

ORIGINAL ARTICLE



Degree of Cyclooxygenase-2 Inhibition Modulates Blood Pressure Response

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BACKGROUND: Large clinical trials compared distinct nonsteroidal anti-inflammatory drugs in terms of their risk of adverse cardiovascular events. However, whether pharmacologically equipotent doses were used, that is, whether a similar degree of COX (cyclooxygenase)-2 inhibition was achieved, was not considered. We compared drug target inhibition and blood pressure (BP) response to celecoxib and naproxen.

METHODS: Sixteen healthy participants were treated with celecoxib (200 mg/d), naproxen (500 mg/d), or placebo for 7 days in a double-blind, crossover design. The degree of COX inhibition was assessed ex vivo using established whole blood assays and in vivo by quantifying urinary metabolites of thromboxane A₂ (COX-1) and prostacyclin (COX-2). Ambulatory BP was measured throughout the final dosing interval.

RESULTS: Both nonsteroidal anti-inflammatory drugs inhibited COX-2 activity relative to placebo, but naproxen inhibited COX-2 activity to a greater degree (62.9±21.7%) than celecoxib (35.7±25.2%; $P<0.05$). Similarly, naproxen treatment inhibited prostacyclin formation in vivo (48.0±24.9%) to a greater degree than celecoxib (26.7±24.6%; $P<0.05$). Naproxen significantly increased BP compared with celecoxib (mean arterial pressure, 2.5 [95% CI, 1.5–3.5] mmHg; systolic BP, 4.0 [95% CI, 2.9–5.1] mmHg; and diastolic BP, 1.8 [95% CI, 0.8–2.8] mmHg; $P<0.05$ for all). The difference in systolic BP relative to placebo was associated with the degree of COX-2 inhibition ($P<0.05$).

CONCLUSIONS: Future studies should consider pharmacokinetic and pharmacodynamic properties, as well as patient-specific factors that may modulate the cardiovascular risk of nonsteroidal anti-inflammatory drug use.

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Key Words: blood pressure ■ cardiovascular diseases ■ drug-related side effects and adverse reactions ■ muscle, smooth, vascular ■ prostaglandin-endoperoxide synthases

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications worldwide, and the opioid crisis has placed a new emphasis on their use.^{1,2} Approximately 20% of adults in the United States receive at least 1 NSAID prescription per year,³ and 12% of adults in the United States reported using NSAIDs chronically, that is, >3 times weekly for >3 months.⁴ Consumption of NSAIDs in individuals

at risk for musculoskeletal injuries is even more common.^{5–7} Given the high prevalence of chronic pain in the United States, >100 million Americans experience chronic pain⁸; NSAIDs are an important nonaddictive option for pain relief. Optimizing NSAID therapy is one strategy to address the current opioid crisis,² and rates of NSAID use have increased in recent years as opioid prescriptions have declined.⁹ Although they lack the

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NOVELTY AND RELEVANCE

What Is New?

Nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of hypertension via suppression of COX (cyclooxygenase)-2-derived prostanoid formation in the vasculature and the kidney. This study finds that commonly compared NSAID doses in major trials are not pharmacologically equivalent in their COX-2 inhibitory potency. Although the pharmacological potency of celecoxib measured with isolated COX-2 enzyme or cellular preparations in vitro is higher than that of naproxen, 200 mg/d of celecoxib inhibited COX-2 activity in vivo to a lesser degree than 500 mg/d of naproxen. This difference in COX-2 inhibition was shown to directly impact systolic blood pressure, with naproxen causing a greater increase in systolic blood pressure compared with celecoxib over a 1-week treatment period.

What Is Relevant?

The results underscore the need to consider both dose and pharmacodynamic equivalence when comparing the safety profiles of different NSAIDs, rather

than relying solely on nominal dose comparisons. The magnitude of blood pressure elevation observed in this cohort aligns with previous studies, reinforcing the clinical relevance of these findings. Notably, the study also observed considerable heterogeneity in individual responses to NSAID treatment, suggesting that patient-specific factors contribute to blood pressure changes and may also influence overall cardiovascular risk.

