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Selective Cyclooxygenase-2 (COX-2) Inhibition and Risk of Acute Myocardial Infarction or Stroke in a Population of Rheumatoid Arthritis and Osteoarthritis Patients From an Administrative Medical Claims Dataset

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SELECTIVE CYCLOOXYGENASE-2 (COX-2) INHIBITION AND RISK OF ACUTE MYOCARDIAL INFARCTION OR STROKE IN A POPULATION OF RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS PATIENTS FROM AN ADMINISTRATIVE MEDICAL CLAIMS DATASET

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ABSTRACT

SELECTIVE CYCLOOXYGENASE-2 (COX-2) INHIBITION AND RISK OF ACUTE MYOCARDIAL INFARCTION OR STROKE IN A POPULATION OF RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS PATIENTS FROM AN ADMINISTRATIVE MEDICAL CLAIMS DATASET

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It has been hypothesized that treatment with selective COX-2 inhibitors (coxibs) creates a prothrombotic state by decreasing the synthesis of the prostaglandin prostacyclin, which has vasodilatory and platelet anti-aggregation effects, leading to adverse cardiovascular (CV) events.

This thesis was based on an analysis of a population based, retrospective cohort study of NSAID use in an adult RA or OA population generated from administrative medical and pharmacy claims data from a large private insurer. We compared incidence rates for CV events in subjects treated with coxibs, NSAIDs, combination users (coxibs and NSAIDs), and non-users of NSAIDs utilizing multivariate Cox proportional hazards models.

Relative to non-users of any NSAID, users of coxibs were found to be at greater risk for a CV event than were subjects treated with nonselective NSAIDs, with the effect most pronounced in treated hypertensive subjects (HR=2.30, 95% CI 2.24-2.37 and HR=1.69, 95% CI 1.29-2.20, respectively). Among coxib treated subjects, those treated with rofecoxib were two times more likely to experience a CV event than were celecoxib treated subjects (HR=2.77, 95% CI 1.36-5.60 and HR=1.44, 95% CI 1.09-1.79, respectively).

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used ever since ancient Egyptians learned that salicylate-containing plants were efficacious in the treatment of rheumatism. [1,2] The first commercially synthesized and marketed NSAID, aspirin, was introduced in 1899. Since then, aspirin and other compounds in the NSAID class of products have become one of the most commonly prescribed pharmacological agents worldwide, with more than 100 million prescriptions filled annually in the United States, United Kingdom, and Canada alone. [3] NSAIDs are efficacious in the treatment of inflammation and pain, and are commonly prescribed for treatment of rheumatoid arthritis (RA), and osteoarthritis (OA), chronic inflammatory conditions of the joints.

Although the efficacy of NSAIDs for the treatment of OA and RA is well documented [4-9,44], they can be associated with adverse gastrointestinal (GI) side effects. [10-13] It has been hypothesized that GI related side effects are attributable to the inhibition of the cyclooxygenase (COX) –1 enzyme, the enzyme that catalyzes prostaglandins that protect the gastric mucosa. [14] It is estimated that 10%-20% of NSAID treated patients experience dyspepsia, and that between 50,000 and 100,000 hospitalizations annually are attributable to NSAID induced ulceration of the GI tract. Approximately 16,000 deaths annually can be attributed to NSAID related complications. [14,15]

In addition to its role in the protection of the gastric mucosa, the expression of the COX enzyme plays numerous housekeeping functions responsible for maintenance of physiologic homeostasis in other body systems,

including the kidney where disturbances in renal function can lead to the development or exacerbation of peripheral edema and hypertension. COX expression also plays a role in the physiologic response to tissue injury and inflammation, and is involved in the mediation of the pain signal originating in the nociceptors of damaged tissue. [2,16,17] There are two known isoforms of the COX enzyme. The COX-1 isoform is ubiquitous and constitutively expressed in all normal tissue cells, and is the isoform primarily involved in physiologic homeostasis. The COX-2 isoform is inducible, and its expression is primarily promoted as a result of pathophysiologic processes. When tissue becomes damaged and inflamed, the COX-2 isoform is expressed in response to the release of inflammatory mediators such as cytokines, mitogens and growth factors, and catalyzes the synthesis of prostaglandins that regulate their function. [2,16,17]

The prostaglandins thromboxane-A_2 (TxA2) and prostacyclin (PGI2) are involved in the regulation of platelet-vessel wall interactions. TXA2 elicits platelet activation, vasoconstriction, and smooth muscle proliferation. PGI2 opposes TXA2 and elicits vasodilatory and anti-aggregatory effects [18]. COX-1 and COX-2 are involved in the synthesis of TXA2 and PGI2, respectively. Because of the antagonistic relationship of TXA_2 and PGI_2, it has been theorized that selective inhibition of the COX-2 enzyme might produce a net prothrombotic state by creating an imbalance between TXA2 and PGI2 synthesis [19], resulting in an overall increase in serious thromboembolic cardiovascular events, including

myocardial infarction and stroke. This increased risk may be particularly evident in patients with an already elevated CVD risk.

Recently, several publications have questioned the cardiovascular safety of the COX-2 inhibitor class of NSAIDs. [18-23] The primary focus of these publications has been the cardiovascular safety results of the Vioxx Gastrointestinal Outcomes Research Study (VIGOR), a 52-week randomized control trial (RCT) designed to assess the GI safety of the selective COX-2 inhibitor rofecoxib compared to the non-selective NSAID naproxen in 8 076 patients diagnosed with rheumatoid arthritis (Table 1). The VIGOR trial revealed that patients treated with high-dose rofecoxib experienced a significantly higher incidence rate of serious thrombotic cardiovascular events compared to those treated with naproxen (1.1% vs. 0.5%, respectively). [24] Rofecoxib treated patients also experienced a significantly higher incidence of myocardial infarctions (0.4% vs. 0.1%, respectively), although the mortality rates due to adverse cardiovascular events were identical in both treatment groups (0.2%). [24] During a CV safety review presented to the FDA, the trial's sponsor hypothesized that the NSAID comparator naproxen has cardioprotective properties similar to aspirin, and that the observed differences in serious thrombotic events of the VIGOR trial were due to these aspirin-like cardioprotective properties. [25]

In contrast to the results observed in VIGOR, the Celecoxib Long Term Arthritis Safety Study trial (CLASS) did not demonstrate a similar increase in CV risk. CLASS was a 52-week, randomized, double-blind study of the GI safety of

celecoxib compared to the NSAID comparators ibuprofen and diclofenac in a population of 8 059 patients with a diagnosis of OA or RA. [28] In the CLASS trial, a serious CV event was defined as an event that was considered life-threatening, required hospitalization, or was otherwise medically significant. None of the CV safety comparisons was statistically significant. Fifty-two events (1.3%) were observed in celecoxib treated patients, and 49 events (1.2%) in the combined NSAID arm (RR=1.1, 95% CI 0.7-1.6). Nineteen (0.5%) total AMIs were observed in the celecoxib cohort compared to 13 (0.3%) in the NSAID cohort (RR=1.46, 95% CI 0.72-2.95, p=0.29). Seven (0.2%) of the celecoxib AMIs were fatal compared to 2 (0.05%) AMI deaths in the NSAID arm (RR=3.49, 95% CI 0.73-16.81, p=0.10). NSAID treated patients experienced a statistically significant greater number of cerebrovascular events compared to those treated with celecoxib, with 12 (0.3%) events versus 4 (0.1%) respectively (RR=3.0, 95% CI 0.97-9.31, p=0.045). [26,27]

