted with caution, since differences between celecoxib and placebo were driven primarily by events in Study IQ5-97-02-001 (patients with early to moderate Alzheimer's Disease); interpretation of cardiovascular safety results in this study is complicated by imbalances between treatment groups in baseline medical history suggesting differences in cardiovascular risk (Table 9).

Figure 4. Kaplan-Meier Plot for Studies ≥12 Weeks in Duration Comparing Celecoxib (Any Dose) Versus Placebo: Time to First APTC-Like Composite Endpoint



Event rates are based on Kaplan-Meier estimates; events with onset >364 days were taken to occur at Day 364. Includes Studies N49-96-02-020, N49-96-02-021, N49-96-02-022, N49-96-02-023, N49-96-02-054, N49-01-02-193, COXA-0508-244, COXA-0508-245, COXA-0508-269, IQ5-97-02-001, and EQ5-98-02-002; celecoxib total daily doses in these studies ranged from 100 mg to 800 mg. APTC-like = Antiplatelet Trialists' Collaboration composite endpoint (cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke, not adjudicated).

2.2.3.3.3. Patient Subgroups, Cardiovascular Risk Factors, and Blood Pressure: Celecoxib Versus Placebo

When studies that compared celecoxib ≥200 mg TDD versus placebo were evaluated according to celecoxib dose (200 mg, 400 mg, or 800 mg TDD), age (<65 years versus ≥65 years), or gender for events in the any serious cardiovascular thromboembolic event category or for the APTC-like composite endpoint (nonadjudicated), confidence intervals were either very wide or extremely wide for all comparisons. Relative risks numerically favored placebo over celecoxib for the following comparisons: celecoxib 400 mg TDD; age ≥65 years, and women. In most of

these cases, differences were primarily driven by events in Study IQ5-97-02-001 (patients with early to moderate Alzheimer's Disease) and its extension, Study EQ5-98-02-002, in both of which the celecoxib dose was 200 mg BID; interpretation of cardiovascular safety results in Study IQ5-97-02-001 is complicated by imbalances between treatment groups in baseline medical history suggesting increased cardiovascular risk in patients treated with celecoxib (Table 9). Meta-analysis of studies that compared celecoxib ≥200 mg TDD versus placebo consistently favored celecoxib ≥200 mg TDD over placebo in patients with OA or RA, although confidence intervals were extremely wide for all of these comparisons due to small numbers of events.

When data from studies comparing celecoxib ≥200 mg TDD versus placebo were evaluated according to cardiovascular risk factors at baseline (as identified using medical history terms indicating hypertension, atherosclerotic heart disease, diabetes, or hyperlipidemia) for events in the any serious cardiovascular thromboembolic event category or for the APTC-like composite endpoint (nonadjudicated), confidence intervals were very wide for all comparisons. Relative risks numerically favored placebo over celecoxib for the following comparisons: patients with history of hypertension, patients with no history of atherosclerotic heart disease, patients with no history of diabetes, patients with history of hyperlipidemia, and patients with one cardiovascular risk factor at baseline. All of these differences were driven primarily by events in Study IQ5-97-02-001 (patients with early to moderate Alzheimer's Disease); interpretation of cardiovascular safety results in this study is complicated by imbalances between treatment groups in baseline medical history suggesting cardiovascular risk (Table 9).

For most patients, blood pressure data were collected only at baseline and the patient's last clinic visit, which usually occurred at the end of treatment. Therefore, no on-treatment blood pressure data are available for patients who terminated the respective studies without this last-visit measurement. Among patients who had events comprising the APTC-like endpoint (not adjudicated), on-treatment blood pressure measurements were not available for 13/23 patients treated with celecoxib ≥200 mg TDD and 3/8 patients treated with placebo in placebo-controlled studies. As a result, meta-analysis comparisons between celecoxib ≥200 mg TDD and either nonselective NSAIDs or placebo are based on very small numbers of events and therefore have minimal value for either hypothesis testing or benefit/risk considerations. Altogether, a total of 2254/6924 patients (33%) treated with celecoxib ≥200 mg TDD and 1040/3595 patients (29%) treated with placebo in placebo-controlled trials had hypertension during treatment with study medication; it is not known what percentages of patients in the respective treatment groups were treated for hypertension during the studies that comprise the meta-analysis.

Due to small numbers of events, confidence intervals associated with relative risk estimates for the APTC-like endpoint (not adjudicated), comparing celecoxib 200 mg TDD versus placebo, either were extremely wide or could not be calculated for patient cohorts defined by blood pressure. Such comparisons therefore have minimal value for either hypothesis testing or benefit/risk considerations.

2.2.3.4. Cardiorenal Adverse Events: Hypertension, Edema, and Cardiac Failure

As expected, percentages of patients with cardiorenal adverse events were greater in the celecoxib (any dose) treatment group compared to the integrated placebo treatment group; for

hypertension and edema peripheral, these differences were statistically significant (Table 11). Moreover, percentages of patients with cardiorenal adverse events tended to increase with increasing celecoxib dose. These observations are consistent with reports in the medical literature indicating that NSAIDs, including selective COX-2 inhibitors, can be associated with cardiorenal effects.[2-12]

Table 11. Meta-Analysis of Studies Comparing Celecoxib Versus Placebo: Cardiorenal Adverse Events

(Number [%] of Patients)

Comparison Adverse Event	Celecoxib	Placebo	p-Value[b]
Celecoxib Any Dose Versus Placebo, N[a]	**8405**	**4057**	
Hypertension	61 (0.7)	13 (0.3)	0.006
Hypertension Aggravated	30 (0.4)	14 (0.3)	--
Edema Generalized	16 (0.2)	2 (<0.1)	0.075
Edema Peripheral	156 (1.9)	33 (0.8)	<0.001
Cardiac Failure	12 (0.1)	1 (<0.1)	0.073
Cardiac Failure Right	1 (<0.1)	0 (0.0)	--
Celecoxib 200 mg TDD Versus Placebo, N[a]	**4834**	**3821**	
Hypertension	30 (0.6)	12 (0.3)	0.044
Hypertension Aggravated	15 (0.3)	12 (0.3)	--
Edema Generalized	9 (0.2)	2 (<0.1)	0.127
Edema Peripheral	75 (1.6)	32 (0.8)	0.003
Cardiac Failure	1 (<0.1)	1 (<0.1)	--
Cardiac Failure Right	1 (<0.1)	0 (0.0)	--
Celecoxib 400 mg TDD Versus Placebo, N[a]	**2013**	**1862**	
Hypertension	26 (1.3)	9 (0.5)	0.010
Hypertension Aggravated	11 (0.5)	6 (0.3)	--
Edema Generalized	4 (0.2)	0 (0.0)	0.126
Edema Peripheral	46 (2.3)	15 (0.8)	<0.001
Cardiac Failure	10 (0.5)	1 (<0.1)	0.012
Celecoxib 800 mg TDD Versus Placebo, N[a]	**615**	**636**	
Hypertension	3 (0.5)	2 (0.3)	--
Hypertension Aggravated	4 (0.7)	2 (0.3)	--
Edema Generalized	2 (0.3)	0 (0.0)	--
Edema Peripheral	15 (2.4)	7 (1.1)	0.086

N = Number of patients treated with study medication.

[a] Because patients treated with placebo in some studies serve as controls for multiple comparisons versus celecoxib, summing the Ns for placebo-treated patients from individual comparisons versus celecoxib 200, 400, or 800 mg TDD results in a total that exceeds the N for patients actually treated with placebo.

[b] P-values based on Fisher's exact test; p-values ≤0.05 are highlighted in gray, and -- indicates p-value >2.0 or cannot be calculated.

Percentages of patients with cardiorenal adverse events were consistently smaller in the integrated celecoxib (any dose) treatment group compared to the integrated nonselective NSAIDs treatment group (any nonselective NSAID, any dose); for most of these comparisons, differences significantly favored celecoxib (Table 12). Generally, when celecoxib (any dose) was compared to the individual nonselective NSAIDs naproxen, diclofenac, and ibuprofen, similar percentages of patients had cardiorenal adverse events; where differences were

statistically significant, celecoxib was consistently favored over the respective nonselective NSAID (diclofenac or ibuprofen).

Table 12. Meta-Analysis of Studies Comparing Celecoxib Versus Nonselective NSAIDs: Cardiorenal Adverse Events

(Number [%] of Patients)

Comparison Adverse Event	Celecoxib	Comparator	p-Value[a]
Celecoxib Any Dose Versus NSAIDs, N[b]	**20463**	**13990**	
Hypertension	239 (1.2)	208 (1.5)	0.012
Hypertension Aggravated	80 (0.4)	75 (0.5)	0.049
Edema	2 (<0.1)	6 (<0.1)	0.069
Edema Generalized	79 (0.4)	81 (0.6)	0.012
Edema Peripheral	421 (2.1)	339 (2.4)	0.025
Cardiac Failure	26 (0.1)	24 (0.2)	--
Cardiac Failure Left	0 (0.0)	6 (<0.1)	0.004
Celecoxib Any Dose Versus Naproxen, N[b]	**6311**	**2953**	
Hypertension	55 (0.9)	25 (0.8)	--
Hypertension Aggravated	24 (0.4)	14 (0.5)	--
Edema	1 (<0.1)	2 (<0.1)	--
Edema Generalized	28 (0.4)	20 (0.7)	0.162
Edema Peripheral	142 (2.3)	73 (2.5)	--
Cardiac Failure	3 (<0.1)	2 (<0.1)	--
Cardiac Failure Left	0 (0.0)	2 (<0.1)	0.102
Celecoxib Any Dose Versus Diclofenac, N[b]	**14921**	**7639**	
Hypertension	200 (1.3)	116 (1.5)	--
Hypertension Aggravated	61 (0.4)	35 (0.5)	--
Edema	1 (<0.1)	4 (<0.1)	0.048
Edema Generalized	67 (0.4)	32 (0.4)	--
Edema Peripheral	322 (2.2)	136 (1.8)	0.058
Cardiac Failure	23 (0.2)	12 (0.2)	--
Cardiac Failure Left	0 (0.0)	4 (<0.1)	0.013
Celecoxib Any Dose Versus Ibuprofen, N[b]	**4512**	**2484**	
Hypertension	85 (1.9)	64 (2.6)	0.057
Hypertension Aggravated	34 (0.8)	26 (1.0)	--
Edema	0 (0.0)	0 (0.0)	--
Edema Generalized	19 (0.4)	20 (0.8)	0.044
Edema Peripheral	154 (3.4)	120 (4.8)	0.005
Cardiac Failure	13 (0.3)	9 (0.4)	--
Cardiac Failure Left	0 (0.0)	0 (0.0)	--

NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely naproxen, diclofenac, ibuprofen, ketoprofen, and loxoprofen (combined totals); N = Number of patients treated with study medication.

[a] Because some studies included multiple NSAID treatment groups, summing the Ns for celecoxib-treated patients from comparisons versus individual NSAIDs results in a total that exceeds the N for patients actually treated with celecoxib (any dose).

[b] P-values based on Fisher's exact test; p-values ≤0.05 are highlighted in gray, and -- indicates p-value >2.0 or cannot be calculated.

2.2.4. Celecoxib Studies With Planned Durations of Exposure of 52 Weeks

As indicated in Table 1, the 41 completed celecoxib clinical studies that comprised the meta-analysis described herein included 2 studies comparing celecoxib versus nonselective NSAIDs with planned durations of exposure of 52 weeks, as follows:

- In the CLASS trial (Study N49-98-02-035/102), patients with OA or RA were treated with celecoxib 400 mg BID (2 to 4 times the maximum labeled dose for OA, twice the maximum labeled dose for RA; 3987 patients), diclofenac 75 mg BID (1996 patients), or ibuprofen 800 mg three times daily (TID; 1985 patients) for up to 15 months (median duration 6 to 9 months). Patient characteristics, including aspirin use (21% to 22% of patients), history of cardiovascular disease (40% of patients in all treatment groups), and cardiovascular risk factors, were balanced across treatment groups. The primary objective of the study was to compare the incidence of clinically significant upper gastrointestinal events across treatment groups.

- In the CAESAR trial (Study A3191006), patients ≥60 years of age with OA of the hip or knee were treated with celecoxib 200 mg QD (458 patients) or diclofenac 50 mg BID (458 patients) for up to 12 months, with a primary objective to compare discontinuation rates due to adverse events across treatment groups. Baseline patient characteristics were balanced across treatment groups, including history of hypertensive disease (40% for celecoxib and 45% for diclofenac) and of ischemic heart disease (9% for celecoxib and 10% for diclofenac). The rate of discontinuations due to adverse events during the course of the study was greater for the diclofenac 50 mg BID treatment group compared to the celecoxib 200 mg QD treatment group, but this difference was not statistically significant.

In meta-analyses presented below, data from studies with planned duration of 52 weeks comparing celecoxib versus nonselective NSAIDs were analyzed using the endpoints and statistical methods described in Section 2.2.2.

In addition to the two studies described above, patients were treated with celecoxib for up to 52 weeks in Study IQ5-97-02-001. In this study, patients ≥50 years of age with early to moderate Alzheimer's disease were treated with placebo (140 patients) or celecoxib 200 mg BID (285 patients) to assess whether treatment with celecoxib would limit or attenuate the progression of Alzheimer's disease and to evaluate the safety of celecoxib 200 mg BID in elderly patients suffering from Alzheimer's disease during long-term treatment. Also, in Study EQ5-98-02-002, a double-blind, parallel-group, placebo-controlled, single-center extension to Study IQ5-97-02-001, 13 patients were treated with placebo and 23 patients were treated with celecoxib 200 mg BID; although the planned duration of treatment in Study EQ5-98-02-002 was 3 years, the study was terminated early when Study IQ5-97-02-001 showed no efficacy with celecoxib in limiting or attenuating the progression of Alzheimer's disease. No other celecoxib studies with planned treatment durations of ≥52 weeks included in this meta-analysis had placebo comparators. As described in Section 2.2.3.3, interpretation of cardiovascular safety results from Study IQ5-97-02-001 is complicated by imbalances between treatment groups in baseline medical history suggesting increased cardiovascular risk in patients

treated with celecoxib (see Table 9). As a result, no meta-analyses of studies with duration ≥52 weeks comparing celecoxib versus placebo are presented in this section.

2.2.4.1. Results: Serious Cardiovascular Thromboembolic Adverse Events

In studies with planned treatment durations of 52 weeks, as in the full meta-analysis presented in Section 2.2.3, the relative risk of serious cardiovascular thromboembolic adverse events (as defined in Section 2.2.2.1) numerically favored treatment with celecoxib ≥200 mg TDD (the great majority of patients were treated with celecoxib 800 mg TDD, a supratherapeutic dose) compared to treatment with nonselective NSAIDs (combined data for diclofenac 50 mg BID, diclofenac 75 mg BID, and ibuprofen 800 mg TID; all of these are approved doses) in the all patients cohort, among non-users of aspirin, and among aspirin users; the 95% confidence intervals for all of these relative risk estimates included 1.0 (Table 13).

Table 13. Meta-Analysis of Studies ≥52 Weeks in Duration Comparing Celecoxib Versus Nonselective NSAIDs: Any Serious Cardiovascular Thromboembolic Adverse Event

Population Treatment Group	Treated Patients	Exposure (pt-years)	Patients With Events	Relative Risk (95% CI)	p-Value[a]
All Patients					
Celecoxib ≥200 mg TDD	4445	2735	59	0.92 (0.64, 1.32)	0.65
NSAIDs	4439	2635	62	--	--
Non-Users of Aspirin					
Celecoxib ≥200 mg TDD	3555	2211	32	0.92 (0.57, 1.49)	0.73
NSAIDs	3570	2136	34	--	--
Aspirin Users					
Celecoxib ≥200 mg TDD	890	524	27	0.94 (0.55, 1.61)	0.83
NSAIDs	869	500	28	--	--

CI = Confidence interval; TDD = Total daily dose; NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely diclofenac and ibuprofen (combined totals).
[a] Relative risks and p-values for treatment effect are based on Cochran-Mantel-Haenszel test stratified by study.

2.2.4.1.1. Serious Cardiovascular Thromboembolic Event Subcategories and Individual Adverse Events

As shown in Table 14, relative risks in studies with planned treatment durations of 52 weeks numerically favored treatment with celecoxib ≥200 mg TDD over treatment with nonselective NSAIDs for the serious cardiovascular thromboembolic adverse events composite endpoint and for the APTC-like composite endpoint (nonadjudicated), as well as for the cerebrovascular event category (statistically significant) and for both stroke (ie, all strokes together, whether ischemic, hemorrhagic, or of unknown cause) and ischemic stroke. Relative risks numerically favored nonselective NSAIDs over celecoxib ≥200 mg TDD for cardiovascular deaths, for adverse events in the myocardial thromboembolic category and specifically myocardial infarction, and for adverse events in the peripheral vascular category; all of these relative risk estimates favoring nonselective NSAIDs had wide confidence intervals.

It should be noted that in the comparisons described above, the great majority of patients in the celecoxib ≥200 mg TDD treatment group were treated with celecoxib at a supratherapeutic dose, 800 mg TDD, versus patients treated with diclofenac or ibuprofen at approved doses. It is also noteworthy that while the comparisons described above cannot exclude with confidence an approximate 2-fold excess in myocardial thromboembolic events (ie, upper limit of the confidence interval for relative risk is 1.88) with celecoxib compared to nonselective NSAIDs, they also cannot exclude with confidence a 10-fold excess of cerebrovascular events with nonselective NSAIDs compared to celecoxib (ie, lower limit of the confidence interval for relative risk is 0.10), including a >10-fold excess in ischemic stroke (ie, lower limit of the confidence interval for relative risk is 0.09).

Table 14. Meta-Analysis of Studies ≥52 Weeks in Duration Comparing Celecoxib ≥200 mg TDD Versus Nonselective NSAIDs: Serious Cardiovascular Thromboembolic Events

Event Category or Adverse Event	Celecoxib N = 4445	NSAIDs N = 4439	Relative Risk (95%CI)	p-Value[a]
Any Serious Cardiovascular Thromboembolic	**59**	**62**	**0.92 (0.64, 1.32)**	**0.65**
Any Cardiovascular Death	**13**	**11**	**1.17 (0.53, 2.59)**	**0.707**
Any Myocardial Thromboembolic	**39**	**32**	**1.18 (0.74, 1.88)**	**0.494**
Myocardial Infarction	24	18	1.29 (0.70, 2.38)	0.407
Non-Fatal Myocardial Infarction	17	15	1.1 (0.55, 2.20)	0.798
Fatal Myocardial Infarction	7	3	2.29 (0.62, 8.52)	0.214
Any Cerebrovascular	**5**	**19**	**0.26 (0.10, 0.64)**	**0.004**
Stroke	5	12	0.41 (0.15, 1.12)	0.082
Stroke, Non-Fatal	4	11	0.35 (0.12, 1.06)	0.063
Stroke, Fatal	1	1	1.04 (0.07, 16.6)	0.977
Stroke, Hemorrhagic	0	2	NA	0.166
Stroke, Ischemic	3	9	0.32 (0.09, 1.11)	0.073
Stroke, Unknown	2	1	2.04 (0.19, 21.9)	0.558
Any Peripheral Vascular	**16**	**12**	**1.29 (0.61, 2.71)**	**0.508**
APTC-like Composite Endpoint	**34**	**37**	**0.9 (0.56, 1.43)**	**0.642**

TDD = Total Daily Dose; NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely diclofenac and ibuprofen (combined totals); N = Number of patients treated with study medication; CI = Confidence interval; NA = Not applicable; APTC-like = Antiplatelet Trialists' Collaboration composite endpoint (cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke), not adjudicated.

[a] Relative risks and p-values for treatment effect are based on Cochran-Mantel-Haenszel test stratified by study; p-values ≤0.05 are highlighted in gray.