Clinical/Pathophysiological Implications?

From a pathophysiological perspective, the study reinforces the role of COX-2 inhibition in mediating blood pressure elevation associated with NSAID use. While a large randomized controlled trial concluded noninferiority of celecoxib compared with naproxen with regard to cardiovascular risk, this is based on a comparison of doses that are not equipotent. Future studies should consider the pharmacokinetic and pharmacodynamic properties of the drugs, as well as patient-specific risk factors, when seeking to compare the cardiovascular risk associated with the use of specific NSAIDs.

Nonstandard Abbreviations and Acronyms

ABP	ambulatory blood pressure
BP	blood pressure
COX	cyclooxygenase
DBP	diastolic blood pressure
LC-MS/ms	liquid chromatography-tandem mass spectrometry
LS	least-squares
MAP	mean arterial pressure
NSAID	nonsteroidal anti-inflammatory drug
PRECISION	Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen
SBP	systolic blood pressure

addictive potential of opioids, NSAIDs have the potential to cause serious and, in some cases, life-threatening adverse events, including gastrointestinal bleeding, renal dysfunction, hypertension, and thrombotic cardiovascular events.¹⁰ Clinically meaningful blood pressure (BP) increases on NSAIDs are a common complication.¹¹

NSAIDs exert their analgesic and anti-inflammatory effects via inhibition of COX (cyclooxygenase)-1 and COX-2, enzymes that catalyze the first committed step in prostaglandin synthesis. PGs produce a diverse array

of biologic effects via activation of prostanoid receptors and play important roles in a variety of pathological and homeostatic processes.¹² The risk of thrombotic events associated with the use of NSAIDs, particularly those selective for COX-2, is mediated via suppression of COX-2-derived prostacyclin formation in endothelial and vascular smooth muscle cells.^{13,14} Prostacyclin possesses potent antithrombotic and vasodilatory effects and, thus, acts as a general inhibitor of platelet activation in vivo.¹² Nonselective NSAIDs also inhibit COX-2 in the vasculature, but the associated risk of thrombosis is mitigated to some extent by inhibition of the formation of thromboxane A₂, a COX-1-derived prostaglandin released by activated platelets that promote platelet activation and aggregation.^{10,15} In addition to their effects on vascular prostaglandin production, NSAIDs inhibit renal prostaglandin formation, resulting in sodium retention and BP increases, which may further augment cardiovascular risk.^{10,15,16}

One of the largest (N=24081) outcome studies to date, the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen), compared the safety of the COX-2 selective NSAID, celecoxib (100–200 mg twice a day), and 2 traditional NSAIDs, naproxen (375–500 mg twice a day) and ibuprofen (600–800 mg 3 times a day), in patients with osteoarthritis (90%) and rheumatoid arthritis (10%). PRECISION concluded that the cardiovascular safety

of moderate doses of celecoxib (average daily dose, 209 ± 37 mg) was noninferior to naproxen (average daily dose, 852 ± 103 mg) or ibuprofen (average daily dose, 2045 ± 246 mg).¹⁷ However, a secondary on-treatment analysis of PRECISION showed a lower risk of cardiovascular events in the celecoxib group than the ibuprofen and naproxen groups.¹⁸ Similarly, a prespecified sub-study (PRECISION-ABPM) reported that the percentage of patients with normal baseline BP who developed hypertension was significantly greater in patients treated with naproxen (19%) or ibuprofen (23%) than with celecoxib (10%).¹⁹ However, the degree of COX-2 inhibition attained has never been assessed in clinical outcome trials, and thus, it is unknown whether the doses used in PRECISION were equipotent.

Here, we compared the pharmacological potency of celecoxib (100 mg twice a day) with naproxen (250 mg twice a day) and how this relates to BP response to NSAIDs in a highly controlled study in apparently healthy volunteers. Both are the lowest recommended daily doses of celecoxib and naproxen for osteoarthritis. We hypothesized that a greater degree of COX-2 inhibition would be associated with a greater increase in BP in response to NSAID treatment.