A meta-analysis (published by Mukherjee et al [19]) reviewed the cardiovascular safety results of 4 randomized clinical trials that included VIGOR, CLASS, and two smaller rofecoxib placebo controlled RCTs (studies 085 and 090). Study 085 was as 6-week randomized, double-blind, placebo-controlled efficacy and safety study of rofecoxib compared to the NSAID nabumetone in 1 042 patients diagnosed with OA of the knee. Study 090 replicated the design of study 085, and enrolled 978 patients. Studies 085 and 090 were not published however, data were made available through the FDA website. In the rofecoxib 085 study, 3 CV events were observed: 1 (0.2%) event in the rofecoxib arm

versus 2 (0.4%) for those treated with nabumetone, and no events observed in the placebo-treated patients. Comparisons between rofecoxib and nabumetone were not statistically significant although the estimate was highly imprecise (RR=0.48, 95% CI 0.04-5.31, p=0.54). In the rofecoxib 090 study, 6 (1.5%) serious CV events were observed among rofecoxib treated patients, 2 (0.5%) among those treated with nabumetone, and 1 (0.5%) in the placebo arm. Comparisons of serious CV incidence rates between rofecoxib and nabumetone were not statistically significant although again the estimate was highly imprecise (RR=3.01, 95% CI 0.61-14.85, p=0.15).

Mukherjee's primary analysis was a comparison of the CV safety results of VIGOR and CLASS relative to the results observed from the combined placebo arms from 4 randomized, long-term (> 4 years) trials that explored the cardioprotective benefit of aspirin (Table 2). From this analysis, Mukherjee reported that the annualized AMI incidence rate of the placebo arms from the combined aspirin trials was lower than that observed in the rofecoxib treated patients in VIGOR (0.52% vs. 0.74%, p=0.04) and celecoxib treated patients in CLASS (0.52% vs. 0.80%, p=0.02). Comparisons of the NSAID treated patients to the placebo group were not reported. From these findings, Mukherjee concluded that long-term exposure to selective COX-2 inhibitors increases risk for a thrombotic cardiovascular event.

Two retrospective cohort studies utilizing administrative medical claims data have been recently published [29,30] that wholly or partially oppose the conclusions of Mukherjee. These studies are important in that their findings

support the CV safety of the COX-2 agents as used in large representative populations.

Ray et al evaluated risk of acute myocardial infarction (AMI) or death from coronary heart disease (CHD) in patients enrolled in the Tennessee Medicare (TennCare) health plan between January 1, 1999 and June 30, 2001. [30] Patients included in the analysis were between the ages of 50 and 84, must have been eligible for TennCare benefits for 365 days continuously, were not in a nursing home, and had no history of non-cardiovascular life-threatening illness. Over 378,000 subjects satisfied the inclusion criteria. Subjects were classified into one of 6 NSAID treatment groups: a) non-user, b) ibuprofen, c) naproxen, d) celecoxib, e) rofecoxib $\leq$ 25 mg, and f) rofecoxib > 25 mg. The mean age of all subjects was 61.5 years, however users of celecoxib and rofecoxib $\leq$ 25 mg tended to be slightly older than the other comparator groups. The population was predominantly female, with users of celecoxib and rofecoxib more likely to be female than non-users. The primary endpoint for the Ray for this analysis was hospital admission for AMI, or CHD related death as coded on death certificates. Ray found no increased risk for AMI or CHD death in users of celecoxib (RR=0.96, 95% CI 0.76-1.21, p=0.19) or low dose rofecoxib (<= 25 mg) (RR=1.03, 95% CI = 0.78-1.35) compared to a non-treated cohort. However, patients exposed to 50 mg doses of rofecoxib experienced a 70% increase in risk. Although these results were not statistically significant, (RR=1.7, 95% CI 0.98-2.95, p=0.056) the point estimate was reasonably precise, and the data

suggests that a threshold effect might exist. A similar analysis of the dose-response for celecoxib was not reported.

Mamdani et al evaluated the CV risk of selective COX-2 inhibitors utilizing administrative health care data from the period of April 1, 1998 through March 31, 2001 for residents of Ontario, Canada. [30] The analysis included only subjects 66 years or older. All elderly residents of Ontario, Canada have universal coverage for prescription drugs, hospital, and primary care, and claims data for more than 1.44 million subjects over the age of 66 was available for analysis. Celecoxib and rofecoxib both became available through the drug benefit program in April, 2000, but were limited to patients that either failed traditional NSAID therapy, had demonstrated an intolerance for NSAIDs, or had a history of upper GI hemorrhage or ulcer. Celecoxib was only approved for use in osteoarthritis and rheumatoid arthritis, and rofecoxib was approved for osteoarthritis only. No similar restrictions were place for NSAIDS. Approximately 167 000 subjects were included in the analysis, of which 100 000 were randomly selected non-users of any NSAID agent. Users of NSAID agents were assigned to one of 4 treatments based on prescription history: a) celecoxib, b) rofecoxib), c) naproxen, and d) non-naproxen nonselective NSAIDs. The mean age of the study population was 75.7 years, and was similar across cohorts. The study population was predominantly female, and users of celecoxib and rofecoxib were more likely to be female than either non-users or users of NSAIDs (70%, 71%, 56%, and 62% respectively). The primary endpoint of the analysis was admission to hospital for AMI. Relative to non-treated controls, Mamdani found no evidence

that users of celecoxib or rofecoxib were at increased risk for an AMI (RR=0.9, 95% CI 0.7-1.2 and RR=1.0, 95% CI 0.8-1.4, respectively). As a secondary analysis, Mamdani also tested the hypothesis that naproxen is cardioprotective. Results of this analysis demonstrated that users of naproxen had a similar incidence rate for AMI as non-treated controls (RR=1.0, 95% CI 0.6-1.7).

Given the variability of findings related to the safety of selective COX-2 inhibitors, no definitive conclusions can be drawn regarding the risk of adverse CV events in users of these agents. However, because of their potential clinical benefit in patients at risk for an upper GI hemorrhage or ulcer, we chose to initiate this study to further add to the evidence regarding exposure to COX-2 inhibitors and CV risk so that the tradeoffs between CV and GI risk can be better understood. This paper reports on the findings of a retrospective cohort analysis exploring the relationship between exposure to selective COX-2 inhibitors and the risk for an acute myocardial infarction or stroke requiring hospitalization in a population of more than 45 000 adult osteoathritis and rheumatoid arthritis patients from a database obtained from a large Northeastern United States insurer. The primary objective of this study was to compare the risk of cardiovascular events between 4 treatment groups: a) user of selective COX-2 inhibitors, b) users of nonselective NSAIDs, c) users of COX-2 inhibitors and nonselective NSAIDs in combination, and d) non-users in a population of arthritis patients. Secondary objectives were to evaluate the cardioprotective properties of naproxen relative to other non-naproxen NSAIDs, and to compare the risk of

adverse cardiovascular events between celecoxib and rofecoxib, the two predominant forms of selective COX-2 inhibitors.

METHODS

Design

This study was designed as a population based retrospective cohort study using data from over 3 million subjects aged 18 years or older from the northeastern United States, who were enrolled in a private medical insurance plan managed by a large regional insurer. The period covered by this analysis was January 1, 1999 through June 30, 2001, and roughly coincides with the product launches of the selective COX-2 agents Celebrex (celecoxib) and Vioxx (rofecoxib), and with the time period in which these products were made available on the formulary of the insurer.