2.2.4.1.2. Serious Cardiovascular Thromboembolic Events in Patient Subgroups: Celecoxib Versus Nonselective NSAIDs

When data from studies with planned durations of treatment of 52 weeks comparing celecoxib versus nonselective NSAIDs were evaluated according to patient subgroups, relative risks for adverse events in the any serious cardiovascular thromboembolic category and for the APTC-like composite endpoint (nonadjudicated) were similar comparing celecoxib versus diclofenac and

comparing celecoxib versus ibuprofen, and similar comparing celecoxib versus combined nonselective NSAIDs across patient subgroups defined by patients with zero, one, or ≥2 cardiovascular risk factors at baseline (Table 15). All of these relative risk estimates were below or very near 1.0, most with wide confidence intervals.

Table 15. Meta-Analysis of Celecoxib Studies ≥52 Weeks in Duration Comparing Celecoxib ≥200 mg TDD Versus Nonselective NSAIDs: Serious Cardiovascular Thromboembolic Adverse Events by Patient Subgroup

Event Category Adverse Event	Celecoxib n/N	NSAIDs n/N	Relative Risk (95%CI)	p-Value[a]
Any Serious Cardiovascular Thromboembolic				
All Patients	59/4445	62/4439	0.92 (0.64, 1.32)	0.65
Diclofenac	35/2455	42/2454	0.82 (0.52, 1.28)	0.374
Ibuprofen	24/1990	20/1985	1.14 (0.63, 2.06)	0.67
No Risk Factors	14/2048	17/2065	0.81 (0.40, 1.64)	0.556
One Risk Factor	20/1443	23/1483	0.85 (0.47, 1.55)	0.591
≥Two Risk Factors	25/954	22/891	1.04 (0.59, 1.85)	0.883
APTC-like Composite Endpoint				
All Patients	34/4445	37/4439	0.9 (0.56, 1.43)	0.642
Diclofenac	20/2455	24/2454	0.83 (0.46, 1.49)	0.527
Ibuprofen	14/1990	13/1985	1.02 (0.48, 2.17)	0.958
No Risk Factors	7/2048	11/2065	0.63 (0.24, 1.60)	0.33
One Risk Factor	12/1443	12/1483	0.98 (0.44, 2.20)	0.969
≥Two Risk Factors	15/954	14/891	0.99 (0.48, 2.05)	0.985

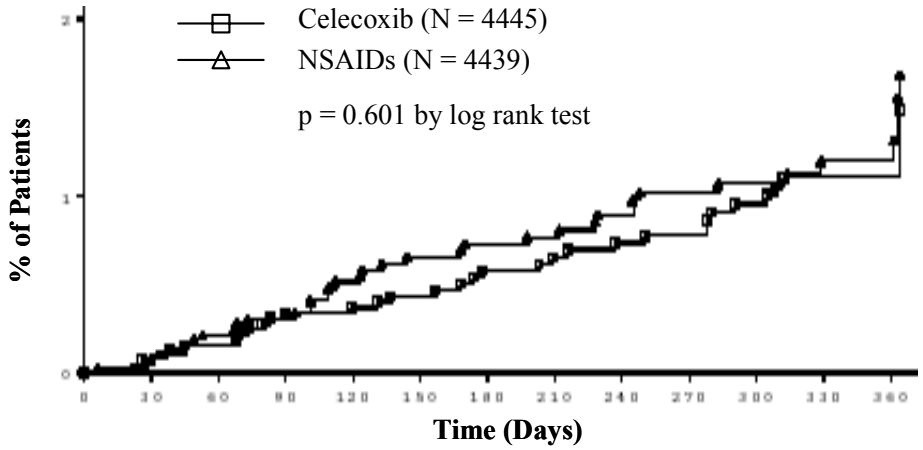
TDD = Total Daily Dose; NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely diclofenac and ibuprofen (combined totals); CI = Confidence interval; N = Number of patients treated with study medication; n = number of patients with events; APTC-like = Antiplatelet Trialists' Collaboration composite endpoint (cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke), not adjudicated.

[a] Relative risks and p-values for treatment effect are based on Cochran-Mantel-Haenszel test stratified by study.

2.2.4.1.3. Time-To-Event Analysis, APTC-Like Composite Endpoint in Studies ≥52 Weeks in Duration Comparing Celecoxib Versus Nonselective NSAIDs

In a time-to-event analysis for the APTC-like composite endpoint (cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke, not adjudicated), using data from studies with planned treatment durations of 52 weeks comparing celecoxib (any dose) versus combined nonselective NSAIDs (diclofenac or ibuprofen), comparison of event rates resulted in a p-value of 0.601 for celecoxib versus nonselective NSAIDs (Figure 5).

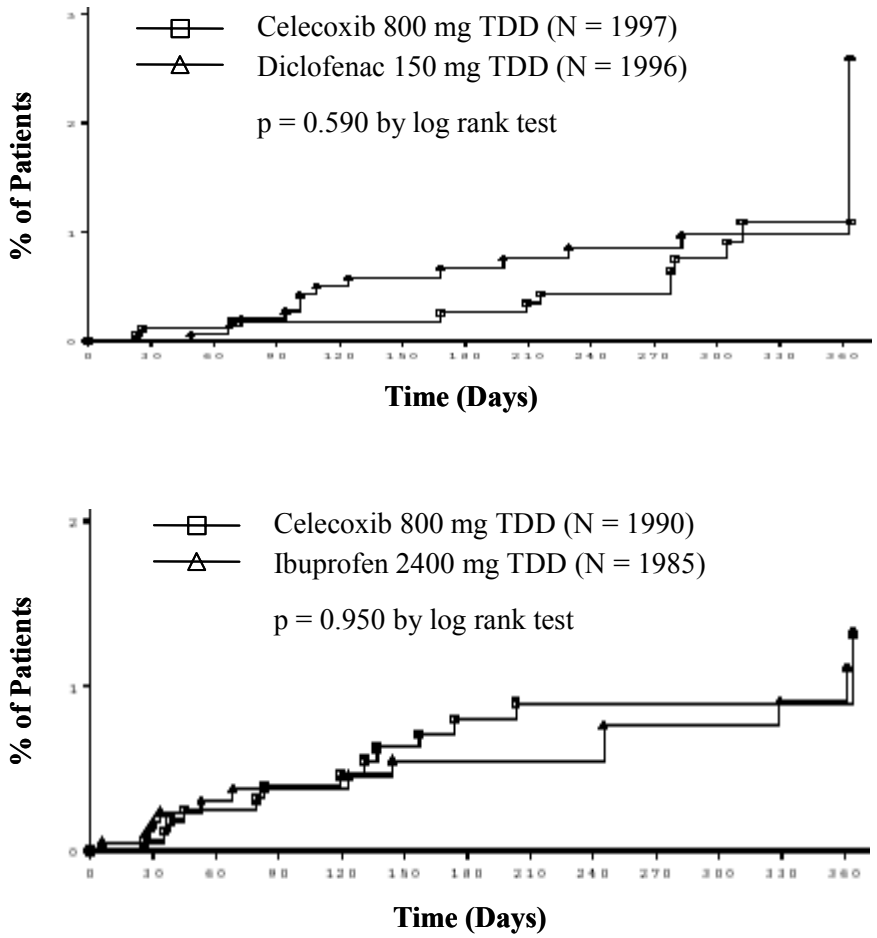
Figure 5. Kaplan-Meier Plot for Studies With Planned Treatment Durations of 52 Weeks Comparing Nonselective NSAIDs Versus Celecoxib: Time to First APTC-Like Composite Endpoint



Event rates are based on Kaplan-Meier estimates; events with onset >364 days were taken to occur at Day 364. Includes Studies N49-98-02-035/102 and A3191006; the celecoxib TDDs in these studies were 200 mg, the diclofenac TDDs were 150 mg and 100 mg respectively, and the ibuprofen TDD in Study N49-98-02-035/102 was 2400 mg. NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely diclofenac and ibuprofen (combined totals). APTC-like = Antiplatelet Trialists' Collaboration composite endpoint (cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke, not adjudicated) ; TDD = Total daily dose.

In time-to-event analyses for the APTC-like composite endpoint using data from only the CLASS trial, in which patients with OA or RA were treated with celecoxib 400 mg BID (2 to 4 times the maximum labeled dose for OA, twice the maximum labeled dose for RA; 3987 patients), diclofenac 75 mg BID (1996 patients), or ibuprofen 800 mg TID (1985 patients) for up to 15 months (median duration 6 to 9 months), comparison of event rates resulted in a p-value of 0.590 for celecoxib versus diclofenac and a p-value of 0.950 for celecoxib versus ibuprofen.

Figure 6. Kaplan-Meier Plots of Time to First APTC-Like Composite Endpoint in the CLASS Trial: Celecoxib Versus Diclofenac (Upper Panel) and Celecoxib Versus Ibuprofen (Lower Panel)



Event rates are based on Kaplan-Meier estimates; events with onset >364 days were taken to occur at Day 364. CLASS = Study N49-98-02-035/102; NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely diclofenac and ibuprofen (combined totals). APTC-like = Antiplatelet Trialists' Collaboration composite endpoint (cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke, not adjudicated); TDD = Total daily dose.

2.3. Emerging Data From Long-Term Prevention Trials: Summary

In the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial, 2586 patients were randomized to take rofecoxib 25 mg QD or placebo for 3 years with the objective to determine the cumulative incidence of recurrence of colon polyps. In an interim analysis after 18 months of treatment,[15] patients treated with rofecoxib 25 mg QD were shown to have a significant increase in the risk of serious cardiovascular thromboembolic adverse events (relative risk 1.92, 95% CI: 1.19 to 3.11 for rofecoxib over placebo for thrombotic events confirmed by adjudication, and relative risk 2.06, 95% CI: 1.16 to 3.64 for rofecoxib over placebo for the APTC composite endpoint). Further, there was no significant difference in thromboembolic risk compared to the respective placebo group between patients who received rofecoxib and took aspirin for cardiovascular prophylaxis compared to patients who received rofecoxib without aspirin. This finding suggests that the increased risk observed with rofecoxib was not due to an imbalance brought about by selective inhibition of COX-2-mediated prostacyclin (PGI_2) production without compensatory inhibition of COX-1-mediated thromboxane (TxA_2) production, but rather due to some other mechanism. The observation of increased cardiovascular risk with rofecoxib in the APPROVe trial prompted the DSMBs of very long-term celecoxib prevention studies (described below) to carefully re-assess cardiovascular safety in these studies, and in the case of the two colon cancer prevention trials, to commission an independent board to carefully adjudicate and analyze cardiovascular events.

In 2 spontaneous adenomatous polyposis (SAP) prevention trials and 1 Alzheimer's disease prevention trial, patients have been treated with celecoxib for up to 4 years at doses up to 400 mg BID, a dose well in excess of the maximum celecoxib doses recommended for OA patients (200 mg TDD) and RA patients (400 mg TDD).

- For one of these SAP prevention trials, the Prevention of Sporadic Colorectal Adenomas with Celecoxib (APC) trial, treatment with study medication was suspended before completion of the trial when a review of preliminary data by the DSMB identified a statistically significant increase in cardiovascular events for patients treated with celecoxib 400 mg BID compared to patients treated with placebo.

- Numerical but not statistically significant increases in cardiovascular risk for celecoxib versus placebo were observed in preliminary data for interim safety evaluations in the remaining 2 of these 3 long-term prevention trials. Treatment with study medication was suspended in both of these remaining trials (the Prevention of Colorectal Sporadic Adenomatous Polyps trial, PreSAP, with celecoxib 400 mg QD; and the Alzheimer's Disease Anti-Inflammatory Prevention Trial, ADAPT, with celecoxib 200 mg BID) in response to the preliminary observation of increase in cardiovascular events with celecoxib observed in the APC trial.

- Efficacy analyses from both colon cancer prevention trials, the APC trial and the PreSAP trial, are expected late in 2005, and if the underlying hypothesis (35% or more reduction in recurrence of colon polyps) is validated, this could have a major impact on SAP prevention.

- In the ADAPT trial, preliminary results from an interim safety review after 18 months of treatment indicate that overall cardiovascular risk trended higher in patients treated with naproxen 220 mg BID or celecoxib 200 mg BID compared to placebo, with naproxen showing the greater numerical increase.

2.3.1. Sporadic Adenomatous Polyposis Prevention Trials: PreSAP and APC

In both the PreSAP trial (Protocol EQ4-00-02-018, sponsored by Pfizer) and the APC trial (Protocol IQ4-99-02-005, sponsored by the Division of Cancer Prevention at the National Cancer Institute [NCI] with the support of Pfizer [NCI Contract N01-CN-95014]), patients who had undergone colonoscopic resection of all evident polyps were randomized in double-blind fashion to receive celecoxib or placebo for 3 years. Repeat colonoscopic surveillance was performed at Year 1 and Year 3 after randomization with the intent of assessing the cumulative proportion of patients who are polyp free at 3 years. Both protocols were powered to be able to detect a 35% reduction in the recurrence of colorectal adenomas. In the PreSAP trial, a total of 1561 patients were randomized in a 2:3 ratio to either placebo or celecoxib 400 mg QD; in the APC trial, a total of 2035 patients were randomized in a 1:1:1 ratio to celecoxib 200 mg BID, celecoxib 400 mg BID, or placebo. The initial 3-year treatment periods of both the PreSAP trial and the APC trial are due to be completed during 2005.

Patient safety in the APC and PreSAP trials has been carefully monitored, and efficacy and safety data were reviewed twice yearly in both studies by independent data safety monitoring boards (DSMBs; reports of unblinded data are prepared for DSMBs by independent statisticians, in order to protect study integrity; only these independent statisticians and DSMB members have had access to unblinded data), paying particular attention to cardiovascular and gastrointestinal events (the DSMB for the APC trial also received monthly reports of serious adverse events while patients were receiving study medication). At all interim reviews of safety and efficacy data prior to 16 December 2004, the respective DSMBs found no reason to stop either trial, and following the September 30th withdrawal of rofecoxib, each of the DSMBs restated that their safety reviews to date had identified no basis for altering the progress of these studies.

In response to the worldwide withdrawal of rofecoxib, the NCI requested the formation of an expert Cardiovascular Safety Committee (CSC) to review cardiovascular safety data from the APC trial. At the request of Pfizer, this same CSC was also asked to review cardiovascular safety data from the PreSAP trial. Members of the CSC, all of whom were experienced in the evaluation of cardiovascular endpoints, reevaluated and adjudicated all potential cardiovascular events from both trials without knowledge of study treatment according to endpoint definitions established 3 December 2004. A CSC statistician then analyzed these adjudicated events with respect to the frequency of occurrence in each treatment arm. On 16 December 2004, based on preliminary evaluation of interim safety data, the CSC concluded that continued exposure to celecoxib placed patients in both trials at increased risk for serious adverse events compared to the as yet unproven benefit. As a result, the respective DSMBs recommended that treatment with study medication in both SAP prevention trials should be suspended.

- Results of the CSC analysis for the APC trial, which have recently been published,[16] are as follows: At 33 months of follow-up, the incidence rates for the APTC composite endpoint (death from cardiovascular causes plus myocardial infarction, stroke, or heart

failure) were 7/679 patients (1.0%) with placebo, 16/685 patients (2.3%) with celecoxib 200 mg BID, and 23/671 patients (3.0%) with celecoxib 400 mg BID. Patients in the celecoxib 200 mg BID treatment group had a hazard ratio of 2.3 (95% CI: 0.9 to 5.5) and patients in the celecoxib 400 mg BID treatment group had a hazard ratio of 3.4 (95% CI: 1.4 to 7.8) compared to placebo.

- Results of the CSC analysis for the PreSAP trial, summarized in a report issued by the CSC on 18 April 2005, are as follows: At 32 months of follow-up, the incidence rates for the APTC composite endpoint (death from cardiovascular causes plus myocardial infarction, stroke, or heart failure) were 12/628 patients (1.9%) with placebo and 22/933 patients (2.4%) with celecoxib 400 mg QD. The relative risk with celecoxib 400 mg QD treatment compared to placebo was 1.2 (95% CI: 0.65 to 2.5).

Treatment with study medication in the APC trial and the PreSAP trial was suspended on 17 December 2004. Both studies remain ongoing for the purpose of collecting further efficacy and safety data. Pfizer and the NCI are currently working to make full study reports for the PreSAP and APC trials, including comprehensive safety and efficacy data, available as quickly as possible after study completion.

2.3.2. The Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT)

The ADAPT trial, sponsored by the National Institute of Aging (NIA) branch of the US National Institutes of Health and administered through the University of Washington and Johns Hopkins University, is a US, multicenter, double-blind, placebo-controlled trial of naproxen 220 mg BID or celecoxib 200 mg BID versus placebo to test the hypothesis that long-term use of a nonselective NSAID (naproxen) or selective COX-2 inhibitor (celecoxib) can prevent Alzheimer's dementia or delay cognitive decline. As of 17 December 2004, the trial had been ongoing for over 3.5 years, with a total of 2,528 subjects randomized (the enrollment target was 4500 subjects total), contributing 3888 patient-years of follow-up. The majority of randomized subjects are between 70 and 74 years (56%), white (97%), and male (54%).

The ADAPT trial's safety monitoring group, the Treatment Effects Monitoring Committee (TEMC), has met twice yearly since the start of the trial to scrutinize closely all safety data, assess the benefit/risk ratio for subjects, and make recommendations regarding the conduct of the trial. At its most recent meeting (10 December 2004), the TEMC analyzed safety data collected up to a cutoff date of 1 October 2004, representing approximately 700 patients with exposure to celecoxib, and found no reason to stop the ADAPT trial. However, on 17 December 2004, in response to the suspension of treatment with study medication in the PreSAP and APC trials, the executive board of the ADAPT trial suspended enrollment and treatment with study medication for ADAPT patients.

When the TEMC for the ADAPT trial released top-line results of the safety analysis prepared for its 10 December 2004 meeting (ie, after 18 months of treatment), these preliminary results indicated that overall cardiovascular risk trended higher in patients treated with low-dose naproxen (220 mg BID) or celecoxib 200 mg BID compared to placebo, with naproxen showing the greater numerical increase. The sponsors of the ADAPT trial are currently working to prepare a complete report for publication.

2.4. Cardiovascular Thromboembolic Events in Prospective Clinical Studies in the Medical Literature: Summary

Reviewed below are publications concerning the cardiovascular safety of celecoxib, rofecoxib, and nonselective NSAIDs as derived from either individual randomized clinical trials or meta-analyses of randomized clinical trials.

- Published data from prospective clinical trials, including a meta-analysis of data from 15 clinical trials representing approximately 30,000 patients, show no cardiovascular safety signal for celecoxib (although confidence intervals for relative risk estimates comparing celecoxib versus placebo and individual NSAIDs were very wide).

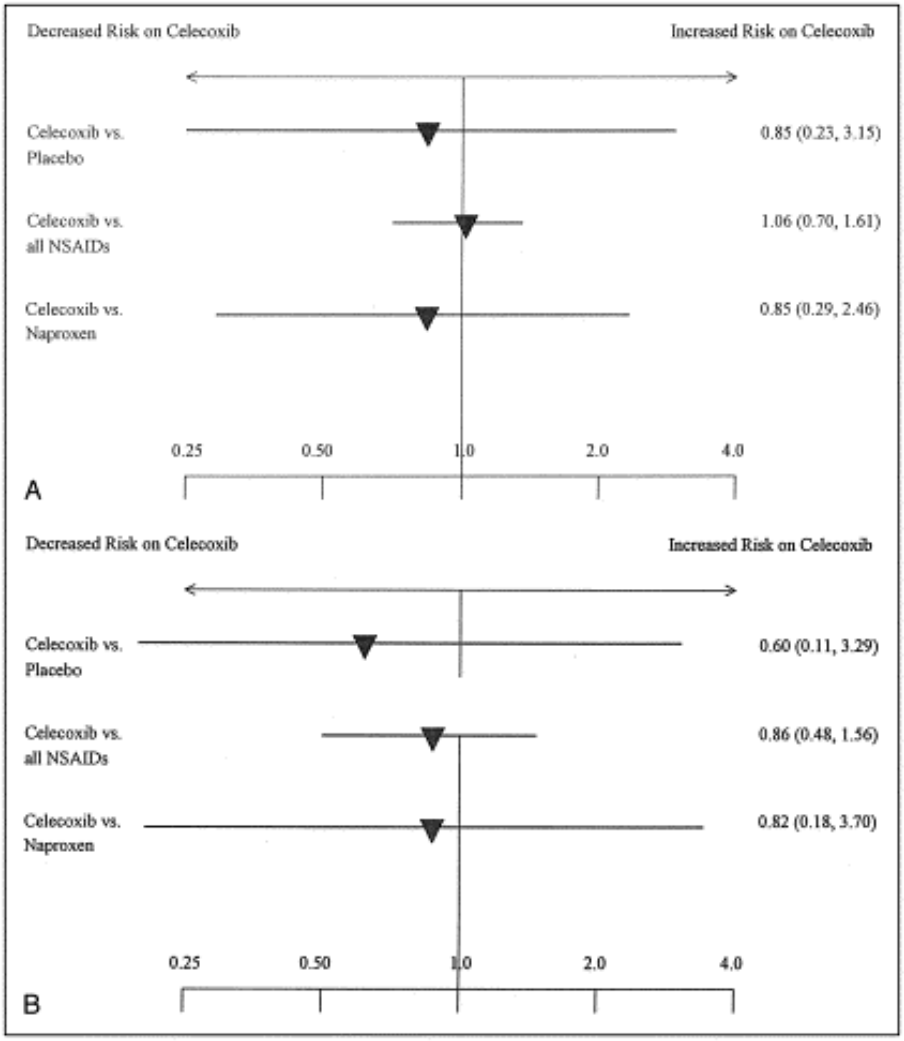
- Nonselective NSAIDs generally have not been studied in the long term except as comparators in trials with selective COX-2 inhibitors, but even aspirin 325 mg QD has shown trends towards increased cardiovascular risk compared to placebo in a recent study similar in design to the APPROVe and APC trials, raising questions about the suitability of such trials for the evaluation of cardiovascular safety (Section 2.4.3).

