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Differences in Safety of Non-Steroidal Anti-Inflammatory Drugs in Patients with Osteoarthritis and Rheumatoid Arthritis: A Randomized Clinical Trial

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ABSTRACT

Objective: To determine relative cardiovascular, gastrointestinal and renal safety of celecoxib, compared with ibuprofen and naproxen during chronic use in patients with osteoarthritis (OA) and rheumatoid arthritis (RA).

Methods: 24,081 patients with OA or RA at moderate or high cardiovascular risk enrolled internationally in a double-blind randomized controlled trial. Interventions included celecoxib 100-200mg bid, ibuprofen 600-800mg tid, or naproxen 375-500mg bid. Main outcomes comprised first occurrence of major adverse cardiovascular events (MACE), gastrointestinal events, renal events, and mortality.

Results: OA subgroup participants had significantly reduced risk of MACE comparing celecoxib to ibuprofen (HR 0.84, 95% CI 0.72 – 0.99), but no significant difference comparing celecoxib to naproxen. In the RA subgroup, comparison of celecoxib vs ibuprofen and celecoxib vs naproxen for MACE events revealed HR of 1.06 (95% CI 0.69 – 1.63) and 1.22 (95% CI 0.78 – 1.92), respectively. The HR for

gastrointestinal events in OA comparing celecoxib with ibuprofen was 0.68 (95% CI 0.51 – 0.91) and with naproxen 0.73 (95% CI 0.55 – 0.98). Duplicate comparisons in RA revealed HRs of 0.48 (95% CI 0.22 – 1.07) and 0.54 (95% CI 0.24 – 1.24), respectively. In OA, comparing celecoxib to ibuprofen for risk of renal events showed an HR of 0.58 (95% CI 0.40-0.82). In RA, celecoxib associated with significantly lower mortality than naproxen (HR 0.47, 95% CI 0.25 – 0.88).
Conclusions: Celecoxib at approved dosages produced similar or lower cardiovascular, gastrointestinal, and renal risk for adverse events compared with ibuprofen and naproxen in OA and RA.

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Prescription of non-steroidal anti-inflammatory drugs (NSAIDs) effectively treats joint pain in patients with osteoarthritis (OA) and rheumatoid arthritis (RA). In the US alone, health care workers write more than 100 million NSAID prescriptions annually;[1] approximately 50% of patients with arthritis require some type of analgesic daily.[2, 3] Many pharmacologic and non-pharmacologic options exist. NSAIDs represent the most widely used medications because of established analgesic benefit, but relative safety across members of this drug class is less certain. Selecting the most appropriate analgesic can challenge treating clinicians because of variable effectiveness and safety of agents.

Previous studies leading to the withdrawal of rofecoxib[4] have underscored the cardiovascular (CV) concerns surrounding selective cyclo-oxygenase-2 (COX-2) inhibitors. However, controversy remained regarding the CV safety of the selective COX-2 inhibitor, celecoxib.[5, 6] In 2005, the FDA strengthened the warning for CV adverse events for all non-aspirin NSAIDs. Subsequent studies have further questioned the safety of non-selective NSAIDs. [7, 8,9] In addition, the relative gastrointestinal and renal safety of different NSAIDs remains poorly defined. These issues are critical in patients with OA and RA, who already have higher CV risk than the general population and often suffer multiple comorbidities.[10, 11]

Based on these concerns, Pfizer initiated a CV safety trial in order to provide new, more definitive and useful information for patients, providers, and regulators about the safety of celecoxib and NSAIDs: the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION). PRECISION, a global safety study among patients with OA or RA, enrolled more than 24,000 patients worldwide.[12] The recently published results demonstrated non-inferiority of moderate dose of celecoxib compared with moderate dose of ibuprofen and naproxen with respect to CV safety based on an intention-to-treat analysis; furthermore, on-treatment analysis including follow-up time while using study drug demonstrated better safety of celecoxib for gastrointestinal endpoints compared

with ibuprofen and naproxen. For renal endpoints, celecoxib exhibited increased safety only when compared to ibuprofen.[13] However, prior literature has not uniformly demonstrated an increased CV risk in RA patients on selective COX-2 inhibitors.[14] We conducted analyses in the pre-specified OA and RA subgroups to define further the relative CV, gastrointestinal and renal safety of celecoxib compared with ibuprofen and naproxen in these common types of arthritis.