These data are comprised of over 95 million medical and 32 million pharmacy claim records. Medical claims data consisted of both outpatient visits and hospital inpatient stays. Outpatient claims include visits to a primary care physician, urgent care facilities, and hospital emergency department not resulting in an admission. Enrollment, medical and pharmacy claim records were linked using an encrypted patient identifier. Patient identifiers were encrypted by the data vendor to maintain patient confidentiality. Subjects are primarily employed individuals and their dependents. The mean age of all enrolled individuals is 37.5 years, with a median age of approximately 40 years. Fifty-two percent of the enrolled population was female.

Cohort Definition

All patients with a previous diagnosis of rheumatoid arthritis or osteoarthritis that were at least 18 years of age were eligible for inclusion in this study. Arthritis status was determined by review of all available outpatient claims records, and patients with at least one claim with a primary or secondary *International Classification of Diseases, Ninth Revision (* ICD-9-CM) diagnosis code in the range of 714 – 715 were identified as eligible for inclusion. Although nonsteroidal anti-inflammatory drugs are used in other inflammatory conditions, this population was selected because the COX-2 class of drugs is primarily indicated for use in an OA and RA population, and because this population would likely require regular and long term exposure to NSAID treatment for relief of inflammation and pain. [41, 42]

For all subjects, continuous enrollment in a medical insurance plan with drug coverage was required. A break in coverage of less than 45 days was considered as having had continuous coverage. Subjects that were continuously enrolled but discontinued drug coverage were only eligible during the period in which drug coverage was available.

Drug Exposure Definition

For the primary analysis, subjects were assigned to one of 4 treatment cohorts; COX-2 only, NSAID only, Combination of COX-2 and NSAID, and non-users. A non-user was deemed as being untreated if no pharmacy claims were

observed for a COX-2 inhibitor or any non-selective NSAID. The COX-2 cohort consisted of subjects dispensed celecoxib, rofecoxib, or both. The NSAID cohort included subjects dispensed naproxen, ibuprofen, diclofenac, or any combination of those agents. Subjects that filed overlapping claims for both NSAID and COX-2 were assigned to the combination cohort unless one therapy exceeded 90% of the exposure, in which case they were assigned to that exposure cohort. In order to eliminate sporadic users, treated subjects were required to be persistent in their use of therapy. Persistency was defined as having been dispensed at least 2 consecutive prescriptions for the treatment to which the subject was assigned. If a break occurred between the calculated end date of the first prescription and the dispense date of the subsequent prescription, a 30 day grace period was applied. Subjects that changed therapy were assigned to the cohort in which they were last observed if they met the criteria for persistency described above, and the observation period began as of the date of the switch. Subjects that failed to meet the persistency criteria following the switch in therapy were dropped from the analysis. For the treated cohorts, the duration of exposure was defined as the period of time in which subjects were first dispensed a prescription for the study drug to which they were assigned, ending when the last prescription would have been exhausted based on intended duration of therapy. The dispense date of the first prescription was established as the index date of observation. Data on the number of days of supply was used as an indicator of the intended duration of therapy, and was added to the dispense date to derive the expected ending date of each prescription. If the next prescription was dispensed prior to the ending

date of the previous prescription, the excess supply was carried over to the next period and added to that prescription's days supply estimate. Subjects that failed to refill their prescription by the end of the 30-day grace period were deemed to have discontinued therapy, and their observation period ended. For the untreated subjects, the index date was established as the earlier of January 1, 1999, or the date at which drug coverage became available if drug coverage began after January 1, 1999. Observation ended when one of the following events occurred; a) admission to hospital with a CV event, b) discontinued therapy with the study drug to which they were assigned, or reached the end of the observation period of June 30, 2001.

Outcome Definition

Subjects were classified as having a major CV event if they were admitted to the hospital with an acute myocardial infarction or stroke. Events were identified by reviewing medical claims for hospital admission that contained a primary ICD-9-CM code in the range of 410-414 (AMI) or 430-436 (Stroke) during the observation period. Subjects that may have had more than one event during the study period were only included once in the analysis, and the date of the event was based on the first event occurrence. The date of the event was assigned as the date of admission to the hospital.

Confounder Definition

Prior CVD or known CV risk factors were regarded as potential confounder of the primary exposure-outcome relationship. Potential confounders were identified using ICD-9-CM codes listed as primary or secondary diagnoses in any outpatient medical claim occurring prior to the CV event. Diagnosis codes were defined as in Table 3. The classification of previous stroke and previous AMI were treated as exceptions. To avoid misclassifying a current outcome disease process as a previous event, outpatient claims with a diagnosis code for AMI or stroke that were observed within 90 days of an admission for one of these two conditions were identified as being part of the disease process that led to the hospital admission.

Statistical Analysis

Time-to-event analysis methods [31] were used to estimate the hazard ratios for a CV event for the four treatment cohorts. Relative risks were calculated using Cox proportional hazards models, with the untreated controls as the referent group. Since all risk estimates are relative to the untreated controls, linear contrasts were used to make statistical comparisons between each of the active treatment groups. The proportional hazards assumption was assessed for each univariate model, and for the final main effects models by plotting the scaled Schoenfeld residuals for each covariate included in the model.

The relationships between potential confounders and the risk of a CV event were assessed using univariate proportional hazards models. All covariates found to be significant predictors of a CV event at the $p \leq 0.05$ level

were assessed in the multivariate modeling process (Table 3). With the exception of age, which was allowed to remain as a continuous variable, all confounders were coded as dichotomous design variables.

Because of the large number of statistically significant covariates that were identified as potential confounders during the univariate analysis phase, we elected to simplify the model by combining covariates into clinically similar groupings as shown in Table 4. These grouped variables were assessed using univariate analysis, and treated in the same manner as the other covariates.

Creation of design variables for hypertension, hypertension treatment, hyperlipidema, and hyperlipidemia treatment required a 3-level design since inclusion of the treatment variable is dependent upon the recognition of the disease. Hence, the logical relationship between disease and treatment was modeled as no disease, disease with no treatment, and disease with treatment (Table 4.).

Proportional hazards models were fit using backward selection methods. Covariates that were not statistically significant at the $p < 0.05$ level in the model were removed one at a time, and the model refit with the remaining covariates. This process was continued until all remaining variables were statistically significant. Age and gender were allowed to remain in the models regardless of their contribution to the final model. Models were also fit using forward selection methods and compared to the final backward selection models. Forward selection resulted in the same models as backward selection.

Each confounder remaining in the main effects model was assessed for treatment interactions by stratifying the analysis on the confounding variable. If marked changes in the estimate of treatment effects were observed after stratification on the confounder, an interaction term between the confounder and treatment was created and tested in the model. Interaction terms that were significant at the $p \leq 0.05$ level were retained in the final model after testing validity of the proportional hazards assumption. All analyses were performed using SAS for Windows, version 8.2 (SAS Institute Inc., Cary NC) and Stata/SE version 8.0 (Stata Corp, College Station TX).

RESULTS

Of the approximately 3 million adult subjects for which medical and pharmacy data were available for analysis, 40 666 subjects satisfied the study inclusion criteria for continuous enrollment and a diagnosis of OA (88%) or RA (12%). The mean age of the study cohort was 54.25 years, and was 61% female. The most common cardiovascular risk factors were hypertension (40.2%), and hyperlipidemia (34.2%). Seven percent of the cohort were identified as having had a previous AMI, and approximately 2% had a previous stroke. Twenty-five percent of the cohort were treated for hypertension, and 19% treated for hyperlipidemia at some time during the study period.

From these subjects, we identified 32 087 (79%) as being treated with nonsteroidal anti-inflammatory agents, and 8 579 non-treated controls for whom no NSAID pharmacy claims wee observed during the 30-month study period.