2.4.1. Published Clinical Studies with Celecoxib

In a previous evaluation of cardiovascular safety data from arthritis clinical trials, for which independent external investigators were given complete access to the entire celecoxib clinical trials database for the purpose of adjudicating cardiovascular adverse events, data from 15 randomized clinical trials in which patients were treated with celecoxib at doses ranging from 25 mg BID up to 400 mg BID, for durations from 4 weeks up to 1 year, were integrated for analysis. Among these 15 studies, which together represent approximately 30,000 patients total and nearly 19,000 patients treated with celecoxib (for a total celecoxib exposure of 5668 patient-years), were the one-year CAESAR and CLASS trials described in Section 2.2.4. The results of the analysis indicate that treatment with celecoxib did not increase the risk of thromboembolic events (APTC composite endpoint) compared to either placebo or nonselective NSAIDs (Figure 7); there also was no significant increase in risk of thromboembolic events with celecoxib when data were stratified for aspirin use versus no aspirin use or for individual NSAID comparators.[17] These results, which reflect an independent compilation, blinded adjudication, and analysis of all serious cardiovascular events in these 15 clinical trials, are similar to those observed in the more recent Pfizer meta-analysis of data from studies in chronic indications presented in Section 2.2.3. However, because confidence intervals associated with relative risk estimates comparing celecoxib versus placebo and individual NSAIDs in this earlier meta-analysis were very wide, these estimates have limited value for the evaluation of cardiovascular risk.

Aside from the publication described above, no other evaluation of integrated cardiovascular safety data from multiple celecoxib clinical trials has been published. Published reports of individual clinical studies in chronic indications generally report similar efficacy for celecoxib relative to nonselective NSAID comparators and superior efficacy relative to placebo, with no cardiovascular safety signals except as described in Section 2.3.

Figure 7. APTC Composite Endpoint for Celecoxib Versus Comparators In Arthritis Studies: Pooled Data From Completed Clinical Trials. (A) All Patients; (B) Non-Aspirin Users.



APTC = Antiplatelet Trialists Collaboration; Endpoint = deaths any cause plus cardiac events plus cerebrovascular events; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs. Triangles indicate point estimates of relative risk; bars indicate 95% confidence intervals. Data from White et al.[17]

2.4.2. Published Clinical Studies With Rofecoxib and Lumiracoxib

A recent meta-analysis of clinical trials data representing over 28,000 patients treated for up to one year showed no statistically significant differences in risk of cardiovascular thrombotic events when rofecoxib was compared to placebo (relative risk 0.84, 95% CI: 0.51 to 1.38), although this risk was greater for patients treated with rofecoxib compared to patients treated with naproxen (relative risk 1.69, 95% CI: 1.07 to 2.69).[18]

In the Vioxx intestinal outcomes research (VIGOR) trial, which compared rofecoxib 50 mg QD to naproxen 500 mg BID in 8076 patients with OA or RA for a mean duration of 8 months (range 6-13 months),[19] more patients treated with rofecoxib had serious cardiovascular thrombotic adverse events compared to patients treated with naproxen (65/4047 rofecoxib patients versus 33/4029 naproxen patients; relative risk 2.38, 95% CI: 1.39 to 4.00 for rofecoxib compared to naproxen, $p < 0.001$).[20] Among the 321 VIGOR patients who entered the study with the highest cardiovascular risk (ie, medical history of stroke, transient ischemic attack, myocardial infarction, unstable angina, angina pectoris, coronary artery bypass graft surgery, or percutaneous coronary interventions) 8 out of 170 patients receiving rofecoxib suffered myocardial infarctions during the study, compared to none of the 151 patients receiving naproxen. Although the use of aspirin for cardiovascular prophylaxis would normally be indicated in such patients, aspirin use was not permitted in the VIGOR trial.

For a description of results in the APPROVe trial indicating significantly increased cardiovascular risk with rofecoxib, see Section 2.3.

In contrast to the results described above for rofecoxib, a prospective clinical study of 18,325 OA patients ≥50 years of age showed that treatment for 18 months with the selective COX-2 inhibitor lumiracoxib 400 mg QD had no significant increase in risk for the APTC composite endpoint (59 events in 9117 treated patients, 0.65%) compared to patients treated with naproxen 500 mg BID (27 events in 4730 treated patients, 0.57%; hazard ratio 1.46, 95% CI: 0.89 to 2.37) or patients treated with ibuprofen 800 mg TID (23 events in 4397 treated patients, 0.52%; hazard ratio 0.76, 95% CI: 0.41 to 1.40), although incidence rates in this trial were very low.[21]

Short-term prospective clinical studies have shown that rofecoxib is associated with significantly increased blood pressure compared to nonselective NSAIDS[22,23] or to celecoxib.[22,24,25] Moreover, in the VIGOR trial, hypertension adverse events occurred in a greater percentage of patients treated with rofecoxib 50 mg QD compared to patients treated with naproxen 500 mg BID,[20] and in a recent 1 year trial in patients with mild to moderate Alzheimer's disease, patients treated with naproxen 220 mg BID or rofecoxib 25 mg QD had significantly greater risk of new onset hypertension compared to patients treated with placebo.[26]

2.4.3. Published Clinical Studies With Nonselective NSAIDs

Current understanding of the cardiovascular safety of nonselective NSAIDs is based primarily on epidemiology studies (Section 2.5); there are no publications of prospective clinical trials that report evaluation of nonselective NSAID safety in terms of cardiovascular thromboembolic adverse events comprising the APTC endpoint. Meta-analyses of interventional clinical trials have shown that nonselective NSAIDs can have lasting effects on blood pressure; these analyses suggest that indomethacin, naproxen, and piroxicam produce the largest increases in blood pressure on average, and that the effect of raising blood pressure is confined primarily to patients being treated for hypertension.[2,3] This blood pressure-destabilizing effect is most prominent in patients using angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and/or diuretics (but not calcium channel blockers) to control hypertension.[4]

Finally, although generally shown to be cardioprotective in other large, long-term, placebo-controlled settings, aspirin 325 mg QD was recently associated with a trend toward increased risk of cardiovascular events including myocardial infarction and stroke compared to placebo in a long-term SAP prevention study similar in design to the APPROVe, PreSAP, and APC trials.[27] In this 3-year study, 14 APTC-type events (5 myocardial infarctions, 5 strokes, 4 deaths) occurred amongst 372 patients treated with aspirin 325 mg QD, versus 4 events (1 myocardial infarction, no strokes, 3 deaths) amongst 372 patients treated with placebo. An aspirin 81 mg QD treatment group had an intermediate number of events (7 events: 2 myocardial infarctions, 2 strokes, 3 deaths) amongst 377 treated patients. These results are not in accord with the well-accepted role of low-dose aspirin in cardioprotection, and therefore call into question the suitability of long-term SAP prevention studies, which were not designed to measure cardiovascular outcomes, for evaluation of cardiovascular risk.

2.5. Epidemiology Studies of Celecoxib, Rofecoxib, and Nonselective NSAIDs: Summary

Other than randomized clinical trials and postmarketing surveillance, epidemiology studies represent the major source of cardiovascular safety data regarding nonselective NSAIDs and selective COX-2 inhibitors. Most of these studies have evaluated cardiovascular safety exclusively in terms of myocardial infarction, rather than more inclusive endpoints that represent the full spectrum of cardiovascular thromboembolic events.

- In 8 published epidemiology studies involving more than 96,000 patients exposed to celecoxib (mean age over 65 years), the risk of myocardial infarction among users of celecoxib was similar to the risk observed among users of nonselective NSAIDs and among non-users of NSAIDs. Moreover, the limited data available suggest that the risk of myocardial infarction is similar for low (≤200 mg/day) and high (>200 mg/day) celecoxib doses, and there is no suggestion of increased risk with increasing duration of use.

- Overall, results from observational studies suggest no class effect of nonselective NSAIDs on risk of myocardial infarction. Pooled estimates for individual nonselective NSAIDs suggest a small increase in risk of myocardial infarction with diclofenac and no effect with ibuprofen or naproxen.

- Results from two studies conducted in Canada show that use of celecoxib at either low or high doses and among users and non-users of aspirin is not associated with an increased risk of myocardial infarction.

- Rofecoxib users generally had increased risk of myocardial infarction compared to users of celecoxib, users of nonselective NSAIDs, and non-users of NSAIDs. This risk generally increases with higher rofecoxib dose and longer duration of use.

- A possible association between use of nonselective NSAIDs and the risk of hypertension has also been observed in epidemiological studies; this association appears to be dose-dependent and higher during the first month of use. In the single study published to date, the risk of new onset hypertension associated with celecoxib is similar to that associated with nonselective NSAIDs, and lower than that associated with rofecoxib.

- A single study conducted in Canada has assessed risk of hospital admission for congestive heart failure in new users of rofecoxib, celecoxib, or nonselective NSAIDs. No increase in risk was observed for celecoxib, whereas a higher risk was observed for users of rofecoxib and users of nonselective NSAIDs. The risk of new onset hypertension has been evaluated in one single study; the risk was similar among celecoxib users compared to users of nonselective NSAIDs and non-users of NSAIDs.

2.5.1. Background: Nonselective NSAIDs and Cardiovascular Risks

2.5.1.1. Nonselective NSAIDs and Cardiovascular Thromboembolic Events

In a recent systematic review[28] of 13 observational studies published from 2000 to 2005 evaluating the risk of myocardial infarction,[29-41] the pooled relative risk associated with use of nonselective NSAIDs (all nonselective NSAIDs combined) compared to non-use was 1.06 (95% CI: 1.00 to 1.08). Pooled relative risks for individual NSAIDs were 0.96 (95% CI: 0.90 to 1.04) for naproxen, 1.03 (95% CI: 0.96 to 1.10) for ibuprofen, and 1.19 (95% CI: 1.06 to 1.51) for diclofenac.[29,33,35-37,42] Within these observational studies, naproxen consistently had lower relative risk estimates for myocardial infarction compared to non-users of NSAIDs than did other individual NSAID medications.

In general, results were similar across studies for fatal and nonfatal myocardial infarction. Results remained the same for different doses and duration of NSAID treatment. Within individual studies, results did not vary by duration of use, recent use, daily dose, or NSAID half-lives.[33,35-38] However, duration of use was evaluated in few studies, and mainly for the overall drug class rather than for individual nonselective NSAIDs.[33-35,37,38] Little is known about the effects of long-term exposure to NSAIDs at high doses, although in one study, exposure to ibuprofen at high doses for longer than 60 days was associated with a statistically significant 33% increased risk of serious coronary heart disease compared to non-users of NSAIDs.[38] Results also did not vary by indication among studies that provided such an analysis. Regarding history of coronary heart disease, there was no difference between patients with and without prior coronary heart disease;[33,38] and regarding a potential effect modification in arthritis patients, only one study restricted the source population to subjects with rheumatoid arthritis,[35] while another found similar results in subjects with rheumatoid arthritis compared to subjects without.[33]

Results from the systematic review of epidemiological studies described above indicate that the lower risk of myocardial infarction in users of naproxen compared to non-users of NSAIDs was more evident among subjects without prior history of cardiovascular disease or subjects who did not use low-dose aspirin. The relative risk for aspirin users was 0.92 (95% CI: 0.83 to 1.03) and for non-users of aspirin 0.79 (95% CI: 0.68 to 0.91).[28] For ibuprofen, the pooled relative risk of myocardial infarction compared to non-users of NSAIDs was 1.11 (95% CI: 1.02 to 1.21) for studies that allowed aspirin users and 0.88 (95% CI: 0.78 to 1.01) for studies that excluded aspirin users. These results might be consistent with a potential interaction of aspirin with ibuprofen. While this hypothesis is supported by another published epidemiological study[43] and a prospective clinical trial,[44] other epidemiological studies did not find any indication of interaction.[33,45]

Little is known about the overall risk of thrombotic events other than myocardial infarction in users of NSAIDs. Two case-control studies on the risk of cerebrovascular events have been published, one of which evaluated the risk of intracerebral hemorrhage and found no increase in risk for nonselective NSAIDs.[46] The other study evaluated the risk of both hemorrhagic and ischemic events and found the risk of ischemic stroke to be 20% higher (a statistically significant difference) in users of nonselective NSAIDs compared to non-users.[47] In addition, a case-control study that evaluated data from patients with rheumatoid arthritis found no association between

use of naproxen and the risk of thrombotic events, with cases defined as a composite of myocardial infarction, sudden death, and cerebrovascular events.[35]

Overall, results from observational studies suggest no class effect of nonselective NSAIDs on the risk of myocardial infarction. Pooled estimates for individual NSAIDs suggest a small risk increase on the risk of myocardial infarction for diclofenac and no effect for ibuprofen and naproxen.

2.5.1.2. Nonselective NSAIDs and Cardiorenal Events

Several observational studies using different study designs and conducted in various populations suggest that treatment with NSAIDs in susceptible patients might trigger the occurrence of heart failure.[9-101112] The risk of heart failure overall was moderate in these studies, was greater during the first month of therapy, and was independent of treatment indication.[9,12] While no dose relationship was observed in two of these studies,[9,12] a dose effect was observed in a third study, but only among patients with prior heart disease.[10] In all 3 of these studies, the risk was greater in patients with history of hypertension, diabetes, renal failure, or heart disease. Based on a single study, the risk of recurrent heart failure was estimated to be 10 times higher for current NSAID users compared to non-users.[11] Only one study presented data for individual NSAIDs;[12] the relative risk of incident heart failure in this study ranged from 1.1 for diclofenac to 3.4 for indomethacin as compared to non-use. The attributable risk of heart failure in this study was calculated to be 2-3 cases per 1,000 NSAID users per year for all subjects, and 6-7 cases per 1,000 NSAID users in the elderly.

Two epidemiology studies have found an association between use of NSAIDs and the risk of hypertension:

- One study evaluated 9,411 cases of initiation of antihypertensive medications and 9,629 control cases among elderly Medicaid beneficiaries in New York, US; the adjusted odds ratio associated with current or recent use of NSAIDs in this study was 1.66 (95% CI: 1.54 to 1.80) compared with non-use.[7] An increase in the odds for initiation of antihypertensive medication with increased average daily NSAID dose was observed: low dose odds ratio = 1.55 (95% CI: 1.38 to 1.74); and high dose odds ratio = 1.82 (95% CI: 1.62 to 2.05). The increase in risk of hypertension was greater for patients with NSAID use between 30 and 90 days (odds ratio = 1.90; 95% CI: 1.65 to 2.18) than for patients with either shorter or longer durations of use.

- The Nurses Health Cohort Study evaluated the incidence of hypertension among 51,630 women aged 44 to 69 years, with analgesic use assessed using a mailed questionnaire.[8] During 381,078 person-years of follow-up in this study, 10,579 incident cases of hypertension were identified. Compared with non-users, women who used NSAIDs during 5 or more days per month had a relative risk of 1.35 (95% CI: 1.25 to 1.46). There was a significant trend toward an increased risk of hypertension with increasing frequency of NSAID use that reached a plateau after 21 days of use.

Most epidemiological studies evaluating the association between NSAIDs and acute renal failure have found an increased risk of developing acute renal failure in patients taking NSAIDs.[48-54]

Generally, risk was greater in the first month of NSAID use in these studies; a strong dose-effect relationship was reported in two studies[52,54] and a weak dose effect was found in a third.[53] More recently, a case-control analysis nested in a cohort of 386,916 patients aged 50-84 years in the United Kingdom has shown a relative risk of hospitalization for acute renal failure for current users of NSAID to be 3.2 (95% CI: 1.8 to 5.8) compared to non-use; this risk declined once treatment was discontinued.[55] The increased risk was present with both short- and long-term therapy and was slightly greater among users of NSAIDs at high doses. History of heart failure, hypertension, diabetes, hospitalizations, and consultant visits in the previous year all were associated with a greater risk of acute renal failure, and there was a suggestion of a modification of the effect of NSAIDs in patients with preexisting hypertension or heart failure. Use of selected cardiovascular drugs was associated with a 5-fold increase in the risk for acute renal failure.

