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ORIGINAL ARTICLE

Cardiorenal risk of celecoxib compared with naproxen or ibuprofen in arthritis patients: insights from the PRECISION trial

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Aims

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used drugs, both prescribed and over the counter. The long-term cardiovascular safety of NSAIDs in patients with arthritis has engendered controversy. Concerns remain regarding the relative incidence and severity of adverse cardiorenal effects, particularly in arthritis patients with established cardiovascular (CV) disease or risk factors for disease as illustrated by the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen) trial participants (NCT00346216). We further investigated whether the selective COX-2 Inhibitor celecoxib has a superior cardiorenal safety profile compared with ibuprofen or naproxen in the PRECISION population.

Methods and results

Twenty-four thousand eighty-one patients who required NSAIDs for osteoarthritis or rheumatoid arthritis (RA) and had increased CV risk randomly received celecoxib, ibuprofen, or naproxen. The current pre-specified secondary analysis assessed the incidence, severity, and NSAID-related risk of the pre-specified composite cardiorenal outcome (adjudicated renal event, hospitalization for congestive heart failure, or hospitalization for hypertension) in the intention-to-treat (ITT) population. An on-treatment analysis assessed safety in those taking the study medication. Following a mean treatment duration of 20.3 ± 16.0 months and a mean follow-up of 34.1 ± 13.4 months, the primary cardiorenal composite outcome occurred in 423 patients (1.76%) in the ITT population. Of these 423 patients, 118 (28%) were in the celecoxib, 166 (39%) in the ibuprofen, and 139 (33%) in the naproxen group. In a multivariable Cox regression model adjusted for independent clinical variables, celecoxib showed a significantly lower risk compared with ibuprofen [hazard ratio (HR) 0.67, confidence interval (CI) 0.53–0.85, $P = 0.001$) and a trend to lower risk compared with naproxen (HR 0.79, CI 0.61–1.00, $P = 0.058$). In the ITT analysis, clinically significant renal events occurred in 220 patients with events rates of 0.71%, 1.14%, and 0.89% for celecoxib, ibuprofen, and naproxen, respectively ($P = 0.052$), while in the on-treatment analysis the rates were 0.52%, 0.91%, and 0.78% ($P < 0.001$).

Conclusion

In the current era, long-term NSAID use was associated with few cardiorenal events in arthritis patients. At the doses studied, celecoxib displayed fewer renal events and hence more favourable cardiovascular safety compared with ibuprofen or naproxen. These results have considerable clinical implications for practitioners managing individuals with chronic arthritis pain and high risk of impaired renal function and/or heart failure.

Clinical Trial Registration: NCT00346216

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Keywords Cyclooxygenase-2 • Major adverse cardiovascular events • Non-steroidal anti-inflammatory drugs • Renal function

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently used pain medication worldwide, taken by over 30 million people daily, many who have osteoarthritis.[1] Pain management, particularly of that due to arthritis, has become increasingly urgent in the face of an ageing population and an opioid overuse epidemic. The first generation of NSAIDs non-selectively inhibited cyclooxygenase (COX), e.g. indomethacin, naproxen, and ibuprofen. The gastrointestinal adverse effects (ulcer, bleeding, perforation) associated with these drugs spurred the development of selective COX-2 inhibitors such as rofecoxib and celecoxib.[2] Since the withdrawal of rofecoxib from the market in 2004 after two randomized controlled trials showed excess adverse cardiovascular outcomes,[3–5] celecoxib remains the sole selective inhibitor available today in the United States. Much of the concern regarding the safety of selective COX-2 inhibitors arose from their lack of antiplatelet activity as well as a loss of potential vasodilator and antiproliferative properties of non-selective COX inhibition, features that could facilitate thrombus formation.[6] Furthermore, as renal tissue constitutively expresses COX-2, many physicians avoid the use of all NSAIDs in patients with reduced renal function. The conflicting results from the Celecoxib Long-term Arthritis Safety Study (CLASS)[7] and Virtual Immersive Gaming to Optimize Recovery in Low Back Pain (VIGOR) trials[3] and multiple subanalysis and *post hoc* studies[8–11] prompted further reservations regarding the cardiovascular safety of selective COX-2 inhibitors. Indeed, many patients with osteoarthritis and rheumatoid arthritis (RA) also have cardiovascular risk factors or established coronary artery disease. Thus, the FDA has issued multiple warnings regarding the risk of heart attack and stroke associated with use of this class of drugs.[12]

The PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen) trial addressed these concerns regarding relative cardiovascular safety among the three study drugs.[13,14] PRECISION revealed that celecoxib is non-inferior to both naproxen and ibuprofen at the doses studied, with numerically fewer numbers of cardiovascular events in the celecoxib group. The primary analysis of PRECISION showed an overall indication of more favourable renal safety of celecoxib,[14] a preliminary finding that required a more detailed analysis. Therefore, the present secondary analysis aimed to characterize further the cardiorenal safety of the three NSAIDs tested in the PRECISION trial.