METHODS

Study Design and Study Population

In brief, PRECISION was a non-inferiority trial designed to assess the CV effects of celecoxib compared to commonly used NSAIDs, ibuprofen and naproxen. The trial was conducted at 923 centers in the United States, Canada, Australia, Brazil, Colombia, Costa Rica, Mexico, Panama, Peru, Philippines, Taiwan, Hong Kong, and Ukraine from October, 2006 to April, 2016. The Institutional Review Board/Independent Ethics Committee for each study site approved the trial and all patients provided written informed consent before participation. The trial could not be performed in Europe because of restrictions placed on prescribing of coxibs by the European Medicines Agency.

Eligible patients included those at least 18 years of age with a clinical diagnosis of OA or RA for at least 6 months duration[15-17] and who required chronic daily therapy with an NSAID. Participants were required to have established CV disease or CV risk factors. These risk factors included: a known history of major adverse cardiovascular events (MACE); occlusive disease of coronary and non-coronary arteries; a clinical diagnosis of diabetes; or evidence of CV risk based on concomitant risk factors, including age ≥ 65 in women and > 55 in men, hypertension, dyslipidemia, left ventricular hypertrophy, microalbuminuria, urine protein/creatinine ratio >2, ankle-brachial Index <0.9, cigarette smoking, waist-hip ratio ≥ 0.90 and family history of premature cardiovascular disease. Exclusion criteria included: any of the following CV events within 3 months -- MACE, unstable angina, evidence of cardiac electrophysiologic unstable rhythm, or any major surgery; a planned coronary, cerebrovascular or peripheral revascularization; NYHA Class III or IV heart failure or known left ventricular dysfunction with ejection fraction ≤35%; active, significant gastrointestinal, hepatic, renovascular or coagulation disorders; history of acute joint trauma; allergy or hypersensitivity to celecoxib, ibuprofen, naproxen or aspirin; poor responders to disease modifying anti-rheumatic drugs or oral corticosteroid treatments; and required treatment with medications excluded during the course of the study. Women were excluded if they were pregnant, might have become pregnant, or were lactating. **Appendix Table 1** shows additional selection criteria. **Appendix Tables 4 and 5** detail the RA patient cohort.

Study Protocol

Patients meeting entry criteria and willing to sign informed consent were randomized in a double-blind fashion to celecoxib 100-mg bid for OA and up to 200mg bid for RA, ibuprofen 600-800mg tid, or naproxen 375-500mg bid with matching placebos in a 1:1:1 allocation. Dose escalation was allowed at the discretion of the patient and investigator if symptom relief was not adequate. Allocation of patients is illustrated in a CONSORT diagram (see **Appendix Figure 1**). Randomization was stratified by geographic region, low-dose aspirin use (yes or no), and arthritis type (OA or RA) and implemented using an Interactive Voice Response System (IVRS). All patients were provided open-label esomeprazole at 20-40mg per day, and allowed aspirin (≤325 mg per day, with 75-100mg considered optimal for CV protection and recommended) for CV prevention. (see **Appendix Table 6**) After randomization and baseline visit, patients had visits at months 1, 2, 4, 8 and 12 and every 6 months thereafter until month 42. Study patients were required to complete at least 18 months of follow up visits. Follow up visits included clinical assessments and laboratory testing as well as identification of new adverse events or changes in CV, renal and gastrointestinal status, and arthritis outcomes.

The primary endpoint of the parent study was the first occurrence of a composite endpoint consisting of CV death, non-fatal myocardial infarction, or non-fatal stroke, identical with the primary composite endpoint of the Antiplatelet Trialists Collaboration. Trial completion required collection of a specific number of primary endpoints: 580 primary endpoints for the intent to treat (ITT) analysis and 420 for an analysis of patients while taking assigned treatments, the on-treatment analysis. Sample size calculations estimated that over 20,000 patients would be required to meet these goals. To reach the requisite number of endpoints, ultimately more than 24,000 participants were enrolled.

The current analyses report findings for patients with OA and RA separately. The primary outcomes for these two subgroups were based on an ITT analysis, with the on-treatment analysis used as a sensitivity analysis. Analyzed outcomes included major adverse CV events (MACE, which include APTC events plus revascularization or hospitalization for transient ischemic attack or unstable angina) plus clinically significant gastrointestinal, renal, and all-cause mortality events. Clinically significant gastrointestinal events were defined as gastroduodenal hemorrhage; gastric outlet obstruction; perforation of the gastroduodenum, small bowel or large bowel; hemorrhage of the large bowel, small bowel, or acute gastrointestinal hemorrhage of unknown origin; new-onset iron deficiency anemia; or symptomatic gastric or duodenal ulcer. Clinically significant renal events included development of renal insufficiency or renal failure, defined based on development of any of the following: serum creatinine ≥ 2.0mg/dl and increase of ≥ 0.7mg/dl from baseline; hospitalization for acute renal failure with a doubling of the baseline serum creatinine or hyperkalemia with ≥ 50% elevation in serum creatinine; or initiation of

dialysis. A Clinical Events Committee blindly adjudicated all of the above endpoints utilizing pre-specified definitions.