2.5.2. Celecoxib and Cardiovascular Risk

2.5.2.1. Cardiovascular Thromboembolic Events in Epidemiology Studies

A total of 8 formal epidemiology studies have been published as of May 2005 that evaluate the risk of coronary heart disease in users of selective COX-2 inhibitors, including rofecoxib and celecoxib. Together, these studies represent more than 96,000 users of celecoxib and 76,000 users of rofecoxib, compared with over 2 million users of nonselective NSAIDs including more than 1 million ibuprofen users and more than 500,000 naproxen users. These studies also represent many hundreds of events, compared to the small numbers of events that have accrued in even the largest, longest-term randomized clinical trials (Section 2.3) or in meta-analyses of multiple randomized clinical trials Section 2.2). Three of the studies were conducted specifically in elderly populations (65 years of age and older),[39,40,56] and the mean age of participants was over 65 years in the other 5 studies. Most of the studies included a high proportion of subjects with prior cardiovascular disease, diabetes, hypertension and use of cardiovascular medications; three studies were conducted in patients with first myocardial infarction hospitalization or without prior history of myocardial infarction. In general, across the studies, users of selective COX-2 inhibitors had a higher cardiovascular risk profile at baseline than non-users and users of nonselective NSAIDs, suggesting that high-risk subjects are preferentially prescribed selective COX-2 inhibitors relative to nonselective NSAIDs. Descriptions of individual studies are as follows:

- In a population-based, retrospective cohort study using administrative health care data from Ontario, Canada, an NSAID-naïve cohort was used to assess the risk of hospitalization for myocardial infarction in subjects over 65 years of age treated with celecoxib (15,271 subjects), rofecoxib (12,156 subjects), naproxen (5669 subjects), or nonselective NSAIDs other than naproxen (33,868 subjects) compared to a cohort of non-users of NSAIDs (100,000 subjects). While the study did not show significant increases in risk of myocardial infarction in subjects treated with celecoxib, rofecoxib, or nonselective NSAIDs compared to non-NSAID users, potential differences were not investigated according to selective COX-2 inhibitor or nonselective NSAID dose.[30]

- In a study conducted in Quebec, Canada, a cohort of individuals 66 years of age and older (mean age 75 years) newly treated with an NSAID between 1 January 1999 and 30 June

2002, was identified. Persons with a prior diagnosis of myocardial infarction were excluded. Overall 113,927 were followed-up during a mean of 2.4 years and 2844 were hospitalized for a first acute myocardial infarction. Overall 22% of controls subjects were using low-dose aspirin (≤325 mg), 50% had hypertension, 17% had coronary heart disease, and 11% diabetes. Among these subjects, 287 cases and 3598 controls were new users of celecoxib. **The risk of first hospitalization for acute myocardial infarction in current users of celecoxib was similar to than in non-users (relative risk = 0.99; 95% CI: 0.85 to 1.16).** Twenty-five percent of current users of celecoxib used doses higher than 200 mg/day. **No celecoxib dose-effect was observed (relative risk = 0.98; 95% CI: 0.83 to 1.17 at celecoxib ≤200 mg/day, and relative risk = 1.00; 95% CI: 0.78 to 1.29 at celecoxib >200 mg/day).** However, a rofecoxib dose effect was observed, with relative risk = 1.21 (95% CI: 1.02 to 1.49) at rofecoxib ≤25 mg/day and relative risk = 1.73 (95% CI: 1.09 to 2.76) at rofecoxib >25 mg/day compared with non-users. In addition, a stratified analysis by concomitant use of aspirin showed no increase in the risk of acute myocardial infarction for celecoxib, neither with nor without concomitant use of aspirin, overall as well as at doses lower or higher than 200 mg/day. However, there was an increased risk of acute myocardial infarction associated with rofecoxib use both without (all rofecoxib doses) and with concomitant use of aspirin (rofecoxib doses >25 mg/day). There was not evidence of increased risk with other NSAIDs.[40]

- In a US FDA-funded, nested case-control study of 1.4 million Kaiser Permanente beneficiaries in California (mean age 67 years) who were treated with celecoxib (40,405 subjects), rofecoxib (26,748 subjects), or nonselective NSAIDs, there was **no increase in the risk of acute myocardial infarction or sudden cardiac death in current users of celecoxib** (relative risk 0.84, 95% CI: 0.67 to 1.04) compared to those patients who had not used NSAIDs for the previous 60 days. In contrast, **rofecoxib >25 mg/day was associated with a 3-fold increase in risk compared to controls** (relative risk 3.00, 95% CI: 1.09 to 8.31), and the relative risk of rofecoxib ≤25 mg/day compared to remote use of NSAIDs was 1.23 (95% CI: 0.89 to 1.71). Comparison of relative risks in this study showed that treatment with rofecoxib ≤25 mg/day increased the risk of acute myocardial infarction or sudden cardiac death significantly compared to celecoxib (relative risk 1.47, 95% CI: 0.99 to 2.17). Relative risks were also increased for users of naproxen (relative risk 1.14, 95% CI: 1.00 to 1.30), diclofenac (relative risk 1.60, 95 CI: 0.92 to 2.79), and indomethacin (relative risk 1.30, 95% CI: 1.06 to 1.59). A telephone survey conducted among study controls in this study showed the distribution of low-dose aspirin use was no different among users regardless the type of selective COX-2 inhibitor or nonselective NSAID.[29]

- In a matched case-control study of 54,475 subjects 65 years of age and older who were Medicare beneficiaries in two US states, current use of **celecoxib (odds ratio 0.93, 95% CI: 0.84 to 1.02) was not associated with an increased relative risk** of hospitalization for acute myocardial infarction compared to control subjects not treated with nonselective NSAIDs, and **rofecoxib was associated with an elevated relative risk of myocardial infarction** compared to celecoxib (odds ratio 1.24, 95% CI: 1.05 to 1.46) or to controls (odds ratio 1.14, 95% CI: 1.00 to 1.31). The relative risk of acute

myocardial infarction was also significantly elevated for rofecoxib subjects compared to celecoxib subjects at low rofecoxib doses (≤25 mg/day) versus low celecoxib doses (≤200 mg/day), at high rofecoxib doses (>25 mg/day) versus high celecoxib doses (>200 mg/day), and when evaluated for subgroups of subjects who took the respective medications for 1 to 30 days, 31 to 90 days, or >90 days. The baseline cardiovascular risk profiles for rofecoxib and celecoxib users in this study were similar, but both showed greater risk compared to users of nonselective NSAIDs; a survey of subjects showed use of aspirin was similar regardless of selective COX-2 inhibitor or nonselective NSAID use.[56]

- A field case-control study (1718 cases and 6800 controls) that evaluated the association between use of selective COX-2 inhibitors and risk of nonfatal myocardial infarction, compared to non-users of NSAIDs, found no significant increase in risk overall in patients treated with selective COX-2 inhibitors. However, although possible bias, confounding, and non-participation may limit interpretation of results for this study, **celecoxib (odds ratio 0.43; 95% CI: 0.23 to 0.79) and rofecoxib (odds ratio 1.16; 95% CI 0.70 to 1.93) had different effects** compared to non-users of NSAIDs.[57]

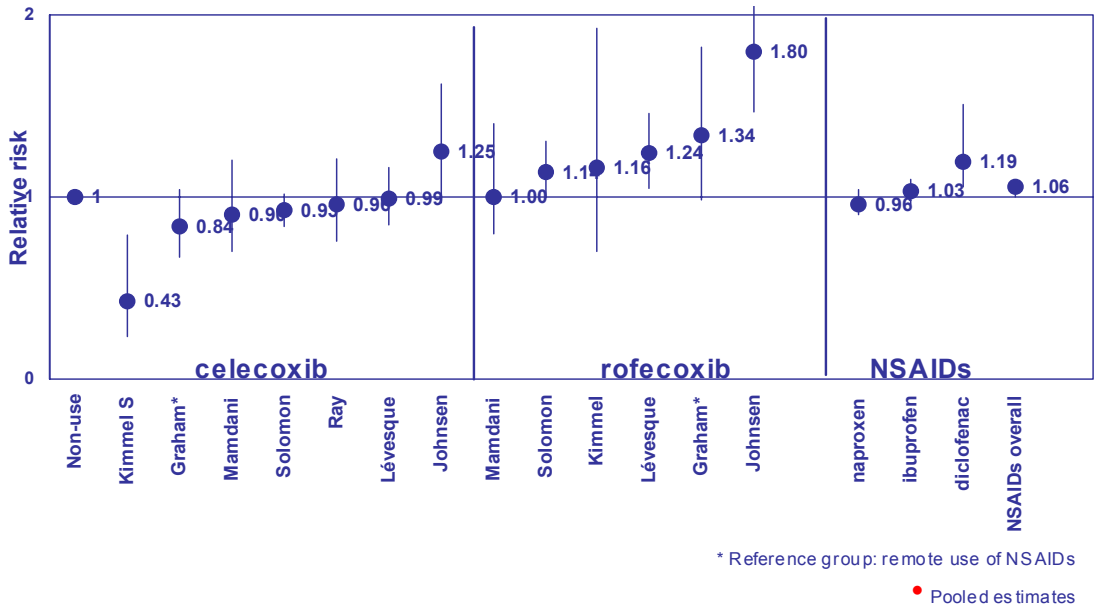
- In a retrospective cohort study using data from the expanded Tennessee Medicaid program, subjects 50-84 years of age who were either new or current users of NSAIDs including naproxen (70,384 subjects), rofecoxib at doses ≤25 mg/day (20,245 subjects) and **celecoxib at any dose (22,337 subjects) showed similar risk of hospitalization acute myocardial infarction or death from coronary heart disease, with no significant increases in risk** (202,916 subjects; relative risks compared to non-users ranging from 0.88 to 1.03; p >0.19 for all comparisons) relative to non-users of NSAIDs. However, users of rofecoxib at doses >25 mg/day (3887 subjects) had an increased risk (not statistically significant) compared to non-users of NSAIDs (relative risk 1.70, 95% CI: 0.98 to 2.95). **New users of rofecoxib at doses >25 mg/day were at significantly greater risk of myocardial infarction compared to non-users of NSAIDs (relative risk 1.93, 95% CI: 1.09-3.42) and to users of celecoxib (relative risk 2.20, 95% CI: 1.17 to 4.10)**.[58]

- A matched case-control study in patients 20 years and older from the National Health Services Registries was conducted in three counties in Denmark between 1 January 2000 and 31 December 2003. A total of 9,287 cases with first time hospital admission for myocardial infarction were matched by age and sex to 93,270 controls at risk of a first hospitalization for myocardial infarction at the case index date to study risk of hospitalization for myocardial infarction among users of COX-2 specific inhibitors and non-specific NSAIDs. Even though no case validation was implemented, prior validation of myocardial infarction discharge diagnoses in Denmark shows a low misclassification rate of below 10%. Current users of rofecoxib had the highest risk of myocardial infarction hospitalization compared to non-users of NSAIDs (relative risk 1.80; 95% CI: 1.47 to 2.21), whereas **users of celecoxib had the lowest risk (relative risk 1.25; 95% CI: 0.97 to 1.62).** There was also an increased relative risk of myocardial infarction associated with naproxen (relative risk 1.50; 95% CI: 0.99 to 2.29) and with other NSAIDs (relative risk 1.68; 95% CI: 1.52 to 1.85). This increase in risk was higher among new users of the study drugs.[41]

- A retrospective cohort study in more than 97,000 subjects aged 18 years or older enrolled in contracted US managed care organizations and who received at least 1 prescription for an NSAID between January 1, 2000 and June 30, 2002 was performed. Among these subjects, 10,677 new users of NSAIDs and COX-2 selective agents were prescribed at least a 60-day supply over the study period and were followed-up. A history of at least 6 months was used to develop a propensity score and stratify patients by quintiles of their distribution. During the study period, about 41% used naproxen, 1005 subjects used selective COX-2 inhibitors, and 5,245 subjects used other NSAID. The overall rate of cardiovascular thrombotic events (defined as the APTC endpoint: cardiovascular, hemorrhagic and unknown deaths; non-fatal myocardial infarction and non-fatal strokes) was 12%. The risk of cardiovascular thrombotic events was similar in users of selective COX-2 inhibitors than in users of non-naproxen, nonselective NSAIDs (odds ratio 1.09; 95% CI: 0.90 to 1.33). **The odds ratio for celecoxib was 1.19 (95% CI: 0.93 to 1.51)** and for rofecoxib was 0.99 (95% CI: 0.76 to 1.30). Similar results were obtained when naproxen users were included or when aspirin prescriptions were excluded in the analysis. Although potential confounding by indication was carefully taken into account, information on the assessment of exposure was not described in much detail. No evaluation of dose and duration of treatment were performed.[59]

In most of these studies celecoxib was not associated with an increased risk of myocardial infarction (Figure 8). Only two studies suggest a small elevated risk for celecoxib, with an odds ratio of 1.19 (95% CI: 0.93 to 1.51) compared to users of non-naproxen nonselective NSAIDs[59] and a relative risk of 1.25 (95% CI: 0.97 to 1.62) compared to non-users of NSAIDs.[41]

Figure 8. Risk of Myocardial Infarction and Use of Selective COX-2 Inhibitors and Nonselective NSAIDs in Epidemiological Studies, compared to non-use of NSAIDs



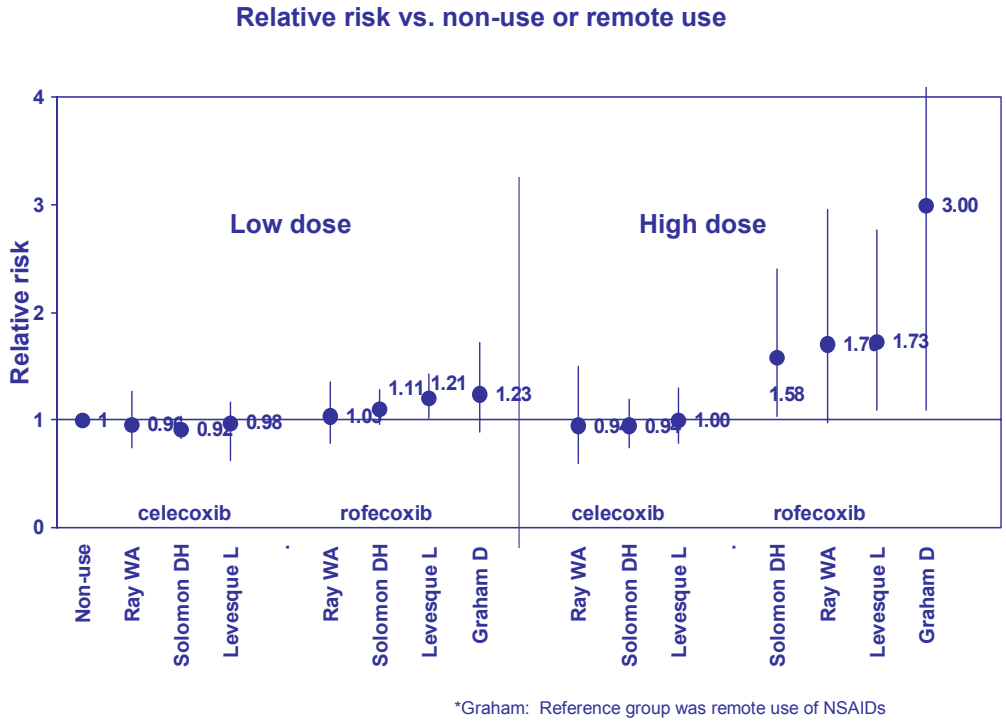
Points indicate relative risk estimates for selective COX-2 inhibitors and nonselective NSAIDs compared to non-use or remote use of NSAIDs; bars indicate 95% confidence intervals. Estimates for selective COX-2 inhibitors are from data published by Solomon DH et al,[56] Kimmel S et al,[57] Ray WA et al,[58] Mamdani M et al[30], Lévesque LE et al[40], and Johnsen SP et al.[41] Estimates of relative risks published by Graham DJ et al[29] (indicated by asterisks) have remote remote NSAID users as the reference group. Relative risks for overall and individual nonselective NSAIDs are from pooled estimates presented in the systematic review of observational studies by Hernandez-Diaz et al.[28]

A total of 4 of these 8 epidemiological studies evaluated the dose effect of celecoxib and rofecoxib. As shown in Figure 9, a dose-response relationship is suggested for rofecoxib with respect to the risk of myocardial infarction, with the highest risk at doses ≥25 mg/day. Relative risks ranged from 1.7 to 3.2 in various studies for high-dose rofecoxib users compared to non-users of NSAIDs. However, no dose-response relationship was suggested for celecoxib.

Altogether, the results of these epidemiological studies provide evidence that an increased risk of myocardial infarction is associated with use of rofecoxib, but not with use of celecoxib, compared to use of nonselective NSAIDs or non-use of NSAIDs. In all of these studies, generally, the effects observed place celecoxib at the favorable end of the range of effects demonstrated for NSAIDs in epidemiology studies. No formal epidemiological studies have been published that evaluated the risk of thromboembolic events, other than myocardial infarction, associated with use of selective COX-2 inhibitors. Results from the two studies conducted in Canada show that use of celecoxib either at low or high doses and among users and non-users of aspirin is not associated with an increased risk of myocardial infarction. The

relative risk for celecoxib users compared to non-users of NSAIDs was 0.9 (95% CI: 0.7 to 1.2) in the Ontario study, and 0.99 (95% CI: 0.85 to 1.16) in the Quebec study. Results did not vary significantly regardless of the celecoxib dose used (low versus high dose), nor did results vary with or without concomitant use of aspirin.

Figure 9. Risk of Myocardial Infarction and Use of COX-2 Inhibitors in Epidemiological Studies by Dose



Points indicate relative risk estimates for selective COX-2 inhibitors compared to non-use or remote use of NSAIDs; bars indicate 95% confidence intervals from data published by Solomon DH et al,[56] Ray WA et al,[58] and Lévesque LE et al.[40] Estimates of relative risks published by Graham DJ et al[29] (indicated by asterisks) have remote NSAID users as the reference group. Low doses were defined as ≤200 mg/day for celecoxib and ≤25 mg/day for rofecoxib; high doses were defined as >200 mg/day for celecoxib and >25 mg/day for rofecoxib.

2.5.2.2. Cardiorenal Events in Epidemiology Studies

To date, only a single published observational study has evaluated the risk of hospital admission for heart failure among new users of celecoxib and rofecoxib, compared with nonselective NSAIDs or non-NSAID users, using administrative health care data from Ontario, Canada.[60] In this population-based, retrospective cohort study, both rofecoxib (relative risk 1.8; 95% CI: 1.5 to 2.2) and nonselective NSAIDs (relative risk 1.4; 95% CI: 1.0 to 1.9) significantly increased the risk of hospital admission for congestive heart failure relative to non-NSAID subjects, but celecoxib (relative risk 1.0, 95% CI: 0.8 to 1.3) did not. Compared with celecoxib users, admission was significantly more likely in users of nonselective NSAIDs (relative risk 1.4;

95% CI: 1.0 to 1.9) and rofecoxib (relative risk 1.8; 95% CI: 1.4 to 2.4). Risk of admission for rofecoxib users was higher than that for users of nonselective NSAIDs (relative risk 1.5; 95% CI: 1.1 to 2.1). Among patients with no admission in the past 3 years, only rofecoxib users were at increased risk of subsequent admission relative to controls (relative risk 1.8; 95% CI: 1.4 to 2.3). No information on dose was provided in this study; durations of use ranged, on average, up to 3 months for users of nonselective NSAIDs and up to 6 months for users of celecoxib.

The risk of hypertension associated with use of selective COX-2 inhibitors has been evaluated in only a single formal epidemiological study published to date: the risk of new onset hypertension requiring treatment was examined in a retrospective case-control study involving 17,844 patients aged ≥65 years who were Medicare beneficiaries in 1999-2000.[56] Patients who used celecoxib (878 patients) or rofecoxib (386 patients) were compared with patients using a nonselective NSAID (869 patients) or no NSAID (15,711 patients). The risk of new onset hypertension was similar among celecoxib users compared to either users of nonselective NSAIDs or non-users. Rofecoxib users were at a significantly increased risk of new onset hypertension compared to patients treated with celecoxib (odds ratio 1.6; 95% CI: 1.2 to 2.1), patients treated with a non-selective NSAID (odds ratio 1.4; 95% CI: 1.1 to 1.9), or non-users of NSAIDs (odds ratio 1.6; 95% CI: 1.3 to 2.0). In patients with a history of chronic renal disease, liver disease, or congestive heart failure, the risk of new onset hypertension was twice as high in those taking rofecoxib compared with those taking celecoxib (odds ratio 2.1; 95% CI: 1.0 to 4.3). There were no clear dosage or duration effects.

2.6. Spontaneous Reports of Adverse Events With Celecoxib

Although it historically represents the least precise of methods for evaluation of cardiovascular risk, analysis of spontaneous reports shows results consistent with both randomized clinical trial data and epidemiology data indicating no increase in cardiovascular risk with celecoxib.

2.6.1. Methods for Analysis

Pfizer's early alert safety database contains cases of adverse events reported spontaneously to Pfizer, cases reported from health authorities, cases published in the medical literature, and cases of serious adverse events reported from clinical studies and Pfizer-sponsored marketing programs (solicited cases) regardless of causality. For this review the database was searched for all celecoxib non-clinical study cases reported from 1 December 1998 through 31 October 2004.

The database was further searched to identify celecoxib cases reporting thrombotic events (including events suggestive of coronary artery disease or thromboembolism or occlusion, cardiac ischemia, myocardial infarction, or arrhythmia events likely to be associated with coronary thromboembolism or ischemia; cerebrovascular thromboembolism or occlusion or ischemia or infarction, cerebrovascular hemorrhage, or neurologic events likely to be associated with cerebrovascular ischemia or hemorrhage; non-coronary or non-cerebrovascular thromboembolism, occlusion, ischemia, or infarction) and cardiorenal events (events suggestive of hypertension, abnormal or fluctuating or inadequately controlled or increased blood pressure, cardiac failure, or edema events possible related to hypertension or cardiac failure). Cases identified by these searches were then further reviewed to characterize the nature of any cardiovascular risk factors present.

In addition, in an effort to compare information on the reporting of these types of adverse events for COX-2 inhibitors and the conventional non-selective NSAIDs, the FDA's Adverse Event Reporting System (AERS) database, available under the Freedom of Information Act, was reviewed using Drug Logic's QScan (version 3.0) for information on adverse events reported to FDA for the COX-2 inhibitors celecoxib and rofecoxib, and for the conventional NSAIDs diclofenac, ibuprofen, naproxen, and piroxicam using the same search strategy that was employed to search for celecoxib cases in Pfizer's database.