Methods

Study design

PRECISION, a multicentre, multinational, randomized, double-blind, non-inferiority parallel group study, investigated the cardiorenal safety of celecoxib, naproxen, or ibuprofen in more than 24 000 patients with osteoarthritis or rheumatoid arthritis and established cardiovascular disease or elevated cardiovascular risk.[13]

Inclusion and exclusion criteria

All the patients enrolled were at least 18 years old and had either osteoarthritis or rheumatoid arthritis and had known or were at risk of developing cardiovascular disease. They were eligible for chronic, daily therapy with an NSAID to control arthritis signs and symptoms, which were not managed effectively with the previously prescribed medical regimen. The Supplementary material online provides a complete list of inclusion and exclusion criteria.

Treatment

Randomized patients were equally allocated (1:1:1) to one of three treatment arms, i.e. 100 mg b.i.d. of celecoxib, 600 mg t.i.d. of ibuprofen, or 375 mg b.i.d. of naproxen with matching placebos. All the patients received esomeprazole (20–40 mg daily) to block gastric acid secretion. In patients who failed to achieve adequate pain relief of their arthritis signs and symptoms, investigators could titrate the dosages of ibuprofen to 800 mg t.i.d. and naproxen to 500 mg b.i.d. In accordance with global labelling and regulatory dosing restrictions, however, celecoxib could be titrated to a dose of 200 mg b.i.d. only in patients with rheumatoid arthritis.

Outcomes

This pre-specified secondary analysis focused on the cardiorenal composite outcome of adjudicated clinically significant renal events, hospitalization for congestive heart failure (CHF), or hospitalization for hypertension (HTN). Additionally pre-specified adjudicated clinically significant renal events were defined as the development of any of the following in trial: (1) an increase in serum creatinine of $\geq$0.7 mg/dL (62 μmol/L) from baseline with a persistently elevated creatinine level of $\geq$2.0 mg/dL (177 μmol/L) for at least 24 h after the initial documented increase; (2) hospitalization for acute renal failure, as defined by doubling of the baseline serum creatinine, or hyperkalaemia (defined as $>$6 mmol/dL) with $\geq$50% elevation in serum creatinine; and/or (3) the necessity for haemodialysis or peritoneal dialysis. A *post hoc* analysis of estimated glomerular filtration rate (eGFR) by treatment group over time provides supportive and vital information, as this analysis was performed on the pre-defined PRECISION *safety population*, which included all randomized subjects who received at least one dose of study medication with data available from randomization up to 30 days post the last dose of the study medication. The Supplementary material online provides a complete list of the patent population and outcome definitions.

Statistical analysis

For baseline characteristics, data are presented as mean $\pm$ standard deviation for continuous variables and count (frequency of patients) for categorical variables (*Table 1*). Baseline characteristics are also presented by 'the presence or absence of the event' (Supplementary material online, *Tables S1 and 2*). Except the *P*-value labelled as being from a non-parametric test, the differences between with the event and without the event were assessed via two-tailed *t*-test for continuous variables and χ^2 test for categorical variables.

Cumulative event curves were constructed for each NSAID treatment (*Figure 1*). The adjudicated cardiorenal outcome reports the raw

Table 1 Baseline characteristics of patients in the intention-to-treat population

Characteristic	Total (*N* = 24 081)	Celecoxib group (*N* = 8072)	Ibuprofen group (*N* = 8040)	Naproxen group (*N* = 7969)
Age—mean	63.2 ± 9.4	63.0 ± 9.4	63.2 ± 9.4	63.3 ± 9.4
Female gender—no. (%)	15 445 (64.1)	5175 (64.1)	5174 (64.4)	5096 (63.9)
Primary arthritis diagnosis—no. (%)				
Osteoarthritis	21 645(89.9)	7259 (89.9)	7208 (89.7)	7178 (90.1)
Rheumatoid Arthritis	2436 (10.1)	813 (10.1)	832 (10.3)	791 (9.9)
Current aspirin use—no. (%)	11 065 (45.9)	3701 (45.8)	3712 (46.2)	3652 (45.8)
Cardiovascular risk category, no. (%)				
Primary prevention	18 601 (77.2)	6209 (76.9)	6206 (77.2)	6186 (77.6)
Secondary prevention	5480 (22.8)	1863 (23.1)	1834 (22.8)	1783 (22.4)
History of hypertension	18 744 (77.8)	6296 (78.0)	6303 (78.4)	6145 (77.1)
Chronic kidney disease	3586 (14.9)	1215 (15.1)	1200 (14.9)	1171 (14.7)
eGFR (mL/min/1.73 m^2)	79.8 ± 17.91	79.9 ± 17.90	79.8 ± 17.99	79.7 ± 17.83

The criteria to identify chronic kidney disease (CKD) at baseline is the estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (CKD stage 3 or beyond) by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