The analgesic efficacy of the treatments was evaluated at baseline and follow-up using a pain visual analog scale (VAS). To assess function, patients completed the Health Assessment Questionnaire Disability Index (HAQ-DI)[18] at baseline, at months 1, 12, 24, 36 and 42, and at premature study drug discontinuation if applicable. All patients who discontinued study drug treatment were followed per protocol through month 42 or to study completion, whichever occurred first.

Statistical Analysis

The primary analyses of PRECISION assessed non-inferiority for CV event frequency on celecoxib versus naproxen and ibuprofen. The current analyses focus on the OA and RA subgroups. Non-inferiority hypotheses were not tested, and no adjustments were made for multiple comparisons. Since each comparison is assumed to be independent, no adjustment to alpha will be made to adjust for the multiple comparisons. Statistical significance, $p<0.05$ for comparisons between treatment groups, or $p<0.10$ for treatment group by OA/RA interaction was based on nominal p-values. Cumulative event curves were constructed for each of the three treatment arms for the OA and RA subgroups separately. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) comparing treatment groups for the four safety outcomes of interest were calculated using Cox proportional hazards regression models, adjusting for stratification factors (geographic region and low-dose aspirin use). An interaction between treatment group and arthritis type was tested in the Cox regression models for each drug to drug comparison by adding the interaction term to the model. Analyses were censored after 30 months for the intention-to-treat population and after 43 months for the on-treatment population. All analyses were performed using the SAS system (version 9.4, Cary, NC).

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RESULTS

Among the 24,081 patients enrolled in the PRECISION Trial, 89.9% (n = 21,645) had OA and 10.1% (n = 2,436) RA. Patients with OA were on average 64 years of age and 63% were female (see **Table 1**). Twenty-three percent of those with OA had a previous CV event; 47% used daily aspirin, and 18% smoked cigarettes. The three treatment arms were well balanced among patients with OA. In contrast, patients with RA were slightly younger than those with OA with a mean age of 61 years, and

73% were female (see **Table 1**). Similar to OA, 24% of those with RA had a previous CV event, but fewer used daily aspirin (37%), and slightly more smoked cigarettes (21%). Participants with RA had well balanced allocation to the three treatment arms. Use of increased dosage was similar in the RA subgroup, but the protocol did not permit celecoxib up-titration in the OA subgroup for regulatory reasons, resulting in different proportions of patients using the maximum allowable dosages (see **Appendix Table 2**). The mean dosages and standard deviations for the OA group were: celecoxib 100± 3 mg, naproxen 426± 52 mg, and ibuprofen 681± 82 mg; and for RA: celecoxib 141± 42 mg, naproxen 425 ±± 52 mg, and ibuprofen 681± 82 mg. The percentages with up-titration by NSAID for OA were celecoxib 0.3%, naproxen 55.3%, and ibuprofen 55.3%. The percentages with up-titration by NSAID for RA were celecoxib 56%, naproxen 54.9%, and ibuprofen 56.5%.

The frequency of adjudicated clinical endpoints is shown in **Table 2**. Among patients with OA, 4.4% experienced MACE compared with 4.8% of those with RA (p = 0.30). The cumulative event curves for the three treatment arms among patients are shown in **Figures 1a and 1b**, OA and RA, respectively. There were significantly fewer MACE among the OA subgroup when comparing celecoxib to ibuprofen (HR 0.84, 95% CI 0.72 – 0.99), but not among the RA group (HR 1.06, 95% CI 0.69-1.63). The treatment by arthritis type (OA vs RA) interaction was not significant (p=0.29). The celecoxib and naproxen groups did not differ significantly in the risk of MACE in either OA or RA.

Patients with OA or RA had similar frequency of gastrointestinal events (1.35% vs 1.77%, p=0.096) (see **Table 2**). The frequency of gastrointestinal events for patients with OA randomized to celecoxib was 1.06%, 1.54% for ibuprofen, and 1.45% for naproxen. Patients with RA had a similar pattern: celecoxib (1.11%), ibuprofen (2.28%) and naproxen (1.90%). The cumulative event curves for gastrointestinal events are provided in **Figures 1c and 1d**. The hazard ratios comparing celecoxib to ibuprofen (HR 0.68, 95% CI 0.51 – 0.91) and celecoxib to naproxen (HR 0.73, 95% CI 0.55 – 0.98) demonstrate significantly reduced GI event risk for patients with OA randomized to celecoxib. Patients with RA showed a similar pattern of gastrointestinal risk, with reduced risk comparing celecoxib to ibuprofen (HR 0.48, 95% CI 0.22 – 1.07) and celecoxib to naproxen (HR 0.54, 95% CI 0.24 – 1.24), but neither comparison excluded null. The treatment by arthritis type interactions did not differ significantly (p>0.10 for both).