Among the treated cohort, we identified 15 950 users of non-selective NSAIDs, 9 608 users of selective COX-2 inhibitors, and 6 529 individuals whose prescription pattern indicated combination therapy (Table 5).

Descriptively, significant differences were observed in baseline characteristics between cohorts. Relative to the total study population, users of selective COX-2 inhibitors were more likely to be older (mean age 57.6 years vs. 54.2 years), and female (67% vs. 61%). Users of selective COX-2 inhibitors only were consistently more likely to have comorbidities at baseline that predispose subjects to risk for CV events, although some observed differences were minor (Table 5). Compared to the study population, the COX-2 only group were more likely to be hypertensive (46.2% vs. 40.2%), and to have been medically treated with anti-hypertensive agents (31.1% vs. 25.2%). Other CV risk factor differences observed were presence of hyperlipidemia (37.7% vs. 28.4%), previous serious thrombotic CV event, including AMI (8.8% vs. 6.9%) and ischemic stroke (1.8% vs. 1.3%). Subjects in the NSAID arm tended to be slightly younger than average (mean age 52.0 years vs. 54.2), and less likely to be female (57.7% vs. 60.7%) relative to the study cohort. In contrast to what was observed in the COX-2 only group, NSAID only treated subjects were consistently less likely to have major CV risk comorbidities at baseline, even though some of the differences were small. Compared to the study cohort, these subjects were less likely to be hypertensive (34.7% vs. 40.2%), medically treated for hypertension (21.7% vs. 25.2%), and had fewer thrombotic CV events, including AMI (4.6% vs. 6.9%) and ischemic stroke (0.8% vs. 1.3%). In direct comparisons between the COX-2 only

group and the NSAID only group, the COX-2 only group was more likely to have other severe coronary heart disease comorbidities, including congestive heart failure (4.1% vs. 1.6%), and cardiomyopathy (1.1% vs. 0.6%). In general, the characteristics of the combination therapy group tended to be similar to those of the COX-2 only group. No differences were observed in the arthritis status between groups. The average length of follow-up was 739 days for the untreated controls, 518 days for combination therapy, 277 days for COX-2 only and 243 days for NSAID only (Table 5).

Primary Analysis

For the entire study cohort, 44 516 person-years of follow-up and 1 111 CV events were observed (Table 6). The COX-2 only cohort had the highest unadjusted crude event rate, with 34.6 events per 1000 person-years, followed by combination therapy (27.2 events/1000 person-years), untreated controls (25.7 events/1000 person-years) and NSAID only (15.1 events/1000 person-years). Relative to untreated controls, subjects treated with selective COX-2 inhibitors, both in the COX-2 only and combination therapy groups, were more likely to have experienced an event after adjusting for age, gender, and presence of CV risk factors (Table 6). The greatest risk was apparent in subjects taking combination therapy, with a 55% increase in the hazard ratio relative to untreated controls, and was statistically significant (HR=1.55, 95% CI=1.31-1.83). The observed risk increase in the COX-2 was similar to that observed in the combination group (HR=1.51, 95% CI 1.28-1.78). The effects of treatment on the

NSAID only group tended to be neutral, with a hazard ratio of approximately 1.0 relative to untreated controls (HR=1.04, 95% CI 0.86-1.26).

All covariates that remained in the main effects model had statistically significant association with the risk of a CV event. The largest effect was observed in subjects that had a coronary artery bypass graft surgery during the study (HR=3.6, 95% CI 1.76-7.29), although this estimate was imprecise. Large and highly precise point estimates were calculated for history of coronary heart disease, including previous AMI (HR=2.59, 95% CI 2.22-3.01), previous stroke (HR=1.77, 95% CI 1.47-2.13), and other miscellaneous heart disease (HR=1.59, 95% CI 1.36-1.84). Treated hypertensive subjects had a 55% increase in CV risk compared to non-hypertensives (HR=1.55, 95% CI 1.34-1.79) however, risk in the non-treated hypertensives was equivalent to that of non-hypertensives (HR=0.98, 95% CI 0.82-1.18).

A statistically significant interaction was identified between treatment group and hypertension status (p=0.01), and the analysis expanded to accommodate exploration of this interaction (Table 7). Inclusion of this term into the model modified the referent group to be non-users of NSAIDS that are also non-hypertensive.

Among non-users of NSAIDs, there was a 36% increase in the risk for a CV event in the treated hypertension group compared to the referent no hypertension group (HR=1.36, 95% CI 1.09-1.70). There was no observed change in risk in non-users of NSAIDs that were hypertensive but not treated (HR=0.97, 95% CI 0.75-1.27) (Table 7). Among users of COX-2 only, a similar

slight increase in risk was observed in both the non-hypertensives (HR=1.33, 95% CI 0.99-1.80, p=0.052) and hypertensive without treatment subgroups (HR=1.27, 95% CI 0.86-1.87, p=0.22) relative to the non-hypertension non-user referent group. Neither estimate was statistically significant although the risk estimate for the COX-2 non-hypertensives was very close to being significant. A greater than two-fold increase in risk was observed among COX-2 only users that were also being treated for hypertension relative to the non-hypertensive non-user referent group, and was highly statistically significant (HR=2.30, 95% CI 2.24-2.37, p<0.0001).

Non-hypertensive users of non-selective NSAIDs had a slightly decreased risk for a CV event compared to the non-hypertensive non-user referent group, and was borderline statistically significant (HR=0.71, 95% CI 0.50-1.00, p=0.052). The risk estimate in the non-treated hypertensives was nearly identical to that observed in the COX-2 only group (HR=1.26, 95% CI 0.86-1.86, p=0.99). There was a statistically significant 69% increase in the risk of a CV event among the NSAID treated subjects that were also being treated for hypertension although the increase in risk was not as pronounced as that observed in the COX-2 only group (HR=1.69, 95% CI 1.29-2.20, p=0.02).

The only statistically significant risk estimate among non-hypertensive subjects occurred in the combination therapy group, where a 67% increase in risk was observed (HR=1.67, 95% CI 1.28-2.19, p=0.0002). Despite the difference observed in the non-hypertension group compared to the other treatments, the combination therapy group tended to be more similar to the other

treatments in the non-treated hypertensives subgroup (HR=1.09, 95% CI 0.72-1.65, p=0.608). Among the treated hypertension subgroup, the risk estimates of the combination therapy group were similar to that observed in the COX-2 only group, and was highly statistically significant (HR=2.23, 95% CI 1.76-2.82, p<0.0001).

Non-selective NSAID Subgroup: Naproxen vs. Non-naproxen vs. Non-treated

Subjects included in this subgroup analysis were selected from the NSAID cohort included in the primary analysis. Subjects were categorized into either a naproxen group that had prescriptions for only naproxen during the observation period, or a non-naproxen group that consisted of subjects dispensed only diclofenac or ibuprofen. The risk of a CV event was then compared to the non-user control population used in the primary analysis.

The average length of follow-up for both the naproxen and non-naproxen treatment groups was 168 days (Table 8). Demographic and medical history characteristics were also similar between treatments (data not reported). Comparisons between treatment groups were made adjusting for age, gender, and pre-existing CV risk factors (previous AMI, previous stroke, diabetes, prior non-CV heart disease, and hypertension status). There were no observed statistically significant differences in CV risk compared to non-users of NSAIDs for either of the naproxen or non-naproxen cohorts (HR=0.92, 95% CI 0.61-1.64 and HR=1.02, 95% CI 0.69-1.50 respectively), nor was there any differences

observed between the two NSAID treatment groups when tested using linear contrasts (p=0.71) (Table 8).