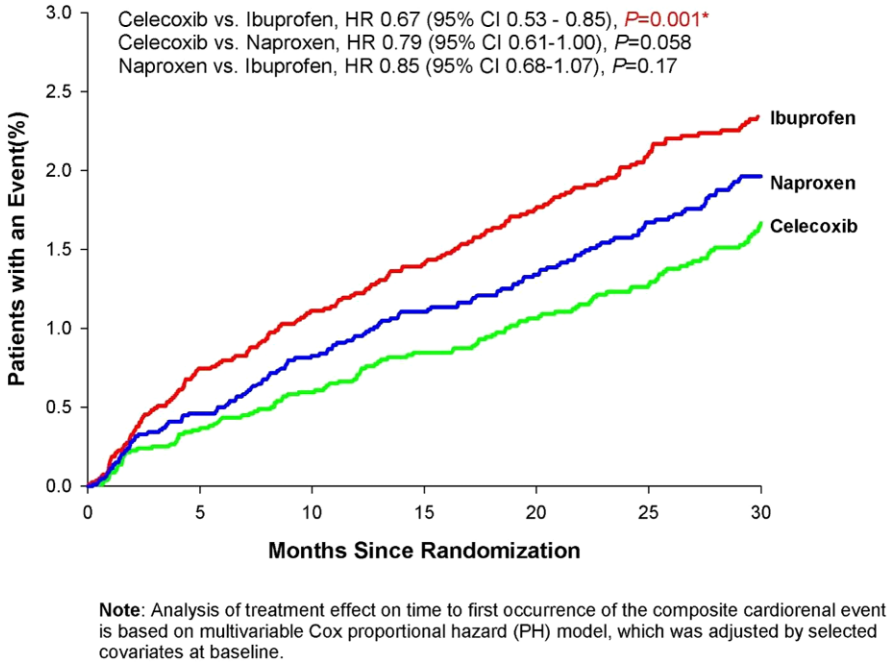


Figure 1 Time to event analysis for the primary composite outcome of cardiorenal events in intention-to-treat population.

number of events (percentage of total patients) (*Table 2*). Calculation of adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the four outcomes of interest used optimized Cox proportional hazard regression models with selected covariates (*Table 2*). Each multivariable Cox model was based on 500 valid Cox proportional hazard models using a bootstrapping methodology. The criterion for variable entry was 0.10. The criterion for variable retention was 0.05. In output estimates of 500 model replicates, the variables with $N \geq 250$ (=500/2) were selected as covariates to run the optimized adjusted Cox model. For composite cardiorenal outcome in the ITT population, the covariates were region, RA status, established cardiovascular disease (CVD), history of dyslipidaemia, diabetes, age, history of HTN, current smoker, body mass index (BMI), baseline creatinine, and health assessement questionaire (HAQ) disability index. For composite cardiorenal outcome in the on-treatment population, the covariates selected were RA status, established CVD, diabetes, age, history of HTN, current smoker, BMI, baseline creatinine, and HAQ disability index. For a clinically significant renal event in the ITT population, the covariates were

Table 2 **Adjudicated cardiorenal outcomes of patients in the intention-to-treat and on-treatment population**

Outcome, *n* (%)	Celecoxib, *N* = 8072	Ibuprofen, *N* = 8040	Naproxen, *N* = 7969	Celecoxib vs. ibuprofen: Adjusted HR[a] (95% CI)	Celecoxib vs. ibuprofen: *P*-value[a]	Celecoxib vs. naproxen: Adjusted HR[a] (95% CI)	Celecoxib vs. naproxen: *P*-value[a]	Ibuprofen vs. naproxen: Adjusted HR[a] (95% CI)	Ibuprofen vs. naproxen: *P*-value[a]
Intention-to-treat population									
The composite cardiorenal	118 (1.46)	166 (2.06)	139 (1.74)	0.67 (0.53, 0.85)	0.001	0.79 (0.61, 1.00)	0.058	1.17 (0.93, 1.47)	0.17
Clinically significant renal	57 (0.71)	92 (1.14)	71 (0.89)	0.55 (0.39, 0.77)	0.001	0.70 (0.49, 1.00)	0.052	1.27 (0.93, 1.74)	0.13
Hospitalization for CHF	45 (0.56)	46 (0.57)	48 (0.60)	0.96 (0.64, 1.45)	0.86	0.90 (0.60, 1.36)	0.63	0.94 (0.63, 1.41)	0.76
Hospitalization for HTN	24 (0.30)	40 (0.50)	34 (0.43)	0.59 (0.36, 0.98)	0.04	0.69 (0.41, 1.16)	0.16	1.17 (0.74, 1.85)	0.50
On-treatment population									
Outcome, *n* (%)	Celecoxib, *N* = 8030	Ibuprofen, *N* = 7990	Naproxen, *N* = 7933	Celecoxib vs. ibuprofen: Adjusted HR[a] (95% CI)	Celecoxib vs. ibuprofen: *P*-value[a]	Celecoxib vs. naproxen: Adjusted HR[a] (95% CI)	Celecoxib vs. naproxen: *P*-value[a]	Ibuprofen vs. naproxen: Adjusted HR[a] (95% CI)	Ibuprofen vs. naproxen: *P*-value[a]
The composite cardiorenal	89 (1.11)	139 (1.74)	120 (1.51)	0.58 (0.44, 0.75)	<0.001	0.68 (0.51, 0.90)	0.006	1.18 (0.92, 1.51)	0.19
Clinically significant renal	42 (0.52)	73 (0.91)	62 (0.78)	0.47 (0.32, 0.69)	<0.001	0.57 (0.38, 0.85)	0.006	1.21 (0.86, 1.70)	0.27
Hospitalization for CHF	28 (0.35)	38 (0.48)	35 (0.44)	0.67 (0.41, 1.10)	0.11	0.75 (0.45, 1.23)	0.25	1.11 (0.70, 1.76)	0.65
Hospitalization for HTN	25 (0.31)	37 (0.46)	32 (0.40)	0.64 (0.39, 1.06)	0.084	0.76 (0.45, 1.27)	0.29	1.18 (0.74, 1.90)	0.49