The frequency of renal events was 0.89% in OA and 1.15% in RA (p=0.20) (see **Table 2**). The cumulative event curve for OA showed fewer renal events in patients using celecoxib (see **Figure 1e**). The risk of renal events among patients with OA was lower for those randomized to celecoxib than ibuprofen (HR 0.58, 95% CI 0.40-0.82) and numerically lower but not statistically different between celecoxib and naproxen (HR 0.77, 95% CI 0.53 – 1.12). The cumulative event curve for RA showed no differences across treatment arms (see **Figures 1f**) and the hazard ratios demonstrated no differences in

risk across agents. The treatment by arthritis type interaction did not reach statistical significance (p>0.10 for both).

The frequency of all-cause mortality was higher in the RA group (2.59%) compared to OA (1.73%, p = 0.003) (see **Table 2**). The risk of all-cause mortality across the three treatment groups in patients with OA was similar (see **Figure 1g**). In patients with RA, however, celecoxib associated with lower mortality compared with naproxen (HR 0.47, 95% CI 0.25 – 0.88) (see **Figure 1h**). The interaction between celecoxib vs naproxen and arthritis type met criteria for statistical significance (interaction p=0.07).

The primary analysis was ITT, but we also performed on-treatment analyses (see **Figure 2**). The on-treatment results qualitatively resembled the ITT analyses, with most estimates showing somewhat larger differences. An exploratory analysis also assessed a composite endpoint of all major safety events that included MACE, serious GI, renal events, and all-cause mortality. The frequency of this endpoint was more common in RA (8.37%) versus OA (6.96%) (p = 0.01) (see **Table 2**). In the OA subgroup, the hazard ratios comparing celecoxib with ibuprofen (HR 0.80, 95% CI 0.70 – 0.90) and celecoxib with naproxen (HR 0.90, 95% CI 0.80 – 1.03) show fewer major safety events with celecoxib. The hazard ratios for the RA subgroup did not demonstrate any difference between treatment arms. The interactions between treatment group and arthritis type were not statistically significant (p>0.10 for both).

Finally, we examined the functional status as measured by the health assessment questionnaire (HAQ) and pain VAS (see Appendix **Figure 3**). At baseline, patients with OA had higher mean pain VAS scores of 54.3mm ± 23.6 compared with RA in whom it averaged 51.9mm ± 24.9 (p<0.001). The improvements in the pain VAS for patients with OA were similar across treatment arms. Patients with RA had statistically significantly greater improvement in pain with ibuprofen compared with celecoxib (p = 0.02), but the modest difference has unclear clinical significance. As with pain VAS, patients with OA had similar changes in HAQ-DI scores across treatment arms, but among patients with RA, it was slightly better for ibuprofen users compared with celecoxib (p = 0.02).

DISCUSSION

Arthritis is the most common cause of disability in the US. Approximately 15 million arthritis patients who may require analgesics reported severe joint pain in 2014.[19] In 2000, more than 100 million NSAID prescriptions were written in the US.[20] NSAIDs differentially affect COX isoforms potentially accounting for their benefits and varying toxicities across agents. The PRECISION trial found similar CV safety for moderate dose of the selective COX-2 inhibitor, celecoxib, and the non-selective NSAIDs, ibuprofen and naproxen.[13] In a set of analyses on pre-specified subgroups by type of arthritis, OA and RA, we found fewer MACE with celecoxib compared with ibuprofen among OA patients. Celecoxib

users in the OA subgroup also experienced less gastrointestinal toxicity than ibuprofen or naproxen users; this was not observed in RA, but the statistical power in this sub-group was limited. Adjudicated renal adverse effects were less common in celecoxib versus ibuprofen users with OA, but not in those with RA.

These subgroup analyses add important and clinically relevant information to our understanding of the safety across selective and non-selective NSAIDs within OA and RA patients. The CV safety findings across both OA and RA lend reassurance to those using or considering celecoxib. Since RA associates with a 1.5 to 2.0-times greater risk of CV events presumed in part to the chronic systemic inflammatory nature of RA (which may promote plaque instability and MACE), the safety of different NSAIDs in RA patients might differ in OA patients.[21] The results presented here suggest slightly lower risk for celecoxib than ibuprofen users with OA, but similar CV risk by NSAID for RA. As expected, the patients with RA had higher frequency of adverse events than those with OA. These findings support the efforts underway to refine risk stratification and CV management strategies in RA.