METHODS

Data Availability

Aggregate data that support the findings of this study have been made publicly available in ClinicalTrials.gov (<https://www.clinicaltrials.gov>; Unique identifier: NCT02502006). Subject-level data cannot be publicly shared due to privacy restrictions. Requests to access the data sets should be directed to the corresponding authors.

Participants

Healthy volunteers were recruited by advertisement and word of mouth. Men and women (≥ 18 years of age) who were in good health based on medical history, physical examination, vital signs, and laboratory tests were eligible for inclusion. Participants were excluded if they were pregnant or nursing a child, smoked or used nicotine-containing products, were obese (body mass index >30 kg/m²); had a history of significant cardiovascular, gastrointestinal, renal, hepatic, respiratory, immune, endocrine, hematologic, or neurological disease, a history of cancer within the last 5 years, or a coagulation or bleeding disorder; were sensitive or allergic to celecoxib, naproxen, aspirin, or other NSAIDs; or had used NSAIDs (including aspirin and acetaminophen), dietary or herbal supplements containing salicylates, vitamin E, fish oil, or any other herbal supplements, within 14 days of study drug administration.

Study Procedures

The study protocol was approved by the University of Pennsylvania institutional review board (820715; <https://www.clinicaltrials.gov>; Unique identifier: NCT02502006), and all participants provided informed consent. The study was a

randomized, double-blind, 3-way crossover study comparing the degree of COX inhibition and the BP response at steady state following treatment with celecoxib (100 mg twice daily), naproxen (250 mg twice daily), or placebo (twice daily) for 7 days. Before beginning treatment, all participants attended a screening visit to obtain a complete medical history and confirm eligibility. They were asked to abstain from analgesics, including products containing NSAIDs (including aspirin and acetaminophen), high-dose vitamins, and nutritional supplements until study completion.

Randomization was performed using a computer-generated sequence to assign participants to 1 of 6 treatment orders to ensure that each treatment occurred with equal frequency and any carryover effects were balanced by sequence. Allocation was provided to the University of Pennsylvania Investigational Drug Service by an investigator not involved in participant enrollment.

On the first day of each treatment phase, baseline blood and urine samples were collected, and participants were given a blister pack with blinded study medication to be taken by mouth twice daily on an outpatient basis. Study medication was blinded by overencapsulation by the University of Pennsylvania Investigational Drug Service. On the morning of day 7, participants returned to the clinical research unit for a 12-hour visit for pharmacokinetic-pharmacodynamic sampling. Ambulatory BP (ABP) was monitored every 15 minutes, while the participants were seated in the clinical research unit, using an automated ABP monitor (Spacelabs 90207) placed on the nondominant upper arm. Blood and urine samples were collected ($T=0$), and the final dose of study medication was administered. Additional samples were collected 0.5 (blood only), 1, 2, 4, 8, and 12 hours after study medication administration. Participants were discharged after the 12-hour sample collection. These study visits were repeated for the next 2 treatment phases, with a washout period of at least 2 weeks between each treatment phase.

Study data were collected and managed using Research Electronic Data Capture hosted at the University of Pennsylvania Perelman School of Medicine.^{20,21}

Quantification of COX Activity and Plasma Drug Concentrations

Whole blood assays were used to assess the degree of COX inhibition *ex vivo* under conditions of maximal stimulation. COX-1 activity *ex vivo* was evaluated by quantifying serum thromboxane B₂ levels, as previously described.²² Briefly, whole blood was collected into vacuum tubes containing clot activator and incubated in a water bath at 37°C for 1 hour. Serum was separated by centrifugation and stored at -80°C until analysis by liquid chromatography-tandem mass spectrometry (LC-MS/ms).