CI, confidence interval; CHF, congestive heart failure; HR, hazard ratio; HTN, hypertension.

[a]Analysis of treatment effect on time to first occurrence of events is based on Cox proportional hazard (PH) model with several baseline characteristics as covariates. Some patients had more than one cardiorenal component during treatment; thus, columns do not always total (since the composite cardiorenal event reached as soon as first component event recorded)

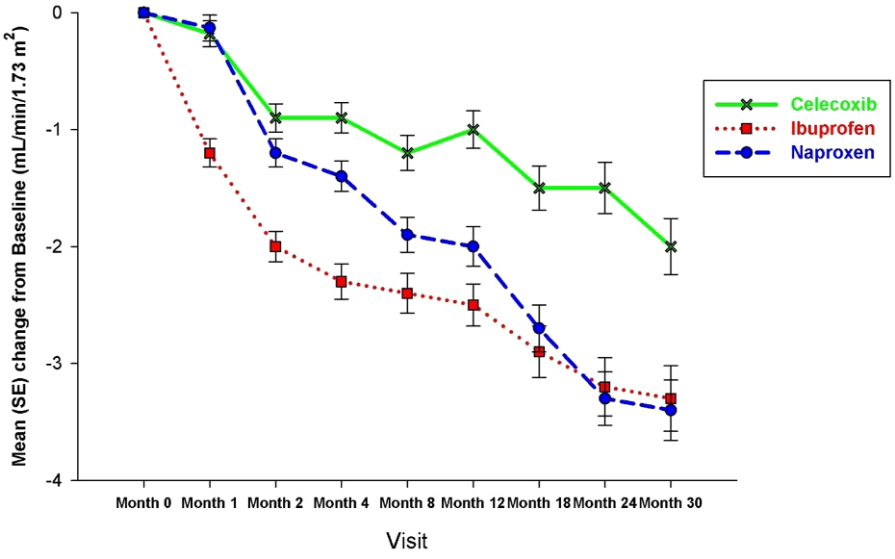


Figure 2 Observed change from baseline in estimated glomerular filtration rate at each visit (intention-to-treat population).

RA status, established CVD, diabetes, age, history of HTN, use of selective serotonin reuptake inhibitors, statin use at baseline, baseline creatinine, and HAQ disability index. For clinically significant renal events in the on-treatment population, the selected covariates were RA status, established CVD, diabetes, age, history of HTN, use of selective serotonin reuptake inhibitors, statin use at baseline, and baseline creatinine. For hospitalization for CHF in the ITT population, the covariates were RA status, established CVD, diabetes, age, history of HTN, current smoker, *Helicobacter pylori* positivity, BMI, and baseline creatinine. For hospitalization for CHF in the on-treatment population, the selected covariates were RA status, established CVD, diabetes, age, current smoker, BMI, and baseline creatinine.

For hospitalization for HTN, the covariates selected were established CVD, history of dyslipidaemia, current smoker, history of prior peptic ulcer, and history of HTN.

eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Post-baseline data include observations made between NSAID treatment start date and last treatment date + 30 days (*Figure 2*). Analysis data for the intention-to-treat (ITT) population were censored after 30 months and for the on-treatment population after 30 days post last study treatment up to 43 months. The analyses were performed using the SAS system (version 9.4, Cary, NC, USA). The Kaplan–Meier curves (*Figure 1*) and the plot of eGFR change (*Figure 2*) were made using Sigma Plot 11.0 (Systat, San Jose, CA, USA).

Results

Patient population

The current analysis included 24 081 participants assigned to three treatment groups, celecoxib [$n = 8072$, mean (±SD) daily dose, 209 ± 37 mg], naproxen ($n = 7969$, 852 ± 103 mg), and ibuprofen ($n = 8040$, 2045 ± 246 mg). The treatment groups had similar baseline characteristics, such as pre-existing cardiovascular disease, history of chronic kidney disease, and eGFR (*Table 1*). The mean duration of treatment was 20.3 ± 16.0 and follow-up was 34.1 ± 13.4 months and this time of exposure did not differ significantly between the three treatment arms. The study characteristics and protocol have been described in detail.[13,14]