Celecoxib users also had reduced risk for other endpoints. OA patients using celecoxib had significantly lower gastrointestinal risk than those taking either ibuprofen or naproxen. This finding is not surprising based on prior meta-analyses,[22] but most individual studies have not clearly demonstrated the improved GI safety of celecoxib..[23] Similar to CV risk, RA patients in the current study experienced a higher frequency of gastrointestinal events compared with OA.

The reduced all-cause mortality found among the RA patients using celecoxib compared with naproxen was not anticipated. The number of deaths was relatively small in each group: 15 among celecoxib users (1.85%) and 30 among naproxen (3.79%), precluding strong conclusions. This reduction resulted from a combination of reduced mortality across various causes (i.e., infection, cancer, respiratory) (see **Appendix Table 3**). Further examination of the deaths is underway, but this finding may have resulted from chance. Future studies of cause-specific mortality with more events will be helpful; such studies will likely require the use of observational datasets.

PRECISION was conducted as a randomized double blind active drug controlled trial. Randomization was stratified based on underlying arthritis diagnosis (OA or RA) and whether patients were taking aspirin for CV prophylaxis. The trial was powered based on the total number of events across all patients and not on the size of each subgroup, so the statistical power for some subgroup analyses does not permit drawing firm conclusions. The ITT population was chosen for the primary analysis, but the on-treatment population gave directionally similar results (see **Figure 2**), some statistically significant but others not. The drop-out rate during PRECISION was higher than expected but was similar across treatment arms among all participants and also in the OA and RA subgroups (see **Appendix Figure 2**). The dosing of the three treatments was slightly different in the OA and RA subgroups based on limitations imposed by drug regulators on using celecoxib 100mg bid in the OA subgroup; this issue may

have influenced results. Prior studies have demonstrated an increased risk of adverse effects with celecoxib as well as non-selective NSAIDs at higher dosages.[9, 25, 26]

In conclusion, these sub-group analyses of the PRECISION trial, based on underlying arthritis diagnosis, yield similar but not identical results as the overall trial. The OA subgroup randomized to celecoxib experienced fewer CV events compared with ibuprofen, but not naproxen. The OA subgroup using celecoxib experienced fewer clinically significant gastrointestinal adverse events than ibuprofen or naproxen, with similar trends in RA. Renal events were less common in the OA subgroup using celecoxib than ibuprofen but not naproxen, and the RA subgroup showed no differences. These findings give providers, patients and regulators a greater understanding of the relative safety of different NSAIDs, COX2-selective and non-selective. Current safety information from the FDA on NSAIDs focuses on CV risk and does not differentiate between agents. The results of the PRECISION trial and these subgroup analyses confirm no increased CV risk for celecoxib. However, celecoxib conferred slight reductions in risk for several outcomes compared with other commonly used NSAIDs. Regulators and professional organizations might consider whether these data regarding differential safety across NSAIDs warrant new recommendations for the optimal use of the agents studied in PRECISION.

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Table 1. Baseline Characteristics of Randomized Patients