2.6.2. Results: Spontaneous Reports of Adverse Events for Celecoxib

Review of Pfizer's early alert safety database identified a total of 47,279 celecoxib non-clinical study cases reported through 31 October 2004 following treatment of approximately 70.6 million patients worldwide. Of these, there were 1072 cases reporting thrombotic events (of which 537 reported cardiac events, 353 reported cerebrovascular events, and 195 reported peripheral vascular events; 980 of these 1072 cases met the reporting criteria for a serious case, and deaths were reported in 198 of these 980 serious cases) and 3603 cases reported cardiorenal events (984 of these 3603 cases met the reporting criteria for a serious case, and deaths were reported in 67 of these 984 serious cases). When the reporting of these events for celecoxib to the FDA's AERS system was compared to the reporting of these events for rofecoxib, diclofenac, ibuprofen,

naproxen, and piroxicam, the proportion of cases reporting these events was generally greatest for rofecoxib, and the proportion of celecoxib cases reporting these events was generally similar to the proportion of diclofenac cases reporting these events.

For celecoxib cases reported to Pfizer, the cases reporting cardiac events, cerebrovascular events, and all thrombotic events had a greater proportion of elderly and male patients, suggesting a patient population generally already at elevated cardiovascular risk. Cases reporting these events were also more likely to have reported co-suspect drugs, concomitant medications, and medical history than were all celecoxib cases, also suggesting that these cases involved patients at greater risk of adverse events. Review of the data for daily dose of celecoxib identified no suggestion of increased risk for any of the event categories reviewed with increased dose. For cardiac, cerebrovascular, and all thrombotic events, the most commonly reported durations of therapy at event onset were ≤ 1 day and 1-6 months. For peripheral vascular events, the most commonly reported duration of therapy was 1-6 months. For cardiorenal events the most commonly reported durations of therapy at event onset were ≤ 1 day and 1-6 months. Interpretation of these data is made difficult by the fact that duration of use was unknown or not reported in more than half of the cases for all event categories reviewed. There was no apparent association between any of the event categories reviewed and concurrent aspirin therapy.

For all event categories reviewed, cases where the patient was reported to have died had a greater proportion of elderly and male patients than did all celecoxib non-clinical study cases and all cases for the corresponding event categories. Cases reporting hypertension were no more likely to have reported concurrent cardiac or cerebrovascular events than were all celecoxib non-clinical study cases, and it is unclear if such events are independent of hypertension in celecoxib-treated patients or if hypertension-related events are underreported in celecoxib cases reporting cardiac and/or cerebrovascular events.

Overall, this review of celecoxib non-clinical study cases did not identify any signal that celecoxib therapy increases risk of cardiac, cerebrovascular, peripheral vascular, all thrombotic, or cardiorenal adverse events independent of risk inherent in the patient population likely to be treated with celecoxib.

2.7. Conclusions, Celecoxib Cardiovascular Safety

Data presented and reviewed in this evaluation of celecoxib cardiovascular safety support the following conclusions:

- Preliminary data from long-term prevention trials (non-arthritis indications, treatment durations up to 4 years; Section 2.3) with chronic celecoxib use have shown a statistically significant increase in incidence of cardiovascular events for celecoxib compared to placebo in one trial (APC) and numerical increases (not statistically significant) in two others (PreSAP and ADAPT). In one of these trials (ADAPT), overall cardiovascular risk trended higher in patients treated with naproxen 220 mg BID or celecoxib 200 mg BID compared to placebo, with naproxen showing the greater numerical increase. Nonselective NSAIDs generally have not been studied in such settings, but even aspirin 325 mg QD has shown trends towards increased cardiovascular risk in this type of study (Section 2.4.3).

- Published epidemiology studies have consistently shown a similar risk of myocardial infarction and cardiorenal adverse events with celecoxib compared to nonselective NSAIDs and to non-use of NSAIDs, although information on chronic use at high doses is limited. This observation of no increase in risk with celecoxib is in contrast to observations with rofecoxib (Section 2.5).

- A meta-analysis of cardiovascular safety data from 41 randomized clinical trials in 24,993 patients treated with celecoxib for durations up to 1 year shows no increase in cardiovascular thromboembolic risk for celecoxib compared to nonselective NSAIDs. Several large 1-year studies contributed to this meta-analysis, and all support these overall conclusions when evaluated individually. The meta-analysis also included an assessment of cardiorenal risk, which demonstrated that celecoxib, while showing more effects than placebo, has a favorable cardiorenal safety profile compared to nonselective NSAIDs.

- Published clinical studies have consistently shown a similar risk of thrombotic and cardiorenal adverse events with celecoxib compared to nonselective NSAIDs, in contrast to observations with rofecoxib, which showed a higher risk (Section 2.4).

- Postmarketing safety surveillance representing a total of 47,279 celecoxib non-clinical study cases reported through 31 October 2004 following treatment of approximately 70.6 million patients worldwide does not show a cardiovascular safety signal for celecoxib (Section 2.6).

These results demonstrate that celecoxib has a cardiovascular safety profile comparable to that of nonselective NSAIDs and different from that of rofecoxib, which is associated with increased cardiovascular risk. The most prominent alternatives to treatment for arthritis with celecoxib are nonselective NSAIDs. Although widely used for decades, the long-term cardiovascular safety of nonselective NSAIDs has not been demonstrated.

3. IS INCREASED CARDIOVASCULAR RISK A CLASS EFFECT OF SELECTIVE COX-2 INHIBITORS?

Executive Summary and Conclusions: To date no specific mechanism for the increased cardiovascular risk consistently observed in patients taking rofecoxib long-term has been positively identified. In particular, there is no direct evidence that this increase in risk results from a class effect common to all selective COX-2 inhibitors, and no evidence that all selective COX-2 inhibitors have less favorable cardiovascular safety profiles than nonselective NSAIDs

- At doses well above those observed to be effectively anti-inflammatory doses, rofecoxib, celecoxib, and valdecoxib spare COX-1 activity; therefore, differences in molecular structure between rofecoxib and celecoxib or valdecoxib must account for any differences in cardiovascular risk. Differences in selectivity only become relevant at much higher doses than are used in any clinical trials or approved indications.

- In contrast to celecoxib and valdecoxib, rofecoxib promotes oxidative damage to low-density lipoprotein (LDL) and phospholipids. This may occur either via a unique interaction between rofecoxib and membrane phospholipids or via the formation of potentially toxic rofecoxib metabolites. These processes may increase cardiovascular risk via damage to endothelial cells and effects on blood pressure, and clinical studies show that treatment with celecoxib can have beneficial effects on endothelial function that are not observed with rofecoxib.

- Published data from clinical studies indicate that treatment with rofecoxib has greater effects on blood pressure than celecoxib, whereas the blood pressure effects of celecoxib and valdecoxib are comparable to those observed with nonselective NSAIDs. The incremental increase in blood pressure with rofecoxib may account for some of the increased risk observed with rofecoxib treatment.

Taken together, the observations described above suggest alternative hypotheses to explain the increased cardiovascular risk observed in patients taking rofecoxib without postulating a class effect common to all selective COX-2 inhibitors. These hypotheses are consistent with the body of clinical trial and epidemiology data presented in this Briefing Document showing that celecoxib and valdecoxib both fit into the spectrum of cardiovascular safety encompassed by nonselective NSAIDs, while rofecoxib lies outside that spectrum.

3.1. Clinical Evidence Does Not Support The Hypothesis That Prostacyclin-Thromboxane Imbalance Accounts for Increased Cardiovascular Risk

Cyclooxygenases help to regulate thrombotic homeostasis and vascular tone through conversion of arachidonic acid to intermediates necessary for the synthesis, respectively, of thromboxane A_2 (TxA_2), a promoter of platelet aggregation and vasoconstriction, and prostacyclin (PGI_2), an inhibitor of platelet aggregation and promoter of vasodilatation.[61] As a result, it has been hypothesized by FitzGerald et al. that selectively blocking COX-2 may predispose patients to increased cardiovascular risk,[62-65] including elevated blood pressure, accelerated atherogenesis,

and a possibly exaggerated thrombotic response to the rupture of atherosclerotic plaques.[66] However, to date no specific mechanism for the increased cardiovascular risk observed in patients taking rofecoxib has been positively identified; in particular, there is no direct evidence that this increase in risk results from an imbalance in levels of TxA_2 versus PGI_2 as postulated by FitzGerald et al. Moreover, there is evidence suggesting alternative hypotheses to explain the increased cardiovascular risk observed in patients taking rofecoxib, without postulating a class effect common to all selective COX-2 inhibitors.

In a pair of clinical trials with similar designs and similar numbers of OA and RA patients (>8000 patients in each trial), treatment with rofecoxib 50 mg QD (6 to 13 months in the VIGOR trial) significantly increased the risk of cardiovascular adverse events compared to treatment with naproxen 500 mg BID (relative risk 2.38, $p < 0.001$),[19] but treatment with celecoxib 400 mg BID (up to 15 months in the CLASS trial; median duration 9 months) did not significantly increase the risk of cardiovascular adverse events compared to treatment with diclofenac 75 mg BID or ibuprofen 800 mg TID ($p = 0.973$ for celecoxib versus diclofenac and ibuprofen combined).[67] FitzGerald and colleagues have suggested that one explanation for this difference in cardiovascular risk may be that celecoxib is less selective than rofecoxib for COX-2 versus COX-1 inhibition; thus, it is inferred that celecoxib is more likely to have antiplatelet effects.[68] However, treatment with celecoxib does not significantly reduce platelet aggregation ex vivo compared to either pre-treatment levels or treatment with placebo, even at a dose (1200 mg BID) greater than the 400 mg BID supratherapeutic celecoxib dose used in the CLASS trial.[69] Therefore, differences in selectivity are probably inadequate to explain the differences in cardiovascular risk observed for rofecoxib versus other selective COX-2 inhibitors in a manner consistent with the FitzGerald hypothesis, since at clinically relevant doses all of these agents remain highly selective.

Additionally, in the APPROVe trial, the subset of patients taking aspirin showed the same increase in risk for cardiovascular events as the subset of patients not taking aspirin (Section 2.3). This is inconsistent with the FitzGerald hypothesis, which would have predicted a reduction of relative risk with aspirin because the putative inhibition by rofecoxib of endothelial cell-generated PGI_2 production would, in patients taking aspirin, be balanced by aspirin inhibition of platelet-generated TxA_2 production.

Alternative hypotheses to explain the adverse cardiovascular effects of rofecoxib, without postulating a class effect and probably involving mechanisms other than COX-2 inhibition, should be considered.

3.2. Alternative Hypotheses May Explain the Unique Effect of Rofecoxib on Cardiovascular Risk

3.2.1. In contrast to Celecoxib and Valdecoxib, Rofecoxib Promotes Oxidative Damage to Low-Density Lipoprotein and Phospholipids

Recently, it was demonstrated that rofecoxib, a methyl sulfone, promotes oxidative damage to LDL and phospholipids in vitro, but that the sulfonamide-type selective COX-2 inhibitors celecoxib and valdecoxib, like nonselective NSAIDs (meloxicam, diclofenac, naproxen, ibuprofen), do not.[70] This pro-oxidant activity of rofecoxib occurs in the absence of COX-2,

increases with increasing rofecoxib concentration, and is attenuated in the presence of an antioxidant. Analysis using small-angle x-ray diffraction has shown that rofecoxib interacts with membrane phospholipids in a manner likely to increase permeability to free radical ions and/or free radical diffusion, whereas celecoxib does not, suggesting that such interactions tend to disrupt membrane structure and expose LDL and phospholipids to oxidative damage.[70] This finding supports the hypothesis that methyl sulfone-containing compounds like rofecoxib are unique among selective COX-2 inhibitors (and NSAIDs generally) in their ability to promote oxidative damage to both LDL and cell membrane phospholipids, using a mechanism that does not involve COX-2 inhibition. Clinically, the presence of oxidized LDL is a marker for plaque instability[71] and acute coronary syndromes.[72]

According to the oxidative-modification hypothesis of atherosclerosis, the activation of macrophages in response to uptake of oxidized LDL via the scavenger receptor[73,74] results in inflammation of the endothelium and underlying intimal tissue,[75-77] with consequences that include foam cell formation and endothelial dysfunction.[78,79] Additionally, non-enzymatic free-radical attack on arachidonic acid during lipid peroxidation can result in the formation of isoprostanes capable of acting as prostaglandin analogs. One major isoprostane product of such a reaction, 8-epi $PGF_{2\alpha}$, has biological activity similar to that of TxA_2,[80] including activation of platelets,[81] promotion of vasoconstriction,[82] and increased neutrophil adhesion.[83] The formation of both oxidized LDL and isoprostanes is significantly increased in vitro in the presence of rofecoxib but not in the presence of celecoxib (Figure 10).[70] These observations together suggest the hypothesis that chemical differences between selective COX-2 inhibitors of the sulfone type and the sulfonamide type, rather than the effect of selective COX-2 inhibition on PGI_2 versus TxA_2 balance, may account for at least some of the increased cardiovascular risk observed in patients taking rofecoxib, using a mechanism that promotes atherogenesis via oxidative stress.

Figure 10. Rofecoxib Increases Formation of Isoprostanes and Oxidized Low Density Lipoprotein In Vitro Through a Non-Enzymatic Process

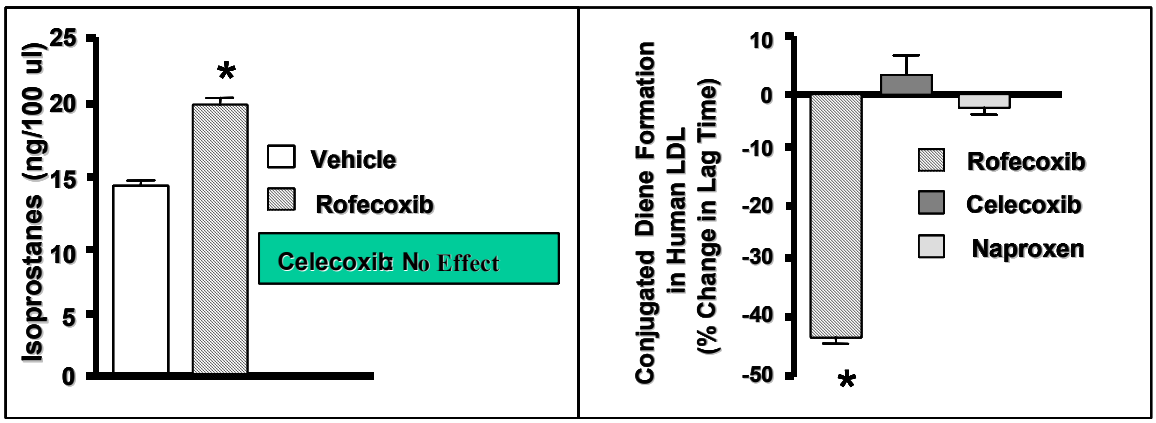


Figure adapted from Walter et al.[70]

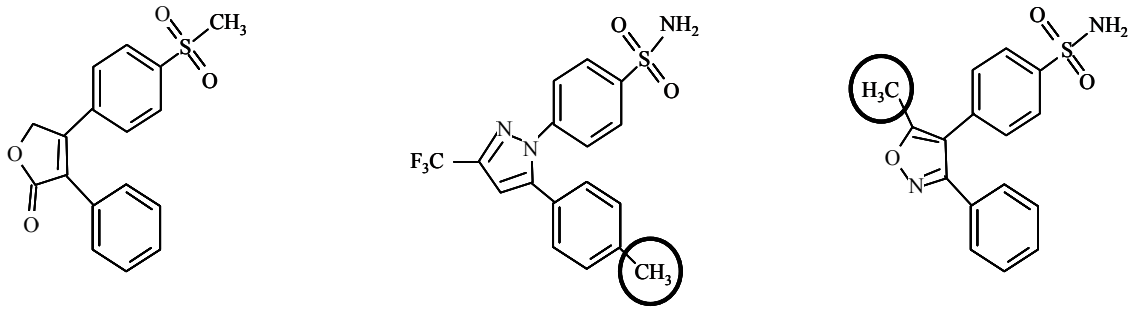
In addition to PGI_2, a number of other factors contribute to the regulation of vasodilatation in opposition to the vasoconstrictive effect of TxA_2. Perhaps the most important of these factors is nitric oxide (NO), which is produced by the endothelium and platelets in response to a variety of

stimuli including increased blood flow. In atherosclerosis, inflammation of the endothelium results in diminished capacity to produce NO, and one result is diminished ability to induce vasodilatation in response to increased blood flow, which increases blood pressure.[84] In animal models, NO has also been shown to modulate the activity of COX-2,[85] and in a head-to-head study of endothelial function in an animal model of hypertension, treatment with celecoxib significantly improved endothelial function, but treatment with rofecoxib or diclofenac did not.[86] Moreover, clinical studies have shown that celecoxib improves endothelial function in patients with hypertension or atherosclerosis, but rofecoxib does not (Section 3.2.3.2), and that rofecoxib has unique effects on blood pressure that are not shared with celecoxib or nonselective NSAIDs (Section 3.2.3.1).

3.2.2. Formation of Potentially Toxic Rofecoxib Metabolites

Structurally, rofecoxib lacks a methyl group that is present on both celecoxib and valdecoxib (circled in Figure 11). During the design of celecoxib and valdecoxib, this methyl group was added intentionally in order to ensure that each could be inactivated via a predictable, high-capacity enzyme system, namely hepatic cytochrome P450.[87,88] As a result, celecoxib and valdecoxib have more predictable metabolism than rofecoxib,[89] which is inactivated via cytosolic reductases (5-beta-reductase) to produce a variety of metabolites.[90,91]

Figure 11. Chemical Structures of Selective COX-2 Inhibitors

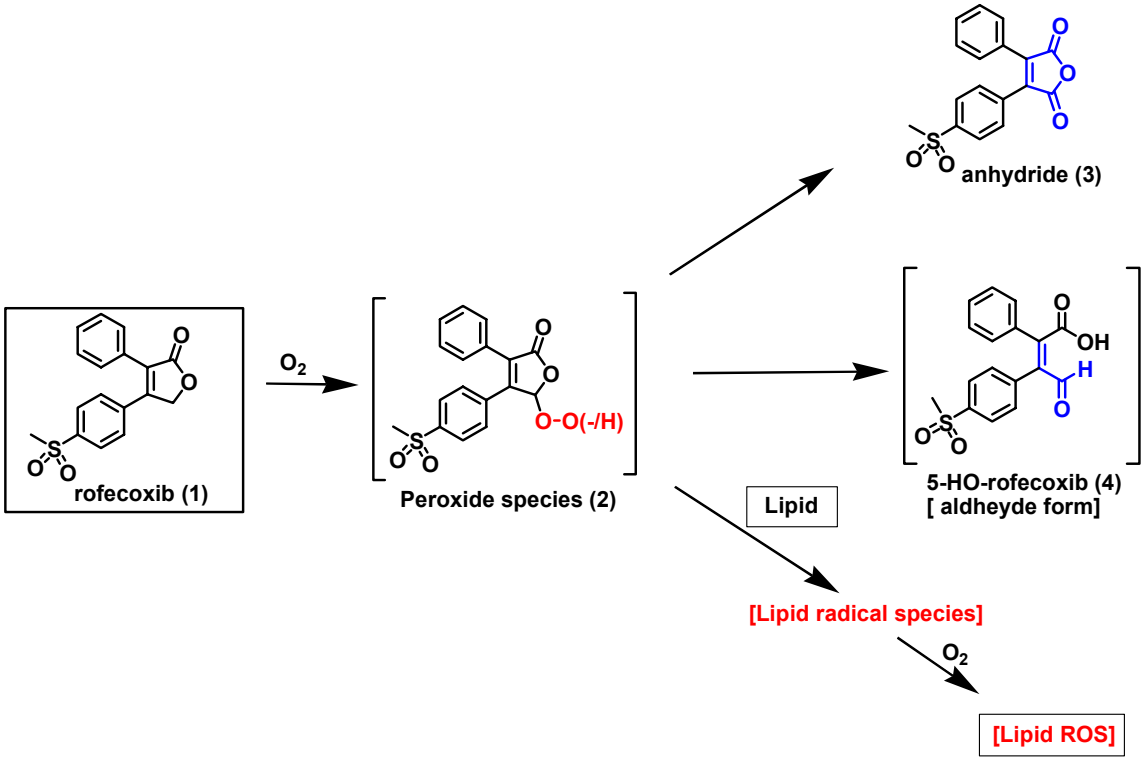


Additionally, rofecoxib has been shown to react with oxygen to form 5-hydroxyrofecoxib (Structure 4 in Figure 12).[92] As there is a precedent for the reaction of organic compounds with oxygen to proceed through a peroxide intermediate, it is possible that a peroxide species (Structure 2 in Figure 12) is produced as an intermediate in the formation of 5-hydroxyrofecoxib. Peroxides are among reactive oxygen species known to oxidize lipids and to diminish the bioavailability of nitric oxide, an important mediator of vasodilation. Notably, following administration of a single dose of radiolabelled rofecoxib to normal human volunteers, only 86% of the original dose could be recovered, suggesting that up to 14% of the dose administered is retained in humans as metabolites.[90]

Furthermore, Reddy and Corey have reported that rofecoxib is capable of undergoing spontaneous oxidation as it circulates to oxygenated tissues in vivo, and that the resulting

rofecoxib metabolites include anhydrides (Structure 3 in Figure 12) that have the potential to react with nucleophilic groups in biomolecules, especially amino acids.[93] One potential result of this reactivity may be a toxicity associated with rofecoxib that is not associated with celecoxib or valdecoxib; Reddy and Corey have hypothesized that this toxicity may have cardiovascular effects in humans that become apparent only with long-term rofecoxib treatment.