Cardiorenal composite outcome

In the ITT population, the composite outcome of adjudicated renal events, hospitalization for CHF, or hospitalization for HTN occurred in 423 patients (1.76%), of whom 118 (1.46%) were in the celecoxib group, 166 (2.06%) in the ibuprofen group, and 139 (1.74%) in the naproxen group (*Table 2*). Compared with those who did not have an event, patients who experienced cardiorenal events were more likely to be older, diabetic, and hypertensive male patients, having more pre-existing CVD, 42.8% vs. 22.4%, respectively .A multivariable Cox regression model for this outcome showed that celecoxib had a significantly lower risk compared with ibuprofen [hazard ratio (HR) 0.67, confidence interval (CI) 0.53–0.85, $P = 0.001$] and a tendency towards lower risk than naproxen [HR 0.79, CI 0.61–1.0, $P = 0.058$). (*Figure 1* and *Table 2*)

In the on-treatment population, the composite cardiorenal outcome (*N*Total = 348) remained significantly lower in the celecoxib group compared with those treated with ibuprofen (HR 0.58, CI 0.44–0.75, $P < 0.001$) or naproxen (HR 0.68, CI 0.51–0.90, $P = 0.006$) (*Table 2*).

Clinically significant renal events

In the ITT population, clinically significant renal events occurred in 220 patients, of whom 57 (0.71%) were in the celecoxib, 92 (1.14%) in the ibuprofen, and 71 (0.89%) in the naproxen group. (*Table 2*). Indeed, this translated into a significant risk reduction for the use

of celecoxib as compared with ibuprofen (HR 0.55, CI 0.39–0.77, $P = 0.001$) and a trend as compared with naproxen (HR 0.70, CI 0.49–1.00, $P = 0.052$). The on-treatment analysis was even more robust, with significantly lower event rates in celecoxib (0.52%) as compared with ibuprofen (0.91%) ($P < 0.001$) and naproxen (0.78%) ($P = 0.006$) (*Table 2*). Differences in baseline characteristics and specifically in renal function between patients with and without renal events are reported within each of the treatment groups in the Supplementary material online, *Table S1*. Of note, patients with renal events were minimally older, more likely to be male, were slightly more obese, and more likely to have comorbidities such as diabetes, hypertension, cardiovascular disease, or baseline reduced renal function (Supplementary material online, *Table S2*).

Changes in the estimated glomerular filtration rate

In the ITT population, celecoxib showed a significantly smaller change in eGFR from baseline at each visit compared with ibuprofen or naproxen treatment, with mean changes in eGFR of -9.0 ± 0.13 vs. -10.7 ± 0.15 vs. -9.7 ± 0.13 ($P < 0.001$), respectively (*Figure 2* and *Table 3*). Moreover, we further analysed the clinically relevant incidences of either a drop of eGFR $\geq$15 mL/min/1.73 m^2 (*Figure 3*) or 30% decrease in eGFR (*Table 3*) in a different set of safety populations, including, but not limited to patients with relatively normal eGFR at baseline and those with abnormal creatinine levels. Celecoxib demonstrated lower rates of loss in renal function, where the incidence of a 30% drop in eGFR in patients with abnormal baseline creatinine occurred in 8.5% of celecoxib patients as compared with ibuprofen (16.4%, $P < 0.001$) and naproxen (9.8%, $P = 0.400$), respectively (*Table 3*), while for patients with normal baseline creatine, celecoxib also demonstrated significantly lower rates of loss in renal function, where the incidence of a 30% drop in eGFR in these patients occurred in 8.7% of celecoxib patients as compared with ibuprofen (13.8%, $P < 0.001$) and naproxen (9.8%, $P = 0.023$), respectively (*Table 3*). Within the different treatment arms, it was, however, clear that those patients with a renal event were more likely to have a higher incidence of CVD at baseline. (Supplementary material online, *Table S1*).

Discussion

These analyses of a large-scale randomized trial show in arthritis patients that in the current era of advanced CV care, long-term NSAID use appears very well tolerated, with an incidence of renal events and hospitalization for hypertension and heart failure of less than 1/100 patient-years. Notably, at all dosages studied, the selective COX-2 inhibitor celecoxib displayed fewer such events and hence superior cardiorenal safety compared with the non-selective NSAID ibuprofen in the ITT and a significantly better safety profile compared with both NSAIDs in the on-treatment analysis. The lower risk of hospitalization for hypertension with celecoxib compared with the non-selective NSAIDs agrees with the results of an ambulatory blood pressure monitoring substudy of PRECISON that supported an advantage of celecoxib at the doses studied.[15] These findings should be considered by practitioners as well as cardiovascular specialists managing individuals with chronic arthritis pain and high cardiorenal risk, particularly in a time of widespread concern regarding opiate use for pain relief.