Characteristic	Osteoarthritis				Rheumatoid arthritis			
	Total (n =21645)	Celecoxib (n = 7259)	Ibuprofen (n = 7208)	Naproxen (n =7178)	Total (n =2436)	Celecoxib (n = 813)	Ibuprofen (n = 832)	Naproxen (n = 791)
Age, mean	64±9.3	63±9.4	64±9.3	64±9.3	61 ± 9.9	59 ± 9.5	61 ± 9.9	61 ± 10.2
Female gender	13,661 (63.1)	4566 (62.9)	4,574 (63.5)	4,521 (63.0)	1,784 (73.2)	609 (74.9)	600 (72.1)	575 (72.7)
BMI, kg/m2, mean	32.8±7.3	32.8±7.3	32.8±7.4	32.7±7.3	30.9±7.1	31.0±7.4	30.6±6.8	31.0±7.1
Aspirin use	10,161 (46.9)	3,403 (46.9)	3,390 (47.0)	3,368 (46.9)	904 (37.1)	298 (36.7)	322 (38.7)	284 (35.9)
Cardiovascular risk category								
Primary prevention[+]	16,748 (77.4)	5600 (77.1)	5569 (77.3)	5579 (77.7)	1852 (76.0)	609 (74.9)	636 (76.4)	607 (76.7)
Secondary prevention[+]	4897 (22.6)	1659 (22.9)	1639 (22.7)	1599 (22.3)	584 (24.0)	204 (25.1)	196 (23.6)	184 (23.3)
History of diabetes	7,717 (36.0)	2581 (36.0)	2629 (36.8)	2507 (35.3)	779 (32.4)	262 (32.5)	256 (31.2)	261 (33.4)
History of hypertension	16,927 (79.0)	5699 (79.4)	5665 (79.3)	5563 (78.3)	1817 (75.5)	597 (74.1)	638 (77.9)	582 (74.4)
History of dyslipidemia	13,670 (63.8)	4617 (64.3)	4526 (63.4)	4527 (63.7)	1378 (57.3)	463 (57.4)	476 (58.1)	439 (56.2)
Current smoker	3,917 (18.3)	1353 (18.9)	1293 (18.1)	1271 (17.9)	500 (20.8)	175 (21.7)	167 (20.4)	158 (20.2)
Prior statin use	11,913 (55.0)	4023 (55.4)	3939 (54.6)	3951 (55.0)	1065 (43.7)	344 (42.3)	368 (44.2)	353 (44.6)
Prior DMARD* use	383 (1.8)	113 (1.6)	124 (1.7)	146 (2.0)	1375 (56.4)	459 (56.5)	460 (55.3)	456 (57.6)
Mean systolic BP, mmHg	125±10.5	125±10.4	125±10.4	125±10.6	125± 11.0	124±11.2	126±10.7	124±11.2
Mean diastolic BP, mmHg	75±8.0	75±8.0	76±8.0	75±8.0	76±7.9	76±8.1	76±7.7	76±7.9
HAQ[†] Disability Index, mean	1.09±0.6	1.10±0.6	1.09±0.6	1.08±0.6	1.27 ± 0.7	1.27 ± 0.7	1.27 ± 0.7	1.27 ± 0.7
Pain Visual Analog Scale, mean	54.31 ± 23.6	54.18 ± 23.4	54.40 ± 23.4	54.37 ± 23.9	51.93 ± 24.9	52.36 ± 24.9	51.75 ± 24.8	51.68 ± 25.2
Laboratory Values								
Mean Total-cholesterol, mg/dL	188.5 ± 43.1	188.6 ± 43.2	188.4 ± 43.5	188.6 ± 42.6	192.3 ± 42.8	193.6 ± 42.2	191.5 ± 42.9	191.8 ± 43.5
Mean LDL-cholesterol, mg/dL	106.4 ± 36.9	106.4 ± 36.9	106.3 ± 37.2	106.4 ± 36.7	108.9 ± 36.0	109.9 ± 35.5	108.5 ± 35.8	108.2 ± 36.9
Mean HDL-cholesterol, mg/dL	51.2 ± 14.8	51.2 ± 14.8	51.0 ± 14.7	51.4 ± 14.9	53.2 ± 15.9	53.0 ± 15.7	53.1 ± 16.5	53.4 ± 15.4
Median triglycerides, mg/dL	134 (97, 188)	133 (97, 189)	135 (97, 189)	134 (97, 186)	128 (94, 185)	131 (96, 190)	125 (92, 183)	128 (95, 182)
Median glycated hemoglobin, %	6.8 (6.2, 8.0)	6.9 (6.2, 8.0)	6.8 (6.1, 8.0)	6.8 (6.1, 7.9)	7.0 (6.1, 8.3)	7.0 (6.1, 8.4)	6.9 (6.0, 8.3)	6.9 (6.1, 8.1)
Mean creatinine, mg/dL	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2

N (%) unless otherwise noted. *DMARD=Disease Modifying Anti-Rheumatic Drug. [†]Health Assessment Questionnaire. [+]Primary intervention=subjects at high risk for CVD. Secondary intervention=subjects with previously diagnosed CVD at the time of study enrollment.

Table 2. Outcome Frequency in Intention-to-Treat Population

	Osteoarthritis				Rheumatoid Arthritis			
	Total N = 21645	Celecoxib N = 7,259	Ibuprofen N= 7,208	Naproxen n = 7,178	Total N = 2,436	Celecoxib N= 813	Ibuprofen N= 832	Naproxen n = 791
MACE endpoint	949 (4.38)	294 (4.05)	343 (4.76)	312 (4.35)	118 (4.84)	43 (5.29)	41 (4.93)	34 (4.30)
APTC endpoint	525 (2.43)	162 (2.23)	190 (2.64)	173 (2.41)	82 (3.37)	26 (3.20)	28 (3.37)	28 (3.54)
Composite serious GI events	292 (1.35)	77 (1.06)	111 (1.54)	104 (1.45)	43 (1.77)	9 (1.11)	19 (2.28)	15 (1.90)
Major clinical GI events	160 (0.74)	50 (0.69)	63 (0.87)	47 (0.65)	23 (0.94)	5 (0.62)	9 (1.08)	9 (1.14)
Anemia of GI origin	143 (0.66)	29 (0.40)	52 (0.72)	62 (0.86)	23 (0.94)	4 (0.49)	12 (1.44)	7 (0.88)