Figure 12. Chemically Active Rofecoxib Metabolites



3.2.3. Clinical Evidence Suggests Unique Effects for Rofecoxib on Blood Pressure and Endothelial Function

3.2.3.1. Blood Pressure Effects: Comparative Data for Rofecoxib and Celecoxib

Renal effects including retention of sodium and water are observed in some patients taking any drug that inhibits COX-2, including both nonselective NSAIDs and selective COX-2 inhibitors. This retention of sodium and water is thought to contribute at least in part to transient increases in mean blood pressure among patients who take NSAIDs.[94] However, meta-analyses of interventional clinical trials have shown that nonselective NSAIDs can have lasting effects on blood pressure beyond this transient effect. These analyses suggest that indomethacin, naproxen, and piroxicam produce the largest increases in blood pressure on average, and that the effect of raising blood pressure is confined primarily to patients being treated for hypertension.[2,3] This blood pressure-destabilizing effect is most prominent in patients using ACE inhibitors, beta-blockers, and/or diuretics (but not calcium channel blockers) to control hypertension.[4] It is believed that modulation of renal hemodynamics and tubular function by prostaglandins may contribute to blood pressure destabilization in patients taking these kinds of medications,[5]

although the role of COX-2 and its inhibition in this effect is unclear.[6] Experimental studies have shown that administration of NSAIDs to susceptible individuals can increase systemic vascular resistance and reduce renal blood flow, glomerular filtration, and sodium excretion.[95] In these individuals, the combination of these mechanisms can be expected to increase the risk of developing clinical heart failure,[96] and even small increases in blood pressure similar to those associated with NSAIDs in these studies can contribute significantly to cardiovascular morbidity and mortality.[97]

In healthy volunteers treated with rofecoxib[98] or celecoxib,[99] sodium and water excretion usually returns to baseline levels within 5-7 days of continuous dosing. However, review of the clinical study database supporting the rofecoxib New Drug Application (NDA; published by the US FDA as indicated in footnotes to Table 16) showed that the percentages of patients who experienced hypertension adverse events increased in a dose-related manner across the approved rofecoxib dose range (12.5 to 50 mg per day), and that hypertension adverse events occurred in a greater percentage of patients treated with rofecoxib 25 mg QD or rofecoxib 50 mg TDD compared to patients treated with ibuprofen 2400 mg TDD or diclofenac 150 mg TDD (Table 16). Similarly, hypertension adverse events in the VIGOR trial occurred in a greater percentage of patients treated with rofecoxib 50 mg QD (8.5%, comparable to the 8.2% observed for rofecoxib 50 mg QD in the NDA database) compared to patients treated with naproxen 500 mg BID (5%).

Table 16. Hypertension Adverse Events in Rofecoxib Clinical Trials

	NDA Database[a]					VIGOR[b]	
	Rofecoxib (mg/day)			Ibuprofen	Diclofenac	Rofecoxib	Naproxen
	12.5	25	50	2400 mg/day	150 mg/day	50 mg/day	1000 mg/day
Number of Patients	1215	1614	476	847	498	4047	4029
Patients with Hypertension[c]	2.8%	4.0%	8.2%	2.9%	1.6%	8.5%	5.0%

NDA = New Drug Application; VIGOR = Vioxx Gastrointestinal Outcomes Research.
[a] Data from US Food and Drug Administration cardiovascular-renal safety review: Rofecoxib NDA 21-042. Available at: http://www.fda.gov/cder/foi/nda/99/021042_52_vioxx_medr_P34.pdf
[b] Data from US Food and Drug Administration review of cardiovascular safety database, Consultation NDA 21-042, S-007. Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.doc.
[c] Indicates percentages of patients for whom hypertension was reported as an adverse event.

In contrast, review of the clinical study database supporting the celecoxib NDA (published by the FDA as indicated in footnotes to Table 17) showed no increase in percentages of patients taking celecoxib who experienced hypertension adverse events compared to patients taking NSAIDs; furthermore, in the CLASS trial, a significantly smaller percentage of patients treated with celecoxib at the supratherapeutic dose of 400 mg BID had hypertension adverse events compared to patients treated with ibuprofen 2400 mg QD (Table 17).

Table 17. Hypertension Adverse Events in Celecoxib Clinical Trials

	NDA Database[a]				CLASS[b]		
	Celecoxib (mg/day)			NSAIDs	Celecoxib	Diclofenac	Ibuprofen
	200	400	800	Any Dose	800 mg/day	150 mg/day	2400 mg/day
Number of Patients	1764	1208	99	1388	3987	1996	1985
Patients with Hypertension[c]	0.7%	1.2%	0.0%	0.9%	2.0%	2.0%	3.1%*

*P < 0.05 versus celecoxib 800 mg/day
NDA = New Drug Application; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs used as comparators, namely naproxen or diclofenac; CLASS = Celebrex Long-Term Arthritis Safety Study
[a] Data from US Food and Drug Administration review of cardiovascular safety Celecoxib NDA 20 998. Available at: http://www.fda.gov/cder/foi/nda/98/20998AP_medr_P10.pdf
[b] Data from US Food and Drug Administration Arthritis Advisory Committee meeting, February 2001. Available at: http://www.fda.gov/ohrms/dockets/as/01/briefing/3677b2_01_merck.pdf
[c] Indicates percentages of patients for whom hypertension was reported as an adverse event.

When the effects of rofecoxib 25 mg QD and celecoxib 200 mg QD were compared directly in two randomized, double-blind clinical trials involving approximately 2400 patients with controlled hypertension and osteoarthritis, significantly more patients treated with rofecoxib developed clinically significant elevations in systolic blood pressure (defined as an increase >20 mmHg together with a value >140 mmHg) compared to patients treated with celecoxib (17% for rofecoxib versus 11% for celecoxib, p = 0.0032, in one study; 14.9% for rofecoxib versus 6.9% for celecoxib, p <0.01, in the other).[24,25] Also in these 2 trials, the percentages of patients treated with rofecoxib who had clinically meaningful elevations in systolic blood pressure increased from Week 1 to Week 2 to Week 6 of treatment; such increases were not observed in patients treated with celecoxib, and mean systolic blood pressure, while increased by approximately 3 mmHg in patients treated with rofecoxib, did not increase in patients treated with celecoxib over the same period.

In a randomized, double-blind clinical trial using ambulatory blood pressure monitoring (ABPM) to evaluate the effects of rofecoxib, celecoxib, and naproxen on 24-hour mean systolic blood pressure in 404 patients with type 2 diabetes, hypertension, and osteoarthritis, rofecoxib 25 mg QD induced significant increases in blood pressure compared to baseline when measured after both 6 and 12 weeks of treatment. In contrast, celecoxib 200 mg BID and naproxen 500 mg BID were not associated with significant changes in blood pressure from baseline. The treatment difference comparing rofecoxib to celecoxib was 3.78 mmHg (95% CI: 1.18 to 6.38 mmHg, p = 0.05), while the treatment difference comparing rofecoxib to naproxen was 3.85 mmHg (95% CI: 1.15 to 6.55 mmHg, p = 0.005).[22] Moreover, in a further study using ABPM in patients with hypertension controlled by the ACE inhibitor benazepril, rofecoxib 25 mg QD increased 24-hour mean systolic blood pressure by 4.5 mmHg (95% CI: 2.2 to 6.8 mmHg); in comparison, indomethacin 75 mg/day increased 24-hour mean systolic blood pressure by 2.0 mmHg (95% CI: -0.3 to 4.4 mmHg) in the same study.[23] In contrast, an ABPM study in patients with hypertension controlled by the ACE inhibitor lisinopril has shown that celecoxib 200 mg BID causes no statistically significant increase in mean blood pressure relative to placebo.[100]

In summary, these cardiorenal data show that treatment with rofecoxib results in sustained increases in systolic blood pressure of approximately 3-4 mmHg relative to treatment with

celecoxib, which has a negligible effect compared to baseline. In clinical trials and epidemiologic studies, differences in systolic blood pressure of this magnitude have been associated with significantly increased incidence of myocardial infarction and stroke.[101-105]

3.2.3.2. Effects on Endothelial Function: Comparative Data for Rofecoxib and Celecoxib

In atherosclerosis, inflammation of the endothelium results in diminished capacity to produce nitric oxide (NO), which is normally produced in response to a variety of stimuli including increased blood flow. As a result, the ability to induce vasodilatation in response to increased blood flow is also diminished; thus, flow-mediated vasodilation (ie, arterial diameter after arterial occlusion with a blood pressure cuff versus arterial diameter before, usually measured using brachial artery ultrasound) can be used to evaluate endothelial function, and diminished flow-mediated vasodilation is characteristic of patients with cardiovascular disease.[84] Clinical studies to evaluate effects of rofecoxib and celecoxib on endothelial function are described below:

- In 3 randomized clinical studies designed to evaluate the impact of prolonged COX-2 inhibition on inflammation and endothelial function in patients with ischemic heart disease, rofecoxib 25 mg QD was compared versus placebo over treatment periods of 3 months,[106] 6 months,[107] and 9 months.[108] In all 3 of these studies, despite evidence of anti-inflammatory effects as expected, no significant differences were observed when patients treated with rofecoxib were compared to patients treated with placebo for endothelium-dependent vasodilation, measured as flow-mediated dilation of the brachial artery.

- In a double-blind, crossover study in which 14 male patients with severe coronary artery disease received celecoxib 200 mg BID or placebo for 2 weeks, endothelium-dependent vasodilation was significantly improved when patients were treated with celecoxib compared to the same patients treated with placebo (3.3 ± 0.4% for celecoxib versus 2.0 ± 0.5% for placebo; $p = 0.026$), whereas endothelium-independent vasodilation (ie, brachial artery diameter after administration of nitroglycerin versus brachial artery diameter before) remained unchanged.[109] Also in this study, plasma levels of C-reactive protein (CRP) and oxidized LDL were significantly reduced after celecoxib treatment compared to placebo, but plasma levels of PGI_2 were unchanged. These results indicate that anti-inflammatory and anti-atherogenic effects that may not have been mediated by PGI_2 accompanied the observed improvement in endothelial function.

- In a double-blind study in which 29 hypertensive patients were randomized to receive celecoxib 200 mg BID or placebo, endothelium-dependent vasodilation in patients treated with celecoxib improved significantly during the 3 hours following the first dose of study medication (from 7.9 ± 4.5% at baseline to 9.9 ± 5.1% at 3 hours; $p = 0.005$), and this improvement was maintained over 1 week of treatment (10.1 ± 6.1% after 1 week; $p = 0.006$ compared to baseline); treatment with placebo had no significant effect.[110] Also in this study, urinary metabolites of PGI_2 but not TxA_2 were significantly reduced in patients treated with celecoxib but not in patients treated with placebo, indicating that PGI_2 activity, measured as a function of urinary metabolites, does not contribute

substantially to flow-mediated dilation in these patients. These findings provide insight into the causes of endothelial dysfunction in hypertension and raise the possibility that celecoxib could be beneficial for hypertensive patients.

Together with mechanistic data described above, these results indicate that although both have significant anti-inflammatory effects, rofecoxib and celecoxib may differ in their effects on endothelial function, probably through a mechanism that does not involve COX-2 inhibition. This can contribute directly to cardiovascular effects with rofecoxib and also, in turn, may result in the incremental effects of rofecoxib on blood pressure, which would also increase cardiovascular effects. If confirmed in longer-term studies of endothelial function with celecoxib, this hypothesis would explain why rofecoxib is evidently an outlier with respect to cardiovascular risk, and why celecoxib and valdecoxib have cardiovascular safety profiles that fall within the range of those observed for nonselective NSAIDs in all settings in which they have been compared.

4. PLANS FOR FURTHER EVALUATION OF CARDIOVASCULAR SAFETY

4.1. Prospective Clinical Trial to Evaluate Celecoxib Cardiovascular Safety

Pfizer currently has plans for a prospective clinical trial, designated Study A3191172, to assess the cardiovascular safety of celecoxib in comparison with a nonselective NSAID in patients with OA. This study is intended to address the following concerns:

- No randomized clinical trial with chronic celecoxib dosing of any duration has been designed specifically to evaluate cardiovascular adverse events. Current long-term trials have been hampered by too few events and limited data collection to support firm conclusions or to be able to identify subsets of patients at cardiovascular risk.

- No long-term randomized clinical trial capable of assessing cardiovascular events with treatment durations longer than one year has been conducted with celecoxib in an arthritis population; such a population would represent the large majority of users of nonselective NSAIDs and selective COX-2 inhibitors in clinical practice. The fact that increased cardiovascular risk was observed in a study of aspirin used longer than 1 year in a colon cancer prevention setting (Section 2.4.3) provides possible evidence of confounding effects in the colon cancer prevention population.

- There are scant comparative data regarding the cardiovascular safety of nonselective NSAIDs in a randomized clinical trial of more than 1 year. The preliminary results of the ADAPT study suggest the need to evaluate the comparative cardiovascular safety of celecoxib versus a nonselective NSAID in addition to placebo in arthritis patients.

- Despite gastrointestinal toxicity, NSAIDs remain an important therapeutic option for patients with chronic arthritic diseases. Therefore, investigation of the comparative benefits and risks of nonselective NSAIDs versus selective COX-2 inhibitors will be of great public health significance, especially as large numbers of patients requiring analgesic therapy for chronic arthritic or other painful and/or inflammatory conditions are elderly and have increased incidence of co-morbidity with cardiovascular risk (including hypertension, diabetes, and atherosclerosis).

For this purpose, the proposed study would assess the cardiovascular effects of celecoxib compared to a commonly prescribed non-selective NSAID in OA patients who have concomitant cardiovascular disease, using a double-blind, double-dummy, randomized, parallel group design at multiple investigational centers. Patients with OA who require chronic (daily) therapy with an NSAID to control arthritis symptoms and who represent a broad range of cardiovascular risk (as evidenced by cardiovascular risk factors) will comprise the study population. Patients will receive celecoxib 200 mg once daily or a non-selective NSAID for a minimum follow-up of 18 months, in addition to the usual standard of care treatment for cardiovascular disease including low-dose aspirin for all patients and other cardiovascular medications (eg, statins, ACE inhibitors, beta-blockers, etc) as needed according to local norms and/or guidelines. Additionally, all patients will be administered omeprazole 20 mg QD as a gastroporotective

agent due to the use of aspirin and non-selective NSAID. Study endpoint adjudication committees will perform blinded adjudications of all cardiovascular and gastrointestinal events, and an independent Data Monitoring Committee will perform rigorous monitoring of all safety data, including cardiovascular and gastrointestinal safety.

Protocol details for Study A3191172 are currently being discussed with regulatory agencies so that suggestions can be incorporated into future design refinements. Upon regulatory concurrence with study plans, Study A3191172 will be implemented globally.

4.2. Registry-based observational study in FAP patients (Study NQ4-00-02-012)

A registry-based observational study in FAP is currently ongoing to meet Phase IV commitments with FDA and EMEA. The study was designed to collect and examine data on long-term clinical and safety outcomes among FAP subjects treated with celecoxib and to compare these data with those from control FAP subjects who have not received celecoxib. The total planned study duration is five years and the first study site was initiated on 01 September 2004. The principal investigator in this observational study is Dr. James Church (Cleveland Clinic US), and participating sites are Cleveland Clinic (US), Hvidovre Hospital Registry (Denmark), Düesseldorf Polyposis Registry (Germany), Mount Sinai Familial GI Cancer Registry (Canada) and The Royal Melbourne Hospital (Australia). As of 16 December 2004, six FAP patients from two registry sites were identified for participation in the study. Currently, two of the sites are active in the study (Toronto Registry participating in the retrospective part of the study and Cleveland Clinic Registry). Pfizer has provided a "Dear Investigator Letter" to the participating study sites and the study informed consent has been updated to include new safety information from the APC trial and has been submitted for local Institutional Review Board approval at each site. A final report from this study is expected to be completed 1Q2010.

4.3. Epidemiological Studies

Epidemiological studies either fully sponsored by Pfizer or partially funded by independent research grants (IRGs), currently ongoing with celecoxib and/or valdecoxib included among the prespecified investigational study drugs, are summarized below. The main characteristics of each study and projected dates for availability of study reports are presented in Table 18.

1. **Risk of acute myocardial infarction in users of COX-2 specific inhibitors in Saskatchewan, Canada.**
   Principal investigator: Varas-Lorenzo C, Pfizer Global Epidemiology
   Final report/manuscript 2Q06

   Retrospective cohort study and nested case-control analysis in the Saskatchewan Health Services population to estimate the risk of acute myocardial infarction and coronary death in patients aged 40-84 years exposed to celecoxib, rofecoxib, and non-selective NSAIDs between November 15, 1999 and December 31, 2001. Effects of dose, duration and use of concomitant medications will be studied. Cases are identified using ICD-9 codes from Hospital Discharge Services and Vital Statistics. Case validation is conducted for a random sample of 200 potential cases of acute myocardial infarction (ICD-9 code 410) and all cases of other acute and subacute forms of ischemic heart disease (ICD-9 code 411).

2. **Risk of cardiovascular events in patients with serious coronary heart disease (Medicaid Tennessee, US; Saskatchewan Health, Canada; GPRD, UK).**
   Principal investigator: Ray W, Vanderbilt University
   Final report/manuscript 4Q06

   Retrospective cohort study conducted in the Medicaid Tennessee, the Saskatchewan Health Services, and the United Kingdom General Practice Research (GPRD) populations to estimate the risk of recurrent cardiovascular heart disease (acute myocardial infarction, unstable angina, and revascularization procedures) associated with the use of COX-2 specific inhibitors, celecoxib and rofecoxib, and non-selective NSAIDs, in patients older than 40 years from January 1, 1999 to December 31, 2003. Cases will be identified using ICD-9 codes from Hospital Discharge services and Vital Statistics. Case validation will be partially conducted. The effect of low and high dose, risk factors, and concomitant medications will also be studied.

3. **Risk of acute myocardial infarction in users of valdecoxib and other COX-2 specific inhibitors in Medicare, US (IRG).**
   Principal investigator: Solomon DH, Harvard Medical School
   Final report 3Q05-Manuscript 4Q05

   Retrospective cohort study conducted in the Pennsylvania and New Jersey Medicare populations to estimate the risk of cardiovascular (acute myocardial infarction and coronary death) and cerebrovascular events (ischemic stroke) associated with the use of COX-2 specific inhibitors, including valdecoxib, celecoxib, rofecoxib, and non-selective NSAIDS, during the years 2002 and 2003. The exposure assessment will be studied for low and high doses and for current and past users. Effects of confounders such as use of over-the-counter NSAIDs and aspirin, body mass index, smoking, and socio-economic status will be estimated from the 2002 Medicare Current Beneficiary Survey. Cases are identified using ICD-9 codes from Hospital Discharge Services and Vital Statistics. Case validation will not be conducted as prior studies in this population have shown a positive predictive value of 93% for ICD-9 code 410 (acute myocardial infarction).