COX-2 activity *ex vivo* was evaluated by quantifying plasma prostaglandin E₂ levels following lipopolysaccharide stimulation in whole blood, as previously described.²³ Briefly, heparinized whole blood was treated with aspirin (1 mmol/L) and incubated at room temperature for 15 minutes. Lipopolysaccharide (*Escherichia coli*, serotype O111:B4, 10- $\mu\text{g/mL}$ whole blood) was added, and the sample was incubated in a water bath at 37°C for 24 hours. Plasma was separated by centrifugation and stored at -80°C until analysis by LC-MS/ms.

COX activity *in vivo* was determined by quantification of urinary prostanoid metabolites by LC-MS/ms as previously

described.¹⁴ This allows for assessment of the degree of COX inhibition under physiological conditions. Systemic production of prostacyclin, prostaglandin E₂, prostaglandin D₂, and thromboxane A₂ was determined by quantifying their major urinary metabolites: 2,3-dinor 6-keto-PGF_{1α}, 7-hydroxy-5,11-diketotetranorprostan-1,16-dioic acid, 11,15-dioxo-9α-hydroxy-2,3,4,5-tetranorprostan-1,20-dioic acid, and 2,3-dinor thromboxane B₂, respectively. Results were normalized to urinary creatinine measured by LC-MS/ms. Urinary 2,3-dinor thromboxane B₂ was used as an index of COX-1 activity in vivo, and urinary 2,3-dinor 6-keto-PGF_{1α} was used as an index of COX-2 activity in vivo, as previously described.¹⁶

Plasma concentrations of celecoxib and naproxen were quantified by LC-MS/ms as previously described.²⁴

Statistical Analysis

Measurements of COX activity ex vivo and urinary prostaglandin metabolite levels were normalized to the mean value during the placebo phase for each subject to calculate the percent of COX inhibition relative to placebo. The area under the curve from T=0 to T=12 hours was calculated as a measure of the degree of COX inhibition throughout the dosing interval. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation as described by Inker et al.²⁵ The degree of COX inhibition was compared by paired *t* test. The effect of treatment on COX activity and ABP over time was analyzed by linear mixed effect modeling using the lme4 R package,²⁶ including time, treatment, and time×treatment as main effects and participant as a random effect. Time was treated as a continuous variable, and all BP measurements, without averaging, were included in the analysis. The effect of treatment was evaluated by comparing the differences in least-squares (LS) means for each treatment averaged over time. The relationship between change in systolic BP (SBP) and COX inhibition at each time point relative to placebo was evaluated by linear mixed effects modeling including COX inhibition as a main effect and participant as a random effect. *P*<0.05 was considered statistically significant. At an α=0.05 level, a sample size of 16 participants provided >90% power to detect a difference of 25% in the degree of COX inhibition and 3 mmHg in SBP, assuming a coefficient of variation of 100%. Statistical analyses were performed in R (version 4.3.1). Figures were created in BioRender and GraphPad Prism.

RESULTS

The flow of participants is shown in Figure 1. The analysis cohort included 16 healthy adults (9 men and 7 women) with a mean age of 34.7±13.4 years. Baseline demographic and clinical characteristics are shown in the Table. Biochemical measures were evaluated in all participants. One participant was excluded from ABP analysis due to an ABP monitor malfunction and incomplete data.

Naproxen 250 mg twice daily inhibited COX-1 activity and COX-2 activity ex vivo by 95.3±4.4% and 62.9±21.7%, respectively, while celecoxib 100 mg twice daily had minimal effects on COX-1 activity ex vivo and inhibited COX-2 activity ex vivo by 35.7±25.2% over the 12-hour dosing interval (Figure 2). Similar results were

observed for COX-1 and COX-2 activity in vivo, assessed by urinary 2,3-dinor thromboxane B₂ and 2,3-dinor 6-keto-PGF_{1α} concentrations, respectively. COX-1 activity in vivo was inhibited by 68.2±18.7% with naproxen treatment and 8.9±35.7% with celecoxib treatment. COX-2 activity in vivo was inhibited by 48.0±24.9% with naproxen treatment and 26.7±24.6% with celecoxib treatment. With all functional parameters, the degree of COX inhibition was significantly greater with naproxen treatment than with celecoxib treatment (*P*<0.05). The maximum plasma concentration of naproxen was 228.0±45.1 μmol/L, and the time to maximum plasma concentration was 1.8±1.2 hours after administration. For celecoxib, the maximum plasma concentration was 1.28±0.55 μmol/L, and the time to maximum plasma concentration was 2.3±1.2 hours.