Renal events	192 (0.89)	48 (0.66)	82 (1.14)	62 (0.86)	28 (1.15)	9 (1.11)	10 (1.20)	9 (1.14)
All major safety events	1507(6.96)	449 (6.19)	558 (7.74)	500 (6.97)	204 (8.37)	62 (7.63)	71 (8.53)	71 (8.98)
All cause mortality	374 (1.73)	117 (1.61)	124 (1.72)	133 (1.85)	63 (2.59)	15 (1.85)	18 (2.16)	30 (3.79)

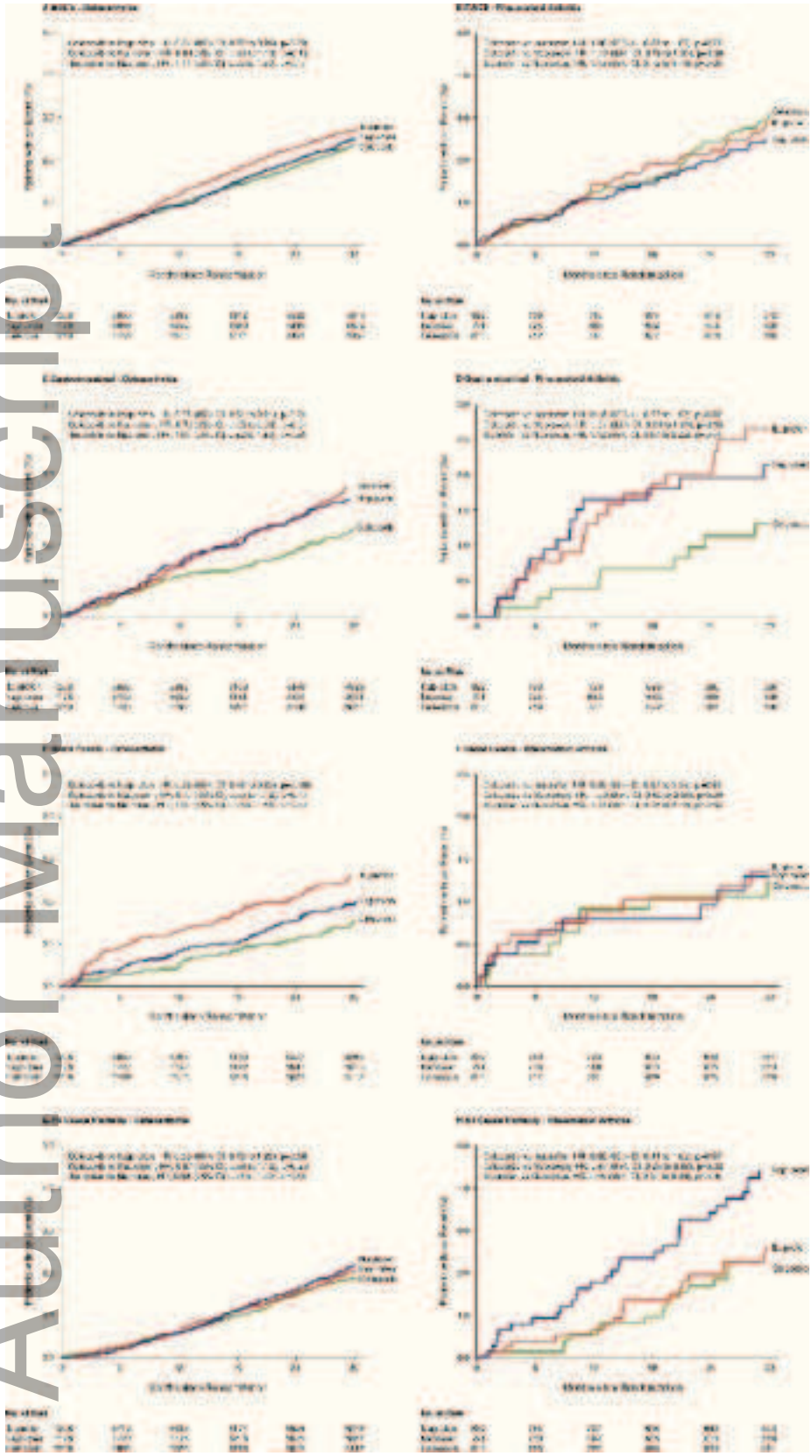
MACE=Major Adverse Cardiovascular Event. The MACE endpoint is defined as the first occurrence of cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, revascularization, or hospital for transient ischemic attack. APTC=Antiplatelet Trialists Collaboration. The APTC endpoint is defined as the first occurrence of cardiovascular death, non-fatal MI, or non-fatal stroke. All major safety events includes MACE, composite serious GI and renal events, and all cause mortality. GI=Gastrointestinal. Composite serious GI events include gastroduodenal hemorrhage, gastric outlet obstruction, gastroduodenal small or large bowel perforation, large or small bowel hemorrhage, acute GI hemorrhage, symptomatic gastric or duodenal ulcer or anemia defined as a decrease in hemoglobin ≥2 g/dl or hematocrit ≥10% with no clinical evidence of acute GI bleed and biochemical evidence of iron-deficiency. All major safety events = MACE, composite serious GI events, renal events, and all-cause mortality.