Second-order interactions between the treatments and included covariates were assessed, with a moderately significant interaction detected between treatment and hypertension status ($p<0.05$). Proportional hazards models were fit with the treatment and hypertension status interaction included, and impact on the conclusions above assessed. In all subgroups, no differences were observed between either of the treatment groups and controls, or between the two treatments that would change the conclusions drawn from the data presented above and so, these data were excluded from this analysis.

COX-2 Subgroup: Celecoxib vs. Rofecoxib

Eligible subjects for this subgroup analysis were drawn from the selective COX-2 inhibitor cohort included in the primary analysis, and for which no other NSAID prescriptions were observed. Subjects were categorized into either a celecoxib group or a rofecoxib group. Subjects that switched between celecoxib and rofecoxib therapy were excluded from the analysis.

The average length of follow-up for the celecoxib treated subjects was 245 days compared to an average follow-up of 174 days for subjects treated with rofecoxib, (Table 9) and demographic and medical history characteristics were similar between treatments (data not reported). Hazard ratio estimates were calculated using proportional hazards models with age, gender, previous AMI, previous stroke, diabetes, and previous non-CV heart disease as covariates.

Rofecoxib treated subjects were used as the referent group. In a direct comparison between all celecoxib and rofecoxib treated subjects, a 27% lower risk for a CV event in the celecoxib group was observed (HR=0.73, 95% CI 0.52-1.02), which was borderline significant.

The second-order interaction between treatment and hypertension status was again assessed and found to be statistically significant (p=0.015), and to have clinically meaningful differences. Consequently, this term was included into the final model, and the results presented according to the 3 treatment subgroups; a) non-hypertensives, b) hypertensive but not treated, and c) hypertensive with treatment. The referent group in this analysis was rofecoxib treated subjects that were not hypertensive.

In non-hypertensive subjects, a slightly higher risk for a CV event was observed in celecoxib treated subjects relative to rofecoxib treated subjects, but this finding was not statistically significant (HR=1.44, 95% CI 0.7102.94, p=0.312). Estimates of relative risk were similar for both celecoxib and rofecoxib treated subjects that were hypertensive but not treated medically, and were not statistically significant (HR=1.09, 95% CI 0.78-1.53 and HR=1.01, 95% CI 0.34-2.98, respectively). Among treated hypertensive subjects, a 44% increase in risk for a CV event was observed in the celecoxib treated subjects relative to non-hypertensive rofecoxib treated subjects, and was statistically significant (HR=1.44, 95% CI = 1.12-1.85). Among users of rofecoxib, subjects that were treated hypertensives were 2.77 times more likely to have a CV event than those subjects that were not hypertensive (HR=2.77, 95% CI 1.36-5.6). A direct

comparison of risk between celecoxib and rofecoxib in treated hypertensives revealed a highly statistically significant difference in risk between treatments in this high-risk subgroup (p=0.002).

DISCUSSION

This study had several important findings that could impact how selective COX-2 inhibitors and non-selective NSAIDS are used in clinical practice. First, it appears that patients already at high risk for a CV event are channeled towards treatment with a COX-2 inhibitor, and away from non-selective NSAIDs. Zhao has previously described this channeling effect. [40] This finding is particularly relevant with regards to patients that are hypertensive or have experienced a CV event for which treatment with angiotensin converting enzyme inhibitors (ACEI), Beta-Blockers, or loop diuretics are indicated. The mechanism of action of these antihypertensive agents are dependent upon the production of vascular prostaglandins and therefore, their efficacy may be blunted when used in combination with NSAIDs that inhibit vascular prostaglandin synthesis. [32, 43] Since the disruption of the mechanism of action of these antihypertensive agents by NSAIDs is well known, and since these drug interaction effects had not been previously reported in the COX-2 inhibitors, it is reasonable to assume that physicians treating patients with antihypertensives would have preferentially selected COX-2 inhibitors over traditional NSAIDs when therapy with nonsteroidal anti-inflammatory agents was necessitated, which likely explains the observed differences in CV risk factors at baseline between NSAID treated and

COX-2 treated subjects. Recently however, two randomized double-blind control trials comparing the treatment effects of celecoxib and rofecoxib on systolic and diastolic blood pressure have demonstrated that a potential drug interaction resulting in blood pressure destabilization may occur in some subjects treated with a selective COX-2 inhibitor and anti-hypertensive agents, particularly ACE inhibitors and Beta-blockers, and that the effect was most pronounced in subjects in the rofecoxib arm. [31,32] The most recent package insert (PI) filed with the FDA requires a warning of a potential interaction between rofecoxib and ACEI that is not similarly required in the PI for celecoxib. [41,42]

The main effects model in our analysis revealed a statistically significant 51% increase in risk for a CV event in COX-2 users versus non-treated control subjects, even after adjustment for baseline risk factors. A similar statistically significant increase of 55% was observed in the combination treatment cohort. Conversely, the NSAID only group had a risk ratio that was essential 1.0 versus non-users of NSAIDs. These findings support the hypothesis of increased CV risk associated with use of selective COX-2 inhibitors proposed by Mukherjee. The finding that the combination treated group had a similar risk ratio as the COX-2 only group was particularly interesting. It was expected that the incidence of CV events in this group would fall somewhere in-between that of the NSAID only and COX-2 only groups. That the combination treated group had a similar incidence rate as that observed in the COX-2 only group suggests that any exposure to COX-2 inhibitors elevates risk, even if not used exclusively.

Our analysis based on the interaction model revealed that the association between COX-2 use and CV events is primarily driven by the increase in risk observed in treated hypertensive subjects. Relative to non-treated controls, a 33% and 27% increase in the incidence of CV events in users of COX-2 inhibitors was observed in non-hypertensives and hypertensives not being treated respectively however, these differences were not statistically significant. A similar increase of 26% was observed among the non-treated hypertensives using nonselective NSAIDs. Given these similar findings, it appears that hypertensives users of any NSAID-type agent may have some increased risk of a CV event. Given that a similar increase in risk was not observed in non-users of NSAIDs, it is likely that this effect is real, even though the results were not significant statistically. A greater than 2-fold increase in CV events was observed in the treated hypertensives using any COX-2 inhibitors, and a 69% increase in risk was observed in NSAID users. Using the 36% increase in CV events observed in the non-users as a reference, users of any NSAID appear to be at increased risk for a CV event if they are also being treated for hypertension, although the magnitude of effect appears to be largest in the COX-2 and combo using groups. However, some of the differences observed between the COX-2 group and the NSAID group are likely attributable to the baseline risk differences and so, the differences observed may have been partially confounded, and are likely to be smaller than what was reported here.

To further explore the risk of CV events in users of COX-2 inhibitors, we elected to conduct a subgroup analysis in subjects that were treated exclusively

with either rofecoxib or celecoxib to determine whether this appeared to be a class effect, or whether the observed risk was related to a specific compound. In the subgroup analysis, no statistically significant differences were observed between these two compounds in non-hypertensive and hypertensive patients not on anti-hypertensive treatment, although point estimates of risk tended to favor rofecoxib. In the treated hypertension subgroup however, a nearly 3-fold increase in the incidence of CV events was observed in the rofecoxib group relative to non-hypertensive users of rofecoxib, and was highly statistically significant. A statistically significant 44% increase in CV events was also observed in users of celecoxib however, assuming that as much as 36% of this increase may be attributable to being hypertensive and on treatment, the increased risk associated with celecoxib appears to be marginal. Conversely, the magnitude of effect observed in the rofecoxib users indicates that an interaction between rofecoxib and anti-hypertensive treatment may be occurring that either; a) negates the treatment effects of the anti-hypertensives, or b) interacts in a fashion that promotes a CV event. This finding is consistent with two double-blind randomized control studies by Whelton that demonstrated a destabilization of blood pressure in rofecoxib treated subjects that were also treated with ACEI and β-blockers that was not observed in similarly treated celecoxib treated subjects. [32,33] The results of this study and those of the randomized control trials support the hypothesis that increased risk for CV events among selective COX-2 users in populations already at high-risk are compound related, and are not a class effect.