During the placebo phase, the average mean arterial pressure (MAP), SBP, and diastolic BP (DBP) were 89.7±8.7, 124.1±11.2, and 73.3±8.7 mmHg, respectively. NSAID treatment affected MAP, SBP, and DBP over the 12-hour dosing interval (Figure 3). Naproxen treatment significantly increased MAP (difference in LS means, 3.1 [95% CI, 2.1–4.1] mmHg; *P*<0.05), SBP (difference in LS means, 2.9 [95% CI, 1.8–4.0] mmHg; *P*<0.05), and DBP (difference in LS means, 3.2 [95% CI, 2.2–4.2] mmHg; *P*<0.05) relative to placebo. In contrast, celecoxib treatment did not affect MAP (difference in LS means, 0.6 [95% CI, −0.3 to 1.6] mmHg; *P*=0.28) but significantly decreased SBP (difference in LS means, −1.1 [95% CI, −2.2 to 0.04] mmHg; *P*<0.05) and increased DBP (difference in LS means, 1.4 [95% CI, 0.4–2.4] mmHg; *P*<0.05) relative to placebo. Compared with celecoxib, naproxen significantly increased MAP (difference in LS means, 2.5 [95% CI, 1.5–3.5] mmHg; *P*<0.05), SBP (difference in LS means, 4.0 [95% CI, 2.9–5.1] mmHg; *P*<0.05), and DBP (difference in LS means, 1.8 [95% CI, 0.8–2.8] mmHg; *P*<0.05). For SBP, a significant time × treatment interaction was observed for naproxen (β, 0.40 [95% CI, 0.16–0.65] mmHg/h; *P*<0.05) but not for celecoxib treatment (β, 0.04 [95% CI, −0.21 to 0.28] mmHg/h; *P*=0.78). No significant time × treatment effects were observed for MAP or DBP.

Mixed effects modeling was performed to determine whether the degree of COX-1 or COX-2 inhibition ex vivo predicted the difference in SBP with NSAID treatment relative to placebo (Figure 4). COX-2 inhibition ex vivo was a predictor of difference in SBP (β, −5.64 [95% CI, −9.36 to −1.92]; *P*=0.003), but COX-1 inhibition ex vivo was not significantly associated with difference in SBP (β, −0.850 [95% CI, −2.99 to 1.30]; *P*=0.43).

DISCUSSION

Given the high prevalence of chronic pain in the United States,⁸ NSAIDs are an important nonaddictive option for pain relief.² Currently, it is recommended that NSAIDs be avoided or used only for a limited duration at the