4. **Risk of acute myocardial infarction in patients with osteoarthritis and rheumatoid arthritis in MediCal, US (IRG).**
   Principal investigator: Singh G, Stanford University
   Final report/manuscript 3Q05

   Nested case-control study conducted in the MediCal Healthcare System population to estimate the risk of acute myocardial infarction associated with the use of COX-2 specific inhibitors, valdecoxib, celecoxib, rofecoxib, and non-selective NSAIDS, in patients aged 18 to 84 years with arthritis (OA/RA) and/or musculoskeletal disorders from January 1, 1999 to June 30, 2004. The study will assess the effect of dose, use of over-the-counter NSAIDs and aspirin, and of other risk factors. Cases are identified using ICD-9 codes from reimbursement records. There is no case validation conducted in this study.

5. **Risk of acute myocardial infarction in France – CADERIS.**
   Principal investigator: Moore N, Victor Segalen University, Bordeaux
   Pilot study. Interim report June 2005-Final report October 2005

   Phase IV commitment cohort study conducted in France among users of COX-2 specific inhibitors and non-selective NSAIDs with the goal of estimating the risk of cardiovascular events, including acute myocardial infarction, associated with the use of these drugs. The study includes a total of 44,746 users identified in the Extractions, Research, Analyses for Economic Medical (ERASME) database. Assessment of events is conducted through a questionnaire sent by mail to users and physicians.

6. **Risk of cerebrovascular events associated with the use of COX-2 inhibitors in Medicaid Tennessee, US.**
   Principal investigator: Griffin M, Vanderbilt University
   Final report/manuscript 2Q06

   Retrospective cohort study conducted in the Medicaid Tennessee population aged 50 to 84 years old to assess the risk of cerebrovascular diseases (ischemic and hemorrhagic stroke) associated with the use of COX-2 specific inhibitors (valdecoxib, celecoxib, rofecoxib, and non-selective NSAIDS), between January 1, 1999 and June 30, 2003. Cases will be identified using ICD-9 codes from Hospital Discharge Services and Vital Statistics. A random sample of 100 cases will be validated through review of medical charts.

7. **Risk of cardiovascular events in users of COX-2 specific inhibitors in patients with OA or RA in a New England Healthcare insured population.**
   Principal investigators: Whelton A, The Johns Hopkins University School of Medicine and Spalding W, Development Operations, Pfizer Inc.; Doctoral candidate, Department of Epidemiology, Michigan State University
   Final report/manuscript 3Q05

   Retrospective cohort study conducted in a source population of over 3 million patients aged 18 years and older enrolled in a private medical insurance plan in the New England states from January 1, 1999 through June 30, 2001. The objective of the study is to estimate the risk of acute myocardial infarction and stroke associated with the use of chronic anti-inflammatory therapy (celecoxib, rofecoxib, and non-selective NSAIDs) in 34,137 patients with a diagnosis of OA and/or RA according to their hypertension status (medical claim with ICD-9-CM code 401-405, hypertension, and receiving therapy with antihypertensive drugs). Cases are identified through hospital discharge ICD-9-CM codes 410-414 and 430-436.

Table 18. Summary of Ongoing Cardiovascular Epidemiological Studies Involving Celecoxib Sponsored by Pfizer or Partially Funded by Independent Research Grants From Pfizer

Study and setting	Principal investigator	Study design	Study drugs	Final report/manuscript
Risk of AMI and coronary death *Saskatchewan, Canada*	Varas-Lorenzo C *Pfizer Global Epidemiology*	Cohort, Nested case-control	celecoxib rofecoxib NSAIDs	2Q06
Risk of cardiovascular events in patients with serious coronary heart disease *Medicaid Tennessee, US - Saskatchewan, Canada – GPRD, UK*	Ray WA *Vanderbilt University*	Cohort	celecoxib rofecoxib NSAIDs	4Q06
Risk of AMI, coronary death, and ischemic stroke *Medicare Pennsylvania-New Jersey, US*	Solomon DH *Harvard Medical School*	Cohort	celecoxib valdecoxib rofecoxib NSAIDs	Report 3Q05 Manuscript 4Q05
Risk of AMI in an OA-RA population *MediCal (California Medicaid), US*	Singh G *Stanford University*	Nested case-control	celecoxib valdecoxib rofecoxib NSAIDs	3Q05
Risk of AMI (pilot study) *CADERIS Phase IV commitment, France*	Moore N *University Victor Segalen, Bordeaux*	Cohort	celecoxib rofecoxib NSAIDs	Interim report June 2005 Final report October 2005
Risk of stroke *Medicaid Tennessee, US*	Griffin M *Vanderbilt University*	Cohort	celecoxib valdecoxib rofecoxib NSAIDs	2Q06
Risk of AMI and stroke *New England Insurance Plan, US*	Whelton A *Johns Hopkins University*	Cohort	celecoxib rofecoxib NSAIDs	3Q05

AMI = Acute myocardial infarction; OA = Osteoarthritis; RA = Rheumatoid arthritis.

5. BENEFIT/RISK ASSESSMENT: CHRONIC PAIN/INFLAMMATION

An estimated 4 million Canadians are suffering from arthritis and other rheumatic conditions. In 1998, arthritis and related conditions were the underlying cause of 2.4 deaths per 100,000 in Canada, making arthritis a more common underlying cause of death than melanoma, asthma, or HIV/AIDS; overall, approximately 12% of Canadians aged 65 years or older were prescribed nonselective NSAIDs in the year 2000, most for the treatment of arthritis and other rheumatic conditions.[111] The nonselective NSAIDs have been widely used for decades despite their risks because they serve a significant medical need and allow mobility and relief from chronic pain. Due to this widespread use, concern regarding the risk of gastrointestinal adverse effects with nonselective NSAIDs, together with new concerns regarding possible cardiovascular safety signals recently observed in preliminary data from the APPROVe and APC trials, will complicate benefit/risk considerations for all NSAIDs, both nonselective and selective COX-2 inhibitors.

Approximately 3.6 times as many NSAID prescriptions are written for elderly patients compared to younger patients.[112] Eighty percent of adults >65 years of age have radiographic evidence of OA, virtually all have this disease by the age of 80,[113] and half of all NSAID prescriptions in the elderly are for this indication.[114] Changes in the usage patterns for selective COX-2 inhibitors and nonselective NSAIDs will affect large numbers of patients in Canada and worldwide, and the problem will increase in scope as populations increase in average age. Increased use of nonselective NSAIDs in an aging population will increase the numbers of gastrointestinal, cardiorenal, and possibly cardiovascular adverse events related to NSAID use. It has been estimated that 5% to 7% of US hospital admissions are related to adverse effects associated with medication use, and hospitalizations for gastrointestinal, nervous system, renal, or allergic effects associated with use of aspirin or non-aspirin nonselective NSAIDs are responsible for approximately 30 percent of this total.[115] In OA patients the balance of positive effects measured against the potential adverse effects is particularly critical given the increased potential for NSAID-induced toxic effects mediated partially by age.

5.1. Celecoxib and Nonselective NSAIDs Treat Pain and Inflammation Effectively

Approval of celecoxib by the Health Canada's TPD with indications for OA and RA was based on demonstration of equivalent efficacy versus nonselective NSAIDs in 5 clinical trials involving >5200 patients; all 5 of these trials had similar parallel-group designs comparing celecoxib at various doses to placebo and naproxen. Statistically significant improvement on multiple co-primary endpoints was observed for celecoxib ≥100 mg BID compared to placebo, and similar improvement compared to naproxen, was observed in all 5 of these studies, including replicate studies in OA patients and in RA patients. Evidence of efficacy comparable to both naproxen and diclofenac in both OA and RA patients has been observed in published clinical trials also.[116-119]

A controversial question in the management of OA is whether NSAIDs are superior to simple analgesics with respect to pain relief. Nonselective, NSAIDs have been shown to provide

benefits including reduced pain, decreased gel phenomena, and improved function in OA patients relative to simple analgesics such as acetaminophen;[120] it is not clear whether any of these benefits are due specifically to anti-inflammatory effects. Recently, 3 important trials have revisited the question of the importance of NSAIDs in the treatment of patients >40 years of age with OA of the hip or knee. These double-blinded, randomized, controlled trials used a crossover design to compare the effects of NSAIDs versus acetaminophen or placebo in OA. The crossover design allowed patients to assess and compare 2 of 3 treatments: Patients were treated for six weeks in each of 2 treatment periods, with a washout period separating the 2 treatment periods; active treatments were diclofenac/misoprostol, (a nonselective NSAID and gastroprotectant in fixed combination) 75 mg/200 mcg BID versus acetaminophen 1000 mg QID in one trial,[121] and celecoxib 200 mg/day versus acetaminophen 1000 mg QID in the other 2 trials.[122] In the respective trials, both diclofenac/misoprostol and celecoxib were always numerically and usually statistically superior to acetaminophen in a patient assessment of pain using visual analog scale and in the Western Ontario and MacMaster Universities Osteoarthritis Index, an assessment of pain, stiffness, and functional outcome. Adverse events were significantly more common with diclofenac/misoprostol treatment than with acetaminophen, but the safety profile of celecoxib was indistinguishable compared to that of acetaminophen. Patient preferences significantly favored both diclofenac/misoprostol and celecoxib over acetaminophen. Together, these data suggest that in patients with OA, where pain is associated with a low-grade inflammatory process, medications with both anti-inflammatory and analgesic activities provide superior efficacy compared to a simple analgesic like acetaminophen.

5.2. Celecoxib Offers a Gastrointestinal Benefit Over Nonselective NSAIDs

As described below, the available data in OA and RA patients demonstrate that celecoxib has an improved gastrointestinal safety and tolerability profile compared to nonselective NSAIDs in clinical trails that examine mucosal ulceration detected by endoscopy, gastrointestinal tolerability including withdrawals from treatment due to gastrointestinal adverse events, and the development of symptomatic ulcers and ulcer complications. Data from individual trials evaluating these outcomes are consistently supported by the results of meta-analyses across multiple trials and by the results of epidemiology studies. Together, these observations suggest that the medical need for improved gastrointestinal safety is fulfilled with the selective COX-2 inhibitor celecoxib.

5.2.1. Background

The incidence rates for serious gastrointestinal complications among non-users of NSAIDs are 0.9 events per 1000 person-years (95% CI: 0.66 to 1.27) for bleeding or perforated lesions, and 1.0 events per 1000 person-years (95% CI: 0.83 to 1.15) for serious gastrointestinal ulcers; rates increase with age, and are approximately twice as high in men compared to women.[123] In a systematic review of epidemiology studies conducted from 1990 to 1999, the risk of upper gastrointestinal bleeding was four times greater in nonselective NSAID users relative to non-users of NSAIDs (pooled relative risk 3.8; 95% CI, 3.6 to 4.1).[124] Moreover, an analysis of data from randomized, controlled clinical trials, observational studies, case-control studies, and case series suggests that after 2 months of nonselective NSAID or therapy, 1 in 5 patients will have an endoscopic ulcer, 1 in 70 patients will have a symptomatic ulcer, 1 in 150 patients will have a bleeding ulcer, and 1 in 1200 patients will die of a bleeding ulcer.[125]

Because COX-1 acts constitutively in the gastric mucosa to produce prostaglandins that promote generation of a protective mucous barrier lining the gastric lumen,[126-128] the most clinically significant and well-characterized adverse effects with nonselective NSAIDs are related to the degradation of this protective barrier. As a result, such agents may precipitate a variety of pathologies including esophagitis, esophageal stricture, gastritis, mucosal erosions, hemorrhage, the development of peptic ulcer or its complications including perforation and obstruction.[129-133] Additionally, there is increasing evidence of small and large bowel mucosal effects including induction of both gut permeability dysfunction and strictures with resulting obstruction.[134-136]

It has been demonstrated in endoscopic studies that nonselective NSAIDs classically produce shallow erosions or submucosal hemorrhages which can occur at any site in the alimentary tract but more commonly are observed in the stomach near the prepyloric area and the antrum. Typically, many of these gastrointestinal lesions are asymptomatic, making prevalence data very difficult to determine. Unfortunately, we also do not know what proportion of these lesions typically progress to develop ulceration and then extend to frank perforation, obstruction of the viscous, or serious gastrointestinal hemorrhage and subsequent death. Although many patients develop important gastrointestinal damage with no warning, there are known risk factors for the development of gastrointestinal effects with nonselective NSAIDs. These risk factors include increased age; history of peptic ulcer disease or gastrointestinal bleeding; prior use of antiulcer therapy for any reason; concomitant use of glucocorticoids, particularly in patients with rheumatoid arthritis; comorbid illness such as significant cardiovascular disease; and extensive or severe rheumatoid arthritis.[137-140] Additionally, combinations of NSAIDs can increase the risk for significant gastrointestinal adverse effects, and all of the presently available nonselective NSAIDs when used at high enough anti-inflammatory doses may induce significant damage to the gastrointestinal mucosa. Thus, the nonselective NSAIDs are clearly associated with increased risk for clinically important gastrointestinal events that may lead to death directly related to therapy.

5.2.2. Endoscopic Ulcers

The COX-1 sparing effects of celecoxib are associated with evidence of less mucosal damage, as demonstrated in pooled data from randomized, controlled trials in the celecoxib US New Drug Application (14 trials in OA and RA patients), which show significantly reduced incidence of complicated ulcers with celecoxib compared to naproxen. Significant benefits were also observed for celecoxib versus naproxen, ibuprofen, and diclofenac in most comparisons for endoscopic ulcers, blood loss, and gastrointestinal tolerability. Representative clinical trials include a surveillance endoscopy trial in which 688 patients with RA were randomly assigned to various doses of celecoxib or to naproxen or placebo for 12 weeks; in this trial, all doses of celecoxib and naproxen improved signs and symptoms of arthritis compared to placebo, and the incidence of endoscopically-determined gastroduodenal ulcers among patients taking celecoxib was similar to that observed with placebo (approximately 4%) and significantly lower than observed with naproxen (26%; $p < 0.001$).[116] Similarly, in a recent systematic review and meta-analysis by Moore and coauthors of 31 celecoxib clinical trials, risk for endoscopic ulcers was significantly reduced with celecoxib 200-400 mg/day relative to combined nonselective NSAIDs (relative risk = 0.30, 95% CI: 0.24 to 0.37 in studies representing 4135 patients with OA or RA across 6 trials).[141]

5.2.3. Gastrointestinal Tolerability

Regarding gastrointestinal tolerability, celecoxib has been shown in a number of clinical trials to be associated with a significantly improved gastrointestinal adverse events profile compared to nonselective NSAIDs. For example, in an analysis of pooled data from 5 trials in OA and RA patients treated for 12 weeks, celecoxib at both 200 mg BID (1125 patients) and 400 mg BID (434 patients), compared to naproxen 500 mg BID (1099 patients), was associated with significantly lower incidence of upper gastrointestinal adverse events (defined as a composite of moderate to severe abdominal pain, dyspepsia, and/or nausea; relative risk = 0.63, 95% CI: 0.47 to 0.83, p = 0.001 and relative risk = 0.56, 95% CI: 0.35 to 0.89, p = 0.015, respectively).[142] Also, in the meta-analysis by Moore and coauthors described above, gastrointestinal adverse events and withdrawals due to adverse events were significantly lower with celecoxib 200-400 mg QD compared to combined nonselective NSAIDs (relative risk for gastrointestinal adverse events = 0.84, 95% CI: 0.81 to 0.87 across 18 trials representing 30,043 patients; relative risk for withdrawals due to gastrointestinal adverse events = 0.7, 95% CI: 0.6 to 0.8 across 11 trials representing 18,639 patients).[141]

5.2.4. Ulcer Complications

The primary rationale for the development of selective COX-2 inhibitors, however, was to reduce the incidence of upper gastrointestinal ulcer complications relative to nonselective NSAIDs. In an analysis of pooled data from 14 randomized, controlled trials in 11,008 OA and RA patients treated for up to 24 weeks, the rate of confirmed upper gastrointestinal ulcer complications (defined as bleeding, perforation, or gastric outlet obstruction, adjudicated) with celecoxib was significantly lower than that seen with nonselective NSAIDs (annualized incidence 0.20% versus 1.68% respectively, p = 0.002); the rate observed with celecoxib in these trials was similar to that seen in 5155 patients treated for up to 2 years in an open label study (annualized incidence 0.20% versus 0.18% respectively).[143] Also, in the meta-analysis by Moore and coauthors described above, the incidence of upper gastrointestinal ulcer complications was lower with celecoxib 200-400 mg QD compared to combined nonselective NSAIDs when evaluated as either symptomatic ulcers and gastrointestinal bleeding (relative risk = 0.35, 95% CI: 0.22 to 0.56 in 17 trials representing 22,075 patients) or reductions of ≥20 g/L in hemoglobin (relative risk = 0.71, 95% CI: 0.55 to 0.91 in 10 trials representing 15,746 patients).[141]

In addition, the results of two large, randomized, controlled clinical trials were as follows:

- In the SUCCESS-1 trial (a 12-week, double-blind, randomized study of 13,274 patients with OA of the knee, hip or hand, randomized to celecoxib 100 mg BID, celecoxib 200 mg BID, diclofenac 50 mg BID, or naproxen 500 mg BID), investigators identified 144 potential serious upper gastrointestinal events. When adjudicated according to lesions, 36 of these events were considered significant upper gastrointestinal events, including 9 events that were considered ulcer complications (defined as gastric or duodenal perforations, gastric outlet obstruction, or upper gastrointestinal bleeding, confirmed by endoscopy). Significantly fewer ulcer complications occurred with celecoxib (0.1 per 100 patient-years) than with nonselective NSAIDs (0.8 per 100 patient-years; odds ratio = 7.02; 95% CI: 1.46 to 33.80; p = 0.008). When adjudicated

according to clinical presentation, 37 events were considered confirmed upper gastrointestinal events, including 12 events considered complicated upper gastrointestinal events. Again, significantly fewer complicated upper gastrointestinal events were seen with celecoxib (0.2 per 100 patient-years) than with nonselective NSAIDs (1.0 per 100 patient-years; odds ratio = 6.02; 95% CI: 1.50 to 34.57; p = 0.002). Additionally, patients treated with celecoxib had significantly fewer significant upper gastrointestinal events and confirmed upper gastrointestinal events.[144]

- In the CLASS trial, 3987 OA and RA patients treated with celecoxib 400 mg BID (2 and 4 times the maximum approved doses in RA and OA, respectively) were compared to 3981 OA and RA patients treated with diclofenac 75 mg BID or ibuprofen 800 mg TID; >20% of patients (an unexpectedly high percentage) in these two treatment groups were taking low-dose aspirin. For a combined endpoint of symptomatic ulcers and complicated ulcers, data over the entire study period (56-65 weeks) showed a significantly reduced annualized incidence with celecoxib (1.85%) compared to combined nonselective NSAIDs (2.82%; p = 0.04). Regarding the prespecified primary endpoint of complicated ulcers, data at 6 months of treatment in nonusers of aspirin significantly favored celecoxib over nonselective NSAIDs; however, when evaluated over the entire study period, or with aspirin users included at 6 months, differences (which favored celecoxib over nonselective NSAIDs) were not statistically significant. The importance of the unexpectedly high percentage of patients in the CLASS trial taking low-dose aspirin is discussed further below.[118]

The data from randomized, controlled trials described above indicating reduced risk of ulcer complications with celecoxib compared to nonselective NSAIDs are supported by data from recent epidemiology studies, which estimate the risk of upper gastrointestinal bleeding in celecoxib users to be comparable to that observed in non-users of celecoxib or nonselective NSAIDs.[145-147] Representative results are as follows:

- In a retrospective observational study from Canada, elderly patients (>65 years) who were new users of nonselective NSAIDs or selective COX-2 inhibitors were compared to patients not receiving anti-inflammatory therapy. Relative to celecoxib users, a significantly higher risk of hospitalization with a diagnosis of upper gastrointestinal hemorrhage was seen among users of nonselective NSAIDs (adjusted relative risk = 4.4; 95% CI: 2.3 to 8.5), diclofenac plus misoprostol (adjusted relative risk = 3.2; 95% CI: 1.6 to 6.5), and rofecoxib (adjusted relative risk = 1.9; 95% CI: 1.2 to 2.8). However, the incidence of this endpoint was similar in celecoxib users compared to patients not receiving anti-inflammatory therapy (adjusted relative risk = 1.0, 95% CI: 0.7 to 1.6).[145]

- In a case control study conducted in Denmark using high-risk patients with previous gastrointestinal disease, odds ratios for upper gastrointestinal bleeding significantly favored untreated patients over patients treated with rofecoxib (adjusted odds ratio = 2.1; 95% CI: 1.2 to 3.5) and patients treated with nonselective NSAIDs (adjusted odds ratio = 3.3; 95% CI: 2.4 to 4.4). However treatment with celecoxib did not differ significantly compared to non-treatment (adjusted odds ratio = 1.3; 95% CI: 0.7 to 2.8).[146]

5.2.5. Aspirin and Gastrointestinal Protection

Robust data from randomized, controlled studies are not available to fully establish the gastrointestinal profile of celecoxib compared to nonselective NSAIDs in patients concurrently using aspirin. However, the available data from comparative clinical trials and epidemiology studies evaluating endoscopic ulcers, gastrointestinal tolerability, and ulcer complications suggest that celecoxib offers improved gastrointestinal safety and tolerability compared to nonselective NSAIDs for patients also using low-dose aspirin. The magnitude of this benefit, however, may be less than in patients not using aspirin, and is yet to be fully established in a large scale prospective randomized controlled trial. In particular, the CLASS trial raised questions regarding the relative gastrointestinal benefit of celecoxib compared to nonselective NSAIDs in patients also using low dose aspirin for cardiovascular prophylaxis. Neither the CLASS trial nor the SUCCESS-1 trial demonstrated significant differences for ulcer complications in patients using aspirin. However, in both of these trials the aspirin-user cohorts were not adequately powered to address differences in ulcer complications with celecoxib versus nonselective NSAIDs; therefore definitive conclusions regarding relative gastrointestinal benefits cannot be made. Moreover, in the CLASS trial >20% of patients in both treatment groups were aspirin users, which was higher than the expected background rate; this observation, together with an unexpectedly high rate of withdrawal due to poor gastrointestinal tolerability among diclofenac users, may explain failure to reach statistical significance for the primary endpoint (complicated ulcers).