The main results of the PRECISION trial showed non-inferiority of celecoxib as regards overall cardiovascular outcomes in the ITT and on-treatment analysis.[13,14] The current analyses specifically examined clinically significant renal outcomes or hospitalizations for hypertension and heart failure. These interrelated events have high clinical importance and merit close attention because the kidney expresses COX-2 constitutively, raising concerns of using drugs that interfere with this enzyme. As a consequence of this action of NSAIDs, a number of patients' renal function worsened on all three tested drugs, but the prevalence of such a clinical composite event was much lower than might have been expected. Indeed, overall, the composite cardiorenal outcome occurred in 423 patients or only 1.75% of the entire ITT patient population. Of those 423 events, 118 or 1.46% occurred in the celecoxib group, 139 or 1.74% on naproxen, and 166 or 2.06% on ibuprofen. In addition, celecoxib showed less worsening of renal function than naproxen or ibuprofen.

Of note, at baseline the three treatment groups had similar blood creatinine concentrations, eGFR, and a comparable prevalence of history of chronic kidney disease. As expected, however, patients who experienced clinically significant renal outcomes or hospitalizations for hypertension and heart failure were more likely to have a higher incidence of CVD at baseline. Indeed, individuals with diabetes and/or hypertension were much more likely to have renal dysfunction.[16–18] Similarly, eGFR declines with age;[19] thus, the elderly—a population enriched for osteoarthritis—have higher risk of cardiorenal events than younger individuals.

Sodium and water retention, which commonly can occur during long-term treatment with NSAIDs, have particular importance in patients with heart failure. Indeed, NSAIDs can cause cardiac decompensation and emergency visits in this patient population.[20] Yet, the overall event rate of heart failure hospitalizations was surprisingly low and numerically lower in those assigned to celecoxib in this trial.

NSAIDS also increase blood pressure both in normotensive individuals and in those with hypertension.[21,22] We have previously shown in a substudy of PRECISION (i.e. PRECISION-ABPM) that the selective COX-2 inhibitor celecoxib did not significantly change the mean blood pressure in this population, while naproxen and, in particular, ibuprofen markedly increased blood pressure.[15]

Randomized controlled trials commonly use an ITT analysis. This approach is most rigorous for assessment of efficacy; however, when seeking safety signals, an on-treatment analysis in addition to the ITT analysis reflects the true exposure to the drug in question. This secondary analysis of PRECISION provides further support for the relative safety of celecoxib regarding clinically important renal outcomes or hospitalizations for hypertension and heart failure, most convincingly in the on-treatment analysis. Indeed, in the on-treatment population, the composite cardiorenal outcome remained significantly lower in the celecoxib group compared with ibuprofen with an HR of 0.58 and in addition revealed a more favourable safety profile compared with those treated with naproxen with an HR of 0.68. Altogether, therefore, this cardiorenal safety study provides convincing evidence in a large patient population with osteoarthritis or

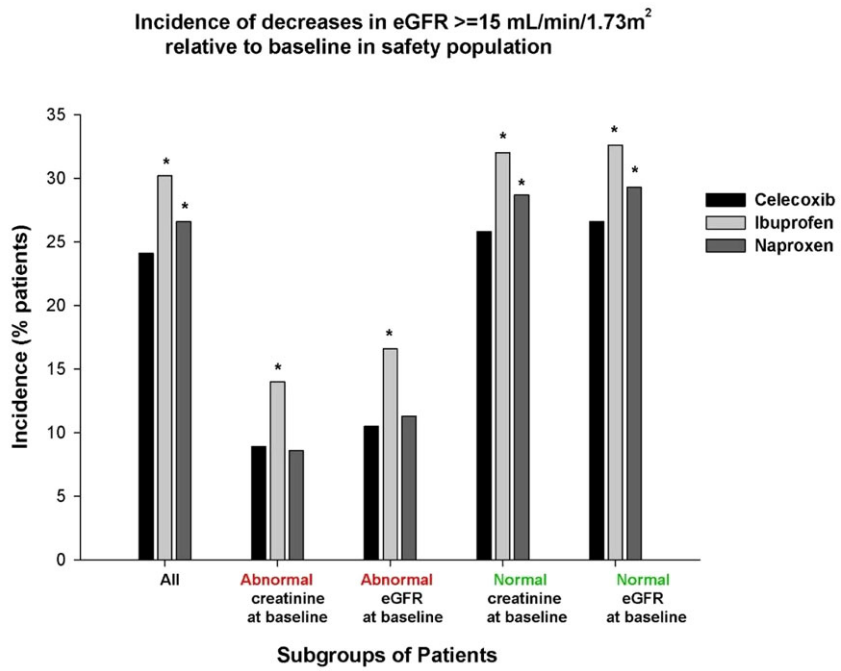
Table 3 **Analysis of serum creatinine and estimated glomerular filtration rate levels in safety population**