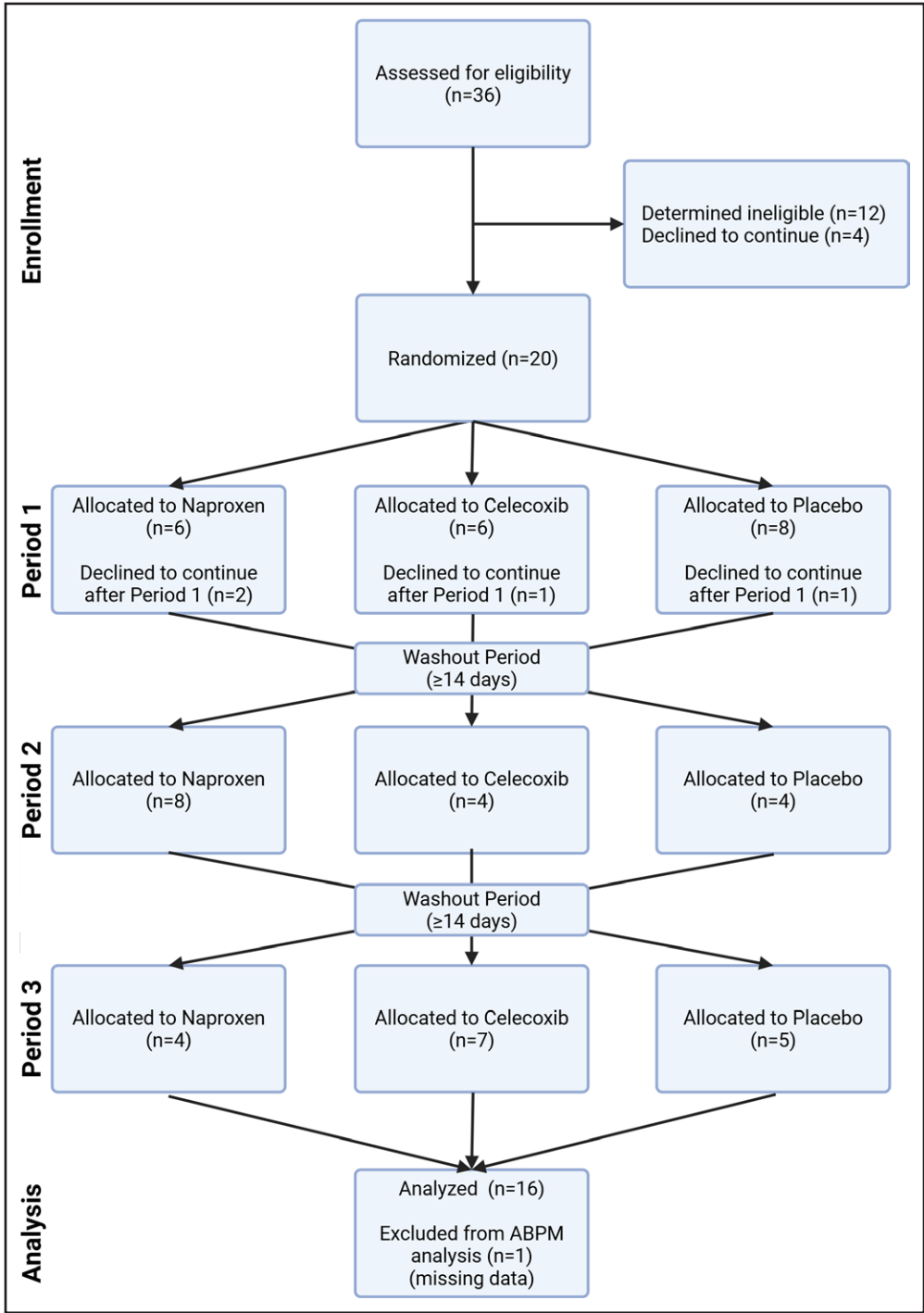


Figure 1. CONSORT diagram showing flow of participants through each stage of the randomized crossover study. ABPM indicates ambulatory blood pressure monitoring.

lowest possible dose in patients considered at high cardiovascular risk.²⁷ As COX-2 inhibition mechanistically underlies the cardiovascular risk, a key question remains whether differences in the cardiovascular safety profile exist between traditional NSAIDs (ie, naproxen), which inhibit both COX-1 and COX-2, and selective inhibitors of COX-2 (ie, celecoxib).²⁸ The largest comparator trial to address this question, PRECISION, indicated that

celecoxib is noninferior to naproxen and ibuprofen with regard to cardiovascular risk.¹⁷ Importantly, the dose of celecoxib was limited to 200 mg/d (100 mg twice per day) in osteoarthritis patients enrolled in PRECISION, which made up the vast majority of the study population, while a dose up to 400 mg/d (200 mg twice per day) was allowed in patients with rheumatoid arthritis. Limiting the dose in patients with osteoarthritis had been a regulatory

Table. Baseline Characteristics of Study Participants

Characteristic	Study cohort
N (men/women)	16 (9/7)
Age, y	34.7±13.4 (range, 19–61)
Race	
White	9
Black	4
Asian	1
Other	2
Ethnicity