With respect to the benefit of celecoxib on gastrointestinal safety when coadministered with low dose aspirin, the following clinical trial and epidemiology results are most relevant:

- In the meta-analysis by Moore and coauthors described above, the risk of endoscopic ulcers was significantly reduced with celecoxib 200-400 mg/day relative to combined nonselective NSAIDs in patients taking low dose aspirin (relative risk = 0.47, 95% CI: 0.27 to 0.83 in 5 trials representing 344 patients) and in patients not taking low dose aspirin (relative risk = 0.28, 95% CI: 0.22 to 0.36 in 5 trials representing 3053 patients).[141]

- Among patients using aspirin for cardioprotection in the SUCCESS-1 trial (up to 325 mg/day, comprising 7% of the study population), the overall gastrointestinal event rate was low, and the risk of ulcer complications was numerically lower in the celecoxib treatment group than in the combined nonselective NSAIDs treatment group (odds ratio for nonselective NSAIDs compared to celecoxib = 1.98; 95% CI: 0.12 to 31.72). The rates of upper gastrointestinal events were 10.5 events per 100 patient-years for celecoxib plus aspirin and 18 events per 100 patient-years for nonselective NSAIDs plus aspirin, compared to 4.2 events per 100 patient-years for celecoxib without aspirin and 6 events per 100 patient-years for NSAIDs without aspirin; analogous results were observed for complicated upper gastrointestinal events and for confirmed upper gastrointestinal events. These results suggest that gastrointestinal risk may be reduced with celecoxib relative to nonselective NSAIDs in patients taking aspirin as well as patients not taking aspirin.[144]

- The incidence of upper gastrointestinal symptoms (such as dyspepsia, nausea, and abdominal pain) associated with concurrent use of low-dose aspirin with celecoxib versus nonselective NSAIDs was evaluated in an analysis of pooled data from patients in the SUCCESS-1 trial and the CLASS trial. Among patients taking aspirin, more patients treated with nonselective NSAIDs experienced upper gastrointestinal symptoms compared to celecoxib-treated patients in both studies (17% versus 13%, respectively, in SUCCESS-1; 46% versus 41%, respectively in CLASS).[148]

- In a pooled analysis of relative gastrointestinal tolerability in 2 double blind, randomized, controlled trials representing 1902 elderly, hypertensive OA patients who received celecoxib 200 mg QD or rofecoxib 25 mg QD with or without low-dose aspirin (≤325 mg TDD) for 6 weeks, a significantly greater percentage of patients had moderate to severe abdominal pain than with rofecoxib than with celecoxib in both the all patients cohort (2.2% vs 1.0%, respectively; $p < 0.05$) and particularly among users of low-dose aspirin (4.7% vs 0.7%, respectively; $p < 0.01$). Also among users of low-dose aspirin, treatment with celecoxib was associated with significantly fewer withdrawals due to moderate or severe abdominal pain, dyspepsia, or nausea compared to treatment with rofecoxib (0.4% vs 3.2%, respectively; $p < 0.05$). There were no serious gastrointestinal events such as perforation, obstructions, or bleeding reported in either treatment group.[149]

- In a retrospective cohort study using managed care data obtained from a Quebec government health insurance database to compared rates of hospitalization for gastrointestinal hemorrhage among elderly patients, use of a selective COX-2 inhibitor (celecoxib or rofecoxib) together with aspirin was associated with a significantly lower risk compared to use of a nonselective NSAID together with aspirin (hazard ratio 0.53; 95% CI: 0.34 to 0.83 for celecoxib and rofecoxib together compared to nonselective NSAIDs; data specific to celecoxib were not presented).[150]

5.3. Cardiovascular Safety Signals With Selective COX-2 Inhibitors are Uncertain

The possibility of increased cardiovascular risk with rofecoxib was first evident in clinical trials data with the results of the VIGOR trial, in which 8076 patients with OA or RA were treated for a median duration of 8 months with rofecoxib or naproxen (Section 2.4.2). The recent preliminary observation of increased cardiovascular risk with rofecoxib compared to placebo in the APPROVe trial is consistent with the VIGOR result, and shows increased risk with increasing rofecoxib dose (Section 2.3). In contrast, no increase in cardiovascular safety risk was observed for celecoxib relative to naproxen or diclofenac in the CLASS trial, in which 7968 patients were treated for a median duration of 9 months at a dose that was supratherapeutic relative to approved doses in OA and RA patients (Section 2.2.4). Neither is there any increase in cardiovascular safety risk observed for celecoxib compared to nonselective NSAIDs in the Pfizer meta-analysis presented in Section 2.2, which represents 24,993 patients with chronic conditions treated with celecoxib in 41 clinical studies for durations up to 1 year. Also consistent with these observations are the results of published epidemiology studies in which myocardial infarction has been compared in users of selective COX-2 inhibitors, users of nonselective NSAIDS, and non-users of NSAIDs (Section 2.5.2.1): These studies generally show increased risk of myocardial infarction in rofecoxib users compared to users of nonselective NSAIDs or non-NSAID users, but no increase in risk of myocardial infarction in

users of celecoxib at any dose compared to users of nonselective NSAIDs or to non-NSAID users.

All of the above, which was known prior to the release of preliminary cardiovascular safety results from the APC, PreSAP and ADAPT trials in December 2004, suggests quite strongly that not all selective COX-2 inhibitors are alike with respect to cardiovascular risk. Additional evidence in support of this hypothesis comes from a recently published trial in which 18,325 patients with OA were treated with lumiracoxib, naproxen, or ibuprofen for 18 months, with no increase in cardiovascular risk for patients treated with lumiracoxib compared to patients treated with naproxen or diclofenac (Section 2.4.2).

Preliminary results from the APC, PreSAP, and ADAPT trials, in which patients have been treated with high-dose celecoxib for 33, 32, and 18 months, respectively (Section 2.3), show significantly increased incidence of serious cardiovascular thromboembolic adverse events for celecoxib compared to placebo in one trial (APC) but only numerical increases (not statistically significant) compared to placebo in 2 others (PreSAP and ADAPT). Moreover, a trend toward increased cardiovascular risk was observed with naproxen relative to celecoxib in one of these trials (ADAPT), and a cardiovascular safety signal has been associated with aspirin in a similar colorectal polyp prevention trial (Section 2.4.3), calling into question the suitability of cancer prevention trials like APC for the evaluation of cardiovascular risk.

Given the unclear picture provided by outcome trials to date, as described above, it is impossible to make a definitive statement regarding the cardiovascular safety of selective COX-2 inhibitors as a class. Moreover, clinical studies of effects on blood pressure and endothelial function distinguish between rofecoxib on the one hand and celecoxib, together with nonselective NSAIDs, on the other: Over and above the increased risk of fluid retention, hypertension, and other renal effects common to nonselective NSAIDs and COX-2 inhibitors due to inhibition of prostaglandin-dependent renal compensatory mechanisms (although these effects are usually manageable, they may contribute to the overall risk of cardiovascular events among chronic users of these agents[151]), treatment with rofecoxib has been shown to result in sustained, incremental blood pressure effects that may contribute to an added increase in risk of cardiovascular events. There is recent evidence that structural features of the rofecoxib molecule not shared with other selective COX-2 inhibitors can promote damage to LDL and membrane phospholipids in vitro in a manner that suggests a mechanism for these effects that is unique to rofecoxib.

Although data from the current prospective outcomes trials are too limited to draw any conclusion, epidemiology data suggest that with respect to cardiovascular outcomes, nonselective NSAIDs may represent a spectrum of risk, since relative risks for myocardial infarction range from <1 to 1.7 for various nonselective NSAIDS across several studies. Clinical trial and epidemiology data to date place celecoxib at the mild end of such a spectrum, together with naproxen. Rofecoxib appears to be an outlier at the upper end of such a spectrum, beyond the range defined by NSAIDs in most epidemiology studies. An important caveat, however, is that clinical setting can be an important variable in the evaluation of cardiovascular risk. As demonstrated in Section 2, in the short-term clinical trial setting (up to one year), celecoxib has shown a similar cardiovascular safety profile compared to nonspecific NSAIDs, while rofecoxib in this setting showed increased cardiovascular risk. No trials longer than 1 year have been

performed with arthritis patients, but in the setting of long-term prevention trials the selective COX-2 inhibitors, like the less well-studied nonselective NSAIDs, have shown mixed results. It remains likely that as more definitive long-term studies are performed specifically to evaluate cardiovascular events, an overlap in the collective cardiovascular safety profiles of selective COX-2 inhibitors and nonselective NSAIDs will be observed, with individual drugs in both classes defining a spectrum of effects in this setting as well.

5.4. Benefit/Risk Conclusions

For patients with chronic inflammatory pain, there are few therapeutic alternatives. Opioids are not effective against inflammatory conditions and are addictive, and acetaminophen efficacy is inadequate for many patients. The only remaining options are NSAIDs, whether nonselective or selective COX-2 inhibitors. As a result, patients requiring both anti-inflammatory and analgesic relief who discontinue treatment with selective COX-2 inhibitors will turn to nonselective NSAIDs. This treatment alternative may actually increase overall risk, as the gastrointestinal safety of the nonselective NSAIDs is inferior, and the cardiovascular risk, given the limited data available, appears indistinguishable compared to that of celecoxib.

Weighing the available total evidence, it appears that, as with the nonselective NSAIDs, all selective COX-2 agents are not alike. Furthermore, there is clear evidence that there are some patients who derive significant benefits using selective COX-2 inhibitors. These medications are equally efficacious compared to nonselective NSAIDs in multiple chronic and acute situations. In addition, for certain patients the selective COX-2 inhibitors provide a better gastrointestinal safety profile than nonselective NSAIDs. These patients are typically older and require chronic pain relief, but are at higher baseline risk for gastrointestinal adverse events and associated complications. It is also clear that these patients may have increased baseline risk for cardiovascular thromboembolic events. Only further study will allow an understanding of apparent cardiovascular risks weighed against the known risks for gastrointestinal complications associated with nonselective NSAIDs and selective COX-2 inhibitors, and whether all of the selective COX-2 inhibitors carry the same risk. Given the available data showing comparability of cardiovascular safety for celecoxib versus nonselective NSAIDs, it is highly important to continue to allow access to celecoxib for patients with OA or RA.

6. BENEFIT/RISK ASSESSMENT: FAMILIAL ADENOMATOUS POLYPOSIS

With respect to cancer risk, the general population represents a spectrum ranging from healthy individuals at background risk, to those at intermediate cancer risk because of personal lifestyle choices (eg, diet, tobacco use) or environmental or occupational carcinogen exposure, to individuals at high cancer risk because of specific genetic predisposition, existing pre-cancerous lesions, or prior invasive cancers. Although an ideal cancer prevention treatment would have the potential for benefit across this entire spectrum, the ability to identify intraepithelial lesions, which may proceed to cancer, assists in the identification a target population for preventive interventions that may include alterations in lifestyle and carcinogen exposure, as well as the use of specific agents aimed at regressing or stabilizing such lesions. Given the potential for adverse effects, however, the benefit/risk considerations supporting use of a particular agent in a particular patient with intraepithelial lesions will necessary vary according to the patient's overall cancer risk.

The potential for celecoxib in cancer prevention was first confirmed clinically in patients with familial adenomatous polyposis (FAP). Patients with FAP are at extremely high risk for cancer due to a rare autosomal dominant mutation that results in a high burden of intestinal adenomatous polyps in early adulthood (100-5000 polyps per patient). In untreated FAP patients, the lifetime incidence of colorectal cancer is 100%. Without drugs to stabilize or regress adenomatous polyps, the appropriate treatment is surgical removal; however, polypectomy alone is ineffective in FAP due to the continuous development of new polyps in large numbers throughout the entire gastrointestinal tract. The current standard of care for FAP is colectomy with either ileorectal anastomosis (IRA) or ileal pouch-anal anastomosis (IPAA), a major surgical procedure with 2 to 6% mortality. Patients who have had an IRA will continue to develop rectal polyps, and a majority will eventually require proctectomy with or without IPAA; even in post-IPAA patients there remains a risk of developing polyps in the resulting ileal pouch. Hence, FAP patients have a substantial risk of developing rectal or ileal cancer even after colectomy, despite regular, life-long surveillance;[152] moreover, all have an additional risk of duodenal carcinoma. Patients with advanced FAP also have a considerable risk of postoperative complications, with about 2% mortality following secondary surgical conversion of an IRA to a pouch, and a 30% complication rate and 5% mortality after major surgery for duodenal disease. Stage IV duodenal disease carries a 36% cancer risk at 10 years, while the development of post-IRA lesions with desmoids (rectal removal impossible) carries a 100% colorectal cancer risk.

As demonstrated in a previous application for registration, celecoxib 400 mg BID is effective in reducing the number of intestinal polyps, which invariably lead to the development of colorectal cancer in patients with FAP. Currently, the available evidence indicates that celecoxib best provides this benefit as an adjunct to usual care, both before and after surgical and endoscopic intervention, by reducing the number and size of recurring polyps. It is still true that celecoxib is not intended to alter standard surveillance or to replace usual surgical management of the disease, but celecoxib may be used in FAP patients to potentially delay intestinal carcinoma and/or the need for surgery. Celecoxib remains the only approved pharmacological intervention for FAP in many countries: in patients who are inoperable, patients who refuse surgery, and

patients who must delay surgery for various reasons, there is no therapeutic alternative except celecoxib.

The primary objective of the APC and PreSAP trials described in Section 2.3.1 was to determine whether the benefits of celecoxib in reducing the number and size of recurring polyps in FAP patients extend also to patients with sporadic adenomatous polyposis (SAP), a frequent condition in an older population (30 to 40% at age 60 years; manifestation usually at ages over 50 years) with a much smaller adenoma burden (up to 10 polyps per patient). Without drugs to stabilize or regress adenomatous polyps, the treatment of choice for SAP is polypectomy, and the lifetime risk of colorectal cancer is about 6%; hence, SAP patients constitute a group with only moderately increased cancer risk compared to FAP patients, and appropriate surgical treatment in these SAP patients is more likely to have life-long benefits and less likely to result in complications than in patients with FAP. Nonetheless, the potential for benefit in reducing the number and size of polyps, or in preventing recurrence after polypectomy, made celecoxib an attractive potential treatment in SAP patients, especially since relatively long-term exposure (up to 1 year) at therapeutic doses (up to 400 mg TDD) in patients with OA or RA had resulted in an acceptable safety profile.

To date, the demonstration of a higher incidence of cardiovascular events in the APC trial with celecoxib 400 mg BID compared to placebo (overall event rate 2-3%) remains the only demonstration of a statistically significant increase in cardiovascular risk with celecoxib in a clinical trial; this significant increase in risk became apparent only after 18 months of treatment, a period longer than those for which celecoxib's safety profile was demonstrated in FAP patients and in OA/RA patients. In light of this apparent increased risk with celecoxib, two important benefit/risk questions arise regarding cancer prevention:

- Will the benefit for SAP patients demonstrated with celecoxib in the APC and PreSAP trials be sufficient to offset the apparent increase in cardiovascular risk observed over the long term in these patients? The answer to this question awaits analysis of efficacy results from the APC and PreSAP trials, which are expected to be available late in 2005.

- Is the demonstrated benefit of celecoxib in FAP patients sufficient to offset the potential cardiovascular risk in these patients that can reasonably be extrapolated from the apparent increase in risk observed in the APC trial with SAP patients? The answer to this question must be understood in the context of known differences between the FAP population and the SAP population.

The median age for diagnosis of FAP in patients screened for colorectal polyps is reported to be 22 years (range 3 to 65 years),[153] whereas the frequency of SAP is low in young patients but increases with age (the largest increase in the prevalence of adenomas occurs in a cohort with age ranging from 50 to 59 years).[154] In the general population, there are major differences in coronary heart disease rates comparing subjects the age of typical FAP patients versus subjects the age of typical SAP patients,[155] and incidence rates for cardiovascular disease increase steeply with age in both men and women. Age-specific incidence rates for myocardial infarction in Sweden have been reported to range from 0.1 to 54.4 events per 1000 inhabitants (men and women together) 30 to 34 years of age and from 0.05 to 32.5 events per 1,000 inhabitants ≥85 years of age; however, data from the same National Registry show myocardial infarction

incidence rates of 0.02 events per 1,000 inhabitants for men and 0 events per 1000 inhabitants for women 20 to 24 years of age, and 0.03 events per 1000 inhabitants for men and 0.01 events per 1000 inhabitants for women 25 to 30 years of age.[156] Therefore, the ability to extrapolate the cardiovascular safety results from a single SAP study with a small number of events (the APC trial) to the FAP population (mostly adolescents and young adults), which can be expected to have a much lower baseline cardiovascular risk than does the SAP population (mostly older adults), may be limited.

Moreover, Pfizer believes that the benefit of reducing the number and size of recurring intestinal polyps in otherwise healthy FAP patients outweighs the risk of cardiovascular events with celecoxib, and that patients with FAP should be afforded the option of celecoxib treatment in full awareness of the increased cardiovascular event rates observed for SAP patients in the APC trial. Although continuous extended treatment with a high dose of celecoxib (400 mg BID) is necessary to reduce polyp size and number meaningfully in FAP patients, a relatively small increase in cardiovascular risk (estimated by applying the relative risk of 3.0 observed for celecoxib 400 mg BID versus placebo in the APC trial to 0.02 to 0.03 myocardial infarctions per 1000 subjects aged 20 to 30 years[156] to give an increase in absolute risk from 2 or 3 myocardial infarctions per 10,000 treated patients to 6 to 9 myocardial infarctions per 10,000 treated patients) should be considered acceptable in light of the benefits of delayed or reduced surgery and reduced cancer risk for FAP patients, for whom this disease, left untreated, is uniformly fatal early in life.

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