All patients					
eGFR change from baseline at the lowest eGFR	**Celecoxib (*N* = 7518)**	**Ibuprofen (*N* = 7478)**	**Naproxen (*N* = 7454)**	**Celecoxib vs. ibuprofen**	**Celecoxib vs. naproxen**
		Mean ± S.E.		***P*-value**	
Mean change in eGFR (mL/min/1.73 m^2)	−9.0 ± 0.13	−10.7 ± 0.15	−9.7 ± 0.13	<0.001NP	<0.001NP
		Number of patients (%)		*P*-value	
Decrease of eGFR ≥15 mL/min/1.73 m^2	1813 (24.1)	2256 (30.2)	1985 (26.6)	<0.001	<0.001
Decrease in eGFR >30%	651 (8.7)	1048(14.0)	731(9.8)	<0.001	0.015
Patients with serum creatinine >1.30 mg/dL (male) and >1.06 mg/dL (female) at baseline					
eGFR change from baseline at the lowest eGFR	Celecoxib (*N* = 762)	Ibuprofen (*N* = 758)	Naproxen (*N* = 757)	Celecoxib vs. ibuprofen	Celecoxib vs. naproxen
		Mean ± S.E.		P-value	
Mean change in eGFR (mL/min/1.73 m^2)	−3.0 ± 0.38	−4.9 ± 0.41	−3.8 ± 0.36	<0.001NP	0.157NP
		Number of patients (%)		*P*-value	
Decrease of eGFR ≥15 mL/min/1.73 m^2	68 (8.9)	106 (14.0)	65 (8.6)	0.002	0.816
Decrease in eGFR >30%	65 (8.5)	124 (16.4)	74 (9.8)	<0.001	0.400
Patients with serum creatinine ≤1.30 mg/dL (male) and ≤1.06 mg/dL (female) at baseline					
eGFR change from baseline at the lowest eGFR	Celecoxib (*N* = 6756)	Ibuprofen (*N* = 6720)	Naproxen (*N* = 6697)	Celecoxib vs. ibuprofen	Celecoxib vs. naproxen
		Mean ± S.E.		*P*-value	
Mean change in eGFR (mL/min/1.73 m^2)	−9.6 ± 0.13	−11.3 ± 0.15	−10.3 ± 0.14	<0.001NP	<0.001NP
		Number of patients (%)		*P*-value	
Decrease of eGFR ≥15 mL/min/1.73 m^2	1745 (25.8)	2150 (32.0)	1920 (28.7)	<0.001	<0.001
Decrease in eGFR >30%	586 (8.7)	924 (13.8)	657 (9.8)	<0.001	0.023

Table 3 Continued

Patients with eGFR <60 mL/min/1.73 m^2 at baseline					
eGFR change from baseline at the lowest eGFR	Celecoxib ($N = 1147$)	Ibuprofen ($N = 1123$)	Naproxen ($N = 1097$)	Celecoxib vs. ibuprofen	Celecoxib vs. naproxen
		Mean ± S.E.		*P*-value	
Mean change in eGFR (mL/min/1.73 m^2)	−3.9 ± 0.29	−6.4 ± 0.31	−4.9 ± 0.29	<0.001NP	0.009NP
		Number of patients (%)		*P*-value	
Decrease of eGFR ≥15 mL/min/1.73 m^2	121 (10.5)	186 (16.6)	124 (11.3)	<0.001	0.567
Decrease in eGFR >30%	110 (9.6)	189 (16.8)	116 (10.6)	<0.001	0.439
Patients with eGFR ≥60 mL/min/1.73 m^2 at baseline					
eGFR change from baseline at the lowest eGFR	Celecoxib ($N = 6371$)	Ibuprofen ($N = 6355$)	Naproxen ($N = 6357$)	Celecoxib vs. ibuprofen	Celecoxib vs. naproxen
		Mean ± S.E.		P-value	
Mean change in eGFR (mL/min/1.73 m^2)	−9.9 ± 0.14	−11.5 ± 0.16	−10.5 ± 0.14	<0.001NP	0.001NP
		Number of patients (%)		*P*-value	
Decrease of eGFR ≥15 mL/min/1.73 m^2	1692 (26.6)	2070 (32.6)	1861 (29.3)	<0.001	0.001
Decrease in eGFR >30%	541 (8.5)	859 (13.5)	615 (9.7)	<0.001	0.020

eGFR is calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Analyses of serum creatinine and eGFR were performed on changes from baseline to the visit with the lowest eGFR for each patient. The lowest eGFR values were obtained during the entire treatment visits (between treatment start date and last treatment date +30 days) per subject.
eGFR, estimated glomerular filtration rate; NP, non-parametric test.



Note: The incidence of decreases in eGFR>=15 mL/min/1.73m^2 relative to baseline are shown for all patients, patients with serum creatinine>1.30 mg/dl (Male) or >1.06 mg/dl (Female) at baseline, patients with eGFR<60 mL/min/1.73m^2 at baseline, and patients with normal serum creatinine or eGFR at baseline who had both a baseline and the lowest eGFR value during the treatment period.
*P<0.01 versus celecoxib by Fisher exact test.

Figure 3 Incidence of decrease in estimated glomerular filtration rate of ≥15 mL/min/1.73 m^2 relative to baseline in the safety population.

rheumatoid arthritis that celecoxib, a selective COX-2 inhibitor, provides better safety compared with the non-selective COX inhibitors naproxen and ibuprofen at the doses studied.