Figure Legends:

Figure 1: Time-to-Event Analysis for Primary and Secondary Outcomes in OA vs RA shows the cumulative event rates across the three treatment arms for patients with osteoarthritis or rheumatoid arthritis. Panels A and B are for MACE, panels C and D are for GI events, panels E and F are for renal

events, and panels G and H are for all-cause mortality. The hazard ratios and p-values were calculated in Cox proportional hazard regression models that adjusted for stratification factors.

Figure 2: Adjudicated Outcomes in the On-Treatment OA and RA Populations – A Sensitivity Analysis shows the hazard ratios with 95% confidence intervals for the on-treatment population for the four outcomes across the two subgroups.



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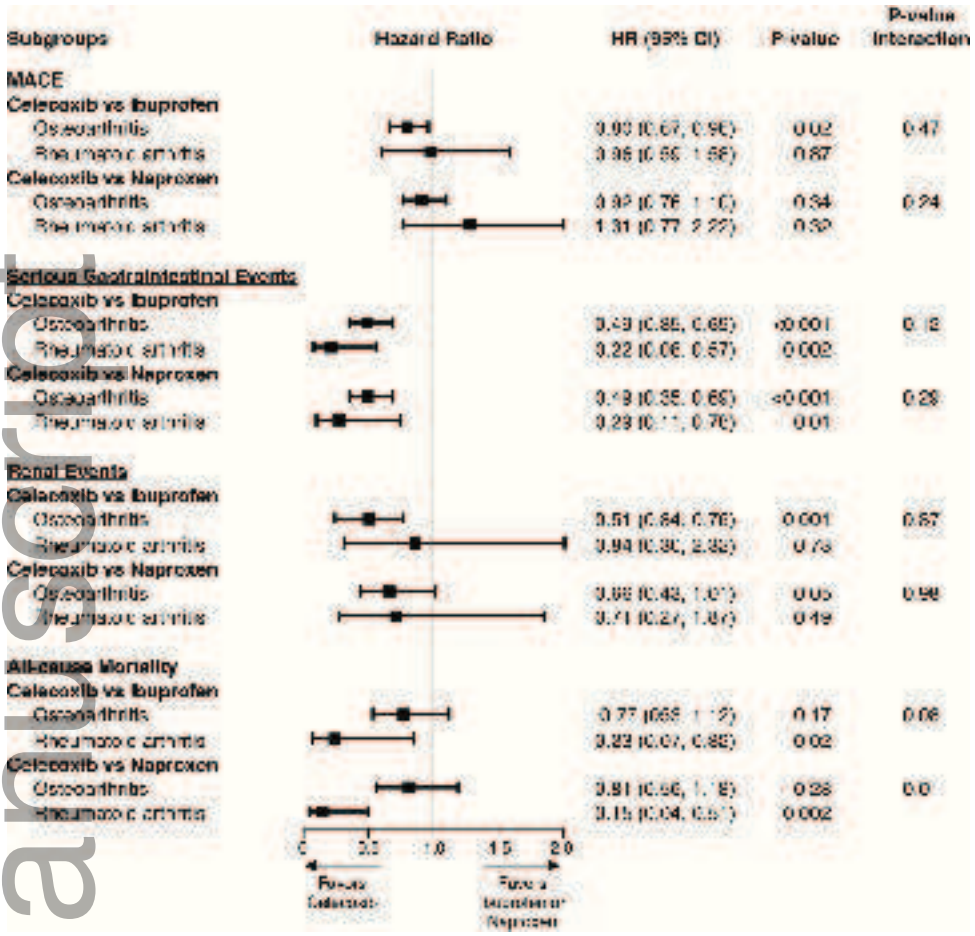

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