To assess the claim by Merck and Company that differences observed in AMI incidence in the VIGOR trial was due to the cardioprotective properties of naproxen, we chose to conduct a subgroup analysis comparing CV event rates in naproxen only users, non-naproxen NSAID users, and non-users of any NSAID agent. Since no significant interactions were discovered between treatments and hypertension status, no stratification of the analysis was done by hypertension status, resulting in three relevant comparisons; a) naproxen versus non-users of NSAIDs, b) non-naproxen NSAID users versus non-users, and c) naproxen versus non-naproxen NSAID users.

Using crude rates as measure, there would appear to be some cardioprotective benefit associated with use of naproxen versus controls (25.7/1000 person-years and 13.9/1000 person-years respectively). However, the non-naproxen users had similar results, with a crude rate of 15.9/1000 person-years. These differences did not hold when the model was adjusted for baseline risk factors. After adjusting for age, gender and CV-related comorbidities, the incidence rate observed in both naproxen and non-naproxen NSAID users were comparable to that observed in non-users ($p=0.68$ and $p=0.71$ respectively). Based on these findings, it is not likely that the results observed in the VIGOR trial can be explained by cardioprotective benefit of the naproxen comparator.

The analysis by Mukherjee (JAMA, 2001) linking COX-2 inhibitors to CV thromboembolic risk was the pivotal study that initiated the debate regarding the CV safety of these agents. The primary analysis of the Mukherjee study is a

comparison of myocardial infarction incidence rates for the selective COX-2 treated subjects in VIGOR and CLASS versus the placebo arm of a meta-analysis of aspirin primary prevention trials. In this analysis, Mukherjee reports that the COX-2 agents rofecoxib and celecoxib had annualized incidence rates for myocardial infarction that exceeded the rate for the placebo treated arm in the meta-analysis (0.74% and 0.80% versus 0.52% respectively), and that these results were statistically significant for both comparisons ($p < 0.05$).

Several authors have published critical reviews of the Mukherjee meta-analysis [34-38], and these publications have raised several valid issues pointing to methodological flaws committed by Mukherjee that are primarily the result of invalid assumptions. First, in making comparisons across studies, an assumption is made that the populations studied are homogenous, classification of events are similar, and that methods of outcome ascertainment would reasonably identify the same number of events. These assumptions did not hold in the Mukherjee meta-analysis. The 4 combined aspirin primary prevention randomized control trials (RCT) were heterogeneous with respect to the base populations from which participants were drawn (Table 2). For instance, 3 of the trials enrolled only male subjects while the fourth was 47% female. One trial enrolled exclusively subjects diagnosed with systemic hypertension whereas in the 3 remaining trials, prevalence of hypertension was between 9% and 26%. Similar differences were observed in the prevalence of smokers between the 4 trials. With regards to outcome, Strand identified a 4-fold difference between the lowest and highest observed crude incidence rates for cardiovascular events

within the placebo arms of the 4 trials, and recommended use of a mean MI incidence rate reported per 100 patient-years rather than the weighted mean incidence rate reported by Mukherjee, which would have changed the placebo MI incidence rate estimate from 0.52% to 0.77%, comparable rates to that observed in CLASS and VIGOR. With regards to baseline characteristics for comparisons of the 4 aspirin RCTs to CLASS and VIGOR, the 4 aspirin RCTs were predominantly male compared to a primarily female population in CLASS and VIGOR (31% and 20% respectively), and tended to be younger. Significant variations in CV risk factors were also observed between the 4 aspirin RCTs, CLASS, and VIGOR.

Because of the findings of Mukherjee, Ray and Mamdani explored the CV risk of COX-2 inhibitors as experienced in clinical practice in population based studies. The Mamdani study did not report any evidence to support the Mukherjee hypothesis however, this study included only subjects aged 66 years or older, thus the study population was about 10 years older than the average age of patients likely to begin NSAID therapy, and therefore may not be representative of the typical NSAID using population. Given the older age of the Mamdani population, it is also very likely that a higher incidence of CV events will be observed regardless of treatment status, potentially biasing results towards the null hypothesis of no difference reported by Mamdani. The Ray analysis selected a population that was more generalizable to the typical NSAID using population with regards to age however, allowing subjects who switched therapies to be observed within multiple treatment groups complicated the

analysis. Although switching of therapy is a common phenomenon in retrospective analyses of NSAID usage, and it is appropriate to model therapy switchers, it is unclear from a biological or mechanistic perspective when the risks from the new treatment begin to override the effects associated with the previous treatment. In the Ray design, the lag and induction periods are not well defined, and it appears that exposure risks for each treatment begin and end at the time of the switch, potentially resulting in misattribution of events to treatments, although this risk is likely to be small. The Ray analysis also did not appear to exclude sporadic users of NSAID agents, and these subjects may bias the results toward the null hypothesis of no effect since it is unlikely to observe an event in short-term exposure periods.

This study had several limitations that deserve mention. This study was conducted utilizing administrative data primarily used for reimbursement. Consequently, use of ICD-9-CM coding for the assignment of risk factors and study endpoints may have led to misclassification of some patients. However, it is likely that misclassification is random and similar across cohorts, resulting in any potential bias towards the null hypothesis. These data also do not provide information on other significant potential confounding effects, such as smoking status, use of cardioprotective low-dose aspirin in high-risk subjects, and use of over-the-counter (OTC) NSAID products. The lack of data regarding use of OTC NSAIDs is particularly important as this could have led to a misclassification of exposure, particularly in subjects identified as non-users of NSAIDs, resulting in biased estimates of CV risk in this cohort towards the null hypothesis. Assuming

that need for regular treatment with NSAIDs would have resulted in a prescription, we believe that the potential bias introduced into this analysis is small as OTC NSAID use would likely be sporadic. With regards to exposure, an assumption was made that study drugs were used regularly over time, and not used sporadically, and that all drug was consumed. It is possible, that exposure time for each drug was overestimated. Lastly, although we attempted to control for confounding through the inclusion of CV related covariates, there were substantial differences in characteristics observed between cohorts at baseline that likely resulted from channeling of subjects with CV risk into the COX-2 treatment group. The channeling of at-risk subjects for CV events towards one of the treatment arms leads to confounding by indication, biasing results such that a greater difference in effects may be observed than would otherwise be expected had patients in both treatment arms had a similar risk profile. It is very likely that our final models did not entirely adjust for confounding by indication and that likewise, our risk estimate differences were biased as a result.

In summary, this study addressed some of the weaknesses identified previously in the Ray and Mamdani studies by including all adults in an OA and RA population who were persistent users of NSAID agents, and by including a novel combined treatment group associated with dual use of selective COX-2 inhibitors and non-selective NSAIDS. Our analysis showed that arthritic subjects requiring NSAID therapy that are at high risk for CV events tend to be channeled towards treatment with a selective COX-2 inhibitor and away from non-selective NSAIDs. There is evidence of increased risk for a CV event in users of COX-2

inhibitors relative to non-selective NSAIDs however, the risks appear to be predominantly associated with use of rofecoxib in treated hypertensive subjects, a finding that was consistent with at least one double-blind randomized control trial. Lastly, this study failed to demonstrate that naproxen has any cardioprotective benefits that are similar to those observed with low-dose aspirin, and that the differences in AMI rates observed in the VIGOR trial are related to exposure to high-dose rofecoxib.

Table 1. Description of COX-2 Randomized Control Trials included in Mukherjee Meta-analysis

	VIGOR	CLASS	Study 085	Study 090
N (ITT)	8056	7968	1042	978
COX-2	Rofecoxib	Celecoxib	Rofecoxib	Rofecoxib
NSAID comparator	Naproxen	Ibuprofen Diclofenac	Nabumetone	Nabumetone
Mean duration of follow-up	9 months	9 months	6 weeks	6 weeks
OA/RA %	0/100	72/28	100/0	100/0
Male %	20	31	32	30
Mean Age	58.2	60.1	63.1	62.7
Smoker %	20	16	NR	NR
Hypertension %	29	39	42	41
Diabetes %	8	9	NR	NR
CV aspirin use %	0	22	11.9	12.2

Table 2. Characteristics of aspirin primary prevention trials included in Mukherjee meta-analysis

	US Physician's Health Study	UK Doctor's Study	Thrombosis Prevention Trial	Hypertension Optimal Treatment Trial
N	2,207	5,139	2,540	18,790
Mean duration of follow-up	5.0 years	6.0 years	6.8 years	3.8 years
Male %	100	100	100	53
Mean Age	75	47	NR	NR
Hypertension %	9	10	26	100
Smoker %	11	13	41	16
Diabetes %	2	2	NR	8

NR=Not Reported

Table 3. Covariates assessed in the analysis as potential confounders of the relationship between treatment and cardiovascular events. Univariate Cox models.

Covariate*	Hazard Ratio[1]	95% CI	Coding[2]
Procedures			
Previous CABG	18.56	9.26 – 37.21	33500-33506 33510-33516 33533-33545
Previous PTCA	8.87	3.32 – 23.67	35450-35460
Diagnosis			
Previous cerebrovascular disease	8.12	6.66 – 9.89	436-437
Previous hemorrhagic stroke	6.92	4.01 – 11.96	430-432
Congestive heart failure	6.58	5.66 – 7.65	428
Previous AMI	6.47	5.70 – 7.34	410-414
Atherosclerosis	5.12	4.19 – 6.26	440
Previous Ischemic Stroke	4.71	3.70 – 6.00	433-434
Previous transient ischemic attack	4.56	3.41 – 6.10	435
Ill-defined conditions of the heart	4.28	3.63 – 5.05	429
Pulmonary heart disease	3.95	2.87 – 5.44	415-416
Cardiomyopathy	3.24	2.31 – 4.56	425
Hyperlipidemia	0.80	0.70 – 0.91	272
Obesity	0.71	0.53 – 0.95	278
Diabetes	2.33	2.04 – 2.66	250
Family history of CVD	1.91	1.08 – 3.38	V17
Hypertension	1.84	1.63 – 2.07	401-405
Drug Treatment[3]			
Treatment with antihyperlipidemics	2.80	2.49 – 3.16	
Treatment with calcium channel blockers	2.69	2.26 – 3.20	
Treatment with diuretics	2.66	2.34 – 3.01	
Treatment with ACE II receptor blocker	2.50	2.05 – 3.05	
Treatment with Beta Blockers	2.38	2.06 – 2.74	
Treatment with ACEI	2.26	1.92 – 2.66	
Demographic			
Gender (female as referent)	1.68	1.49 – 1.89	
Age (5 year increments)	1.41	1.38 – 1.44	

[1] Hazard Ratio for CV event given presence of risk factor versus no risk factor
[2] Diagnosis coded using ICD-9-CM, procedures coded using CPT-4
[3] Drugs identified by generic compound and brand
* All covariates were significant at $p<0.05$ level

Table 4. Covariate groupings assessed as potential confounders of the relationship between treatment and cardiovascular events. Univariate Cox models.

Grouped Covariate	Included covariates	Hazard Ratio[1]	95% CI
Hypertension Treatment[2]	ACEI ACE II Receptor Blocker Calcium Channel Blocker Beta Blocker Diuretic	2.15	1.82-2.54
Prior Miscellaneous Coronary Heart Disease	Ill-defined conditions of the heart Congestive heart failure Pulmonary heart disease	5.04	4.42-5.75
Prior Stroke	Prior ischemic stroke Prior hemorrhagic stroke Prior transient ischemic attack Prior cerebrovascular disease	5.75	4.84-6.83
Hypertension Status[3]	No hypertension Hypertension with no treatment Hypertension with treatment	1.0 1.61 3.47	Reference 1.35-1.93 3.03-3.97
Hyperlipidemia Status[4]	No hyperlipidemia Hyperlipidemia without treatment Hyperlipidemia with treatment	1.0 0.45 1.19	Reference 0.37-0.56 1.02-1.38

[1] Hazard Ratio for CV event given presence of risk factor versus no risk factor
[2] Group variable assessed with hypertension included in the model.
[3] The 2 level hypertension treatment and hypertension design variables were combined into a single design variable containing 3 levels: No hypertension, hypertension with no treatment, hypertension with treatment.
[4] The 2 level hyperlipidemia treatment and hyperlipidemia design variables were combined into a single design variable containing 3 levels: No hyperlipidemia, hyperlipidemia but no treatment, hyperlipidemia with treatment.

Table 5. Characteristics of NSAID Treatment Groups

	Study Cohorts				
	Non-users	**COX-2**	**NSAID**	**Combo**	**Totals**
No. of subjects (% Female)	8579	9608	15950	6529	40666
Age					
Median	54	57	52	54	54
Mean	54.5	57.6	52.0	54.5	54.2
SD	14.1	12.3	12.4	11.4	12.8
Range	18–101	18–99	18–103	18–97	18-103
Female %	56.1	66.9	57.7	65.2	60.7
Rheumatoid Arthritis %	11.3	11.5	13.1	12.0	11.9
Osteoarthritis %	88.7	88.5	86.9	88.0	88.1
CV risk factors %					
Diabetes	12.7	14.0	10.3	14.1	12.3
Hypertension	38.6	46.2	34.7	47.1	40.2
Atherosclerosis	2.1	2.2	1.1	1.9	1.7
Pulmonary heart disease	0.9	1.0	0.4	1.0	0.75
Ill-defined conditions of heart	3.5	4.4	2.1	4.2	3.27
Cardiomyopathy	1.0	1.1	0.6	1.0	0.8
Congestive heart failure	3.5	4.1	1.6	3.7	2.9
Obesity	4.1	5.1	4.0	6.3	4.7
Hyperlipidemia	34.6	37.7	29.3	40.4	28.4
Previous AMI	11.1	8.8	4.6	4.2	6.9
Previous hemorrhagic stroke	0.3	0.2	0.1	0.1	0.2
Previous TIA	1.8	1.3	0.4	0.4	0.9
Previous ischemic stroke	2.4	1.8	0.8	0.6	1.3
Previous cerebrovascular disease	2.5	1.7	0.7	0.5	1.3
Previous PTCA	0.03	0.05	0.03	0.03	0.04
Previous CABG	0.07	0.04	0.0	0.05	0.03
Family history of CVD	0.6	0.5	0.7	0.8	0.6
Treatment of CVD %					
Any antihypertensive	21.0	31.1	21.7	30.9	25.2
ACEI	5.9	7.9	5.8	8.2	6.7
ACE II receptor blocker	3.1	5.4	2.9	5.4	3.9
Beta Blockers	9.1	12.0	9.1	11.7	10.2
Calcium Channel Blockers	4.2	7.0	3.7	6.1	5.0
Diuretics	11.6	18.5	11.8	19.1	14.5
Any antihyperlipidemia	16.1	23.0	15.8	23.4	18.8
Grouped Factors					
Prior non-CV CHD	6.7	8.1	3.6	7.3	5.9
Prior Stroke	5.1	3.6	1.5	1.2	2.7
Treated Hypertension	21.0	31.1	21.7	30.9	25.2
Treated Hyperlipidemia	11.5	15.4	10.9	16.9	13.1

Table 6. Primary Analysis: Relationship between NSAID use and CV events using the main effects Cox Proportional Hazards model – Adjusted Hazard Ratios + 95% CI

	Study Cohorts			
	Non-users	**COX-2**	**NSAID**	**Combo**
Number of observed events	446	252	161	252
Days of follow-up, mean ± SD	739 ± 247	277 ± 247	243 ± 272	518 ± 270
Total follow-up, person years	17 353	7 278	10 628	9 257
Crude event rate/1000 person years	25.7	34.6	15.1	27.2
Main Effects Model				
Hazard Ratios (95% CI)*	1.0 (reference)	1.51 (1.28-1.78)	1.04 (0.86-1.26)	1.55 (1.31-1.83)

Model Details

Variable	**Hazard Ratio**	**95% CI**	**p-value**
COX-2 treatment	1.508	1.28-1.78	<.0001
NSAID treatment	1.041	0.86-1.26	0.6846
Combination treatment	1.548	1.31-1.83	<.0001
Age	1.050	1.04-1.06	<.0001
Gender	1.707	1.51-1.93	<.0001
Coronary Artery Bypass Graft	3.581	1.76-7.29	0.0004
Prior AMI	2.585	2.22-3.01	<.0001
Family history of heart disease	2.088	1.18-3.70	0.0115
Atherosclerosis	1.233	1.00-1.53	0.0554
Diabetes	1.321	1.15-1.52	<.0001
Prior coronary heart disease	1.586	1.36-1.84	<.0001
Prior stroke	1.769	1.47-2.13	<.0001
Hypertension treatment no[1]	0.983	0.82-1.18	0.8542
Hypertension treatment yes[1]	1.550	1.34-1.79	<.0001
Hyperlipidemia treatment no[2]	0.512	0.41-0.63	<.0001
Hyperlipidemia treatment yes[2]	0.805	0.69-0.94	0.0061

[1] Referent group is no hypertension
[2] Referent group is no hyperlipidemia
* Adjusted for age, gender, CV risk factors

Table 7. Primary Analysis: Relationship between NSAID use and CV events using the Cox Proportional Hazards interaction model – Adjusted Hazard Ratios + 95% CI

	Study Cohorts			
	Non-users	**COX-2**	**NSAID**	**Combo**
Interaction Model				
Hazard Ratios (95% CI)*				
No Hypertension	1.0 (reference)	1.33 (0.99-1.80)	0.71 (0.50-1.00)	1.67 (1.28-2.19)
Hypertension with no treatment	0.97 (0.75-1.27)	1.27 (0.86-1.87)	1.26 (0.86-1.86)	1.09 (0.72-1.65)
Hypertension with treatment	1.36 (1.09-1.70)	2.30 (2.24-2.37)	1.69 (1.29-2.20)	2.23 (1.76-2.82)
Linear Contrasts*	**COX-2 vs. Control**	**NSAID vs. Control**	**COX-2 vs. NSAID**	**Combo vs. Control**
No Hypertension	0.061	0.052	0.002	0.0002
Hypertension with no treatment	0.212	0.220	0.992	0.608
Hypertension with treatment	<0.0001	0.113	0.02	<0.0001
Model Details				
Variable	**Hazard Ratio**	**95% CI**	**p-value**	
COX-2 treatment	1.333	0.99-1.80	0.0608	
NSAID treatment	0.710	0.50-1.00	0.0519	
Combination treatment	1.674	1.28-2.19	0.0002	
Age	1.050	1.04-1.05	<.0001	
Gender	1.699	1.51-1.92	<.0001	
Coronary artery bypass graft	3.648	1.79-7.43	0.0004	
Prior AMI	2.608	2.24-3.03	<.0001	
Family history of heart disease	2.052	1.16-3.63	0.0137	
Atherosclerosis	1.233	1.00-1.53	0.0556	
Diabetes	1.319	1.15-1.51	<.0001	
Prior coronary heart disease	1.587	1.37-1.84	<.0001	
Prior stroke	1.775	1.47-2.14	<.0001	
Hypertension treatment no[1]	0.973	0.75-1.27	0.0402	
Hypertension treatment yes[1]	1.364	1.09-1.70	7.6468	
Hyperlipidemia treatment no[2]	0.507	0.41-0.63	<.0001	
Hyperlipidemia treatment yes[2]	0.802	0.69-0.94	0.0053	
COX-2*hypertension treatment no[3]	0.976	0.59-1.62	0.9238	
COX-2*hypertension treatment yes[3]	1.266	0.88-1.82	0.2024	
NSAID*hypertension treatment no[3]	1.828	1.07-3.12	0.0266	
NSAID*hypertension treatment yes[3]	1.742	1.14-2.66	0.0104	
Combo*hypertension treatment no[3]	0.670	0.40-1.11	0.1215	
Combo*hypertension treatment yes[3]	0.975	0.69-1.38	0.8848	

[1] Three level design variable combining status of hypertension and treatment for hypertension
[2] Three level design variable combining status of hyperlipidemia and treatment for hyperlipidemia
[3] Interaction term between treatment and hypertension status

Table 8. Secondary Analysis: Relationship between naproxen and non-naproxen NSAID use and CV events relative to non-users using the Cox Proportional Hazards model – Adjusted Hazard Ratios + 95% CI

	Study Cohort		
	Non-users	**Naproxen**	**Non-naproxen NSAID**
Number of observed events	446	26	31
Days of follow-up, mean ± SD	739 ± 247	168 ± 233	168 ± 236
Total follow-up, person years	17 353	1 870	1 954
Crude event rate/1000 person years	25.7	13.9	15.9
Relative Risk Ratios (95% CI)*	1.0 (Reference)	0.92 (0.61-1.64)	1.02 (0.69-1.50)
Linear Contrasts*	**Naproxen vs. Non-users**	**Non-naproxen vs. Non-users**	**Naproxen vs. Non-naproxen**
p-value	0.683	0.937	0.707

* Adjusted for age, gender and prior CV comorbidities

Table 9. Secondary analysis: Relationship between Celecoxib and Rofecoxib and CV Events using the Cox Proportional Hazards Model – Adjusted Hazard Ratios + 95% CI

	Celecoxib	Rofecoxib
Number of observed events	102	57
Days of follow-up, mean ± SD	245 ± 242	174 ± 173
Total follow-up, person years	2896	1378
Crude event rate/1000 person years	35.2	41.4
Main Effects Model[1]		
Hazard Ratios (95% CI)	0.73 (0.52-1.02)	1.0 (reference)
Interactions Model[2]		
No hypertension	1.44 (0.71-2.94)	1.0 (reference)
Hypertension with no treatment	1.09 (0.76-1.49)	1.01 (0.34-2.98)
Hypertension with treatment	1.44 (1.09-1.79)	2.77 (1.36-5.60)
Linear Contrasts*	**p-value**	
No Hypertension	0.312	
Hypertension without treatment	0.899	
Hypertension with treatment	0.002	

[1] Adjusted for age, gender, previous AMI, previous stroke, diabetes, previous non-CV heart disease

[2] Adjusted for age, gender, previous AMI, previous stroke, diabetes, previous non-CV heart disease, hypertension status, treatment*hypertension status

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