For clinicians, the clinical profile of patients prone to clinically meaningful renal outcomes or hospitalizations for hypertension and heart failure when exposed to an NSAID has importance. Of note, patients with such events were older, more likely males, and typically exhibited comorbidities such as pre-existing CVD, hypertension, dyslipidaemia, and diabetes. Surprisingly, patients with events also were more likely to take aspirin and/or a statin, which most likely reflects their comorbid conditions.

Furthermore, we were able to provide substantial evidence demonstrating the relative renal safety of celecoxib in the safety population. Indeed, in patients with reduced eGFR, <60 mL/min/1.73 m^2 at baseline, the lowest mean changes in GFR from baseline occurred in patients on celecoxib as compared with ibuprofen (−3.9 ± 0.29 vs. −6.4 ± 0.31; $P < 0.001$) and naproxen (−3.9 ± 0.29 vs. −4.9±0.29; $P = 0.009$). Undoubtedly a 30% reduction in eGFR is of major clinical significance and the fact that such events occurred significantly more in patients on ibuprofen is challenging to justify; however, this might emphasize the different cardiorenal effects selective COX-2 inhibition exhibits on renal function. Furthermore, the overall age and the incidence of diabetes in patients with any renal event were both lower in the celecoxib group as compared with the other groups. While less than 50% of the patients were diabetics in the celecoxib group, more than 55% of those had diabetes in the comparative groups. Generally, the results are in accordance with those previously published from smaller-scale studies such as the CLASS study,[7] which showed that significantly fewer patients taking celecoxib exhibited clinically important reductions in renal function (3.7%), compared with diclofenac (7.3%; $P < 0.05$) and ibuprofen (7.3%; $P < 0.01$). Despite this being true for four other major publications analysing similar renal outcomes,[23–26] a *post hoc* meta- analysis of the renal safety of celecoxib conducted by Whelton *et al.*[27] using the safety database generated from the products clinical development programme showed that the overall incidences of renal adverse events in the celecoxib (4.3%) and other NSAID (4.1%) groups were similar.

Of note, in the on-treatment analysis, patients who experienced clinically significant relevant renal events had a similar profile with all NSAIDs in the study, i.e. were more males and showed comorbidities such as CVD, hypertension, dyslipidaemia, or diabetes. Thus, the use of NSAIDs requires additional attention in such patients, but overall, these data indicate that celecoxib confers a relatively favourable safety profile.

This study has limitations. Although the current analysis was prespecified in the protocol, the interpretation of such secondary examinations requires caution since the study was only powered for the primary endpoint. Furthermore, the overall prevalence of renal events and hospitalizations for hypertension and heart failure was surprisingly low which could further reduce power. Ethical concerns precluded a comparison with a placebo group, so the study is only

able to examine the relative safety compared to other NSAIDs. 2. The relatively low incidence of outcomes could be explained by the limited regulatory restrictions of 200 mg daily for most patients, which may have provided a potential safety advantage for celecoxib. Finally, the large number of patients lost for follow-up in PRECISION may have led to an underestimation of the true incidence of outcomes.

In summary, these results have important clinical implications as various NSAIDs are among the most used drugs in the Western world. Patients with OA and RA or chronic musculoskeletal conditions are commonly older and are more likely to have comorbidities such as decreased renal function, hypertension, diabetes and/or pre-existing ischemic cardiovascular disease. Thus, if necessary, practitioners should consider the use of celecoxib at the dosages used in this trial in such patients. The lack of risk of addiction with agents of this class offers an important advantage and also requires consideration in clinical decision-making regarding pain management.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Conflict of interest: None of the investigators received speaking or advisory board honoraria related to the compounds investigated in this trial or any other NSAID by Pfizer or any other company. T.F.L. reports receiving grant support to his institutions from Pfizer. P.L. reports receiving consulting fees from Med Intelligence, lecture fees from Med Intelligence, Omniprex, and Health Science Media, and travel support from the Academy for Continued Healthcare Learning (ACHL), Healthcare21 Communications, PSL Group Services, MEDCON International, Regeneron Pharmaceuticals, Esperion Therapeutics, Takeda, Bayer Yakuhin, and Amgen, serving on advisory boards (uncompensated) for Regeneron Pharmaceuticals, Merck, and Novartis, chairing a peer review of grant applications (uncompensated) for Healthmatters Communications, providing consulting (uncompensated) for GlaxoSmithKline, Med Intelligence, and Regeneron Pharmaceuticals, and giving talks (uncompensated) at meetings held by RX Worldwide Meetings, PriMed, VHA-UHC Alliance NewCo (now Vizient), AstraZeneca, and Tarsus. E.H. reports receiving fees for serving on advisory boards from AbbVie, Bristol Myers Squibb, Amgen, UCB Pharma, Regeneron, and Janssen, and grant support from Sanofi–Genzyme. F.R. reports receiving personal fees from St. Jude Medical, Servier, ZOLL Medical, AstraZeneca, HeartWare, Sanofi, Cardiorentis, Novartis, Amgen, and Bristol Myers Squibb, and grant support from St. Jude Medical. W.B. and F.X. report being employees of Pfizer. The authors report no other potential conflict of interest relevant to this article.

Data availability

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or EU or (2) in programmes that have been terminated (i.e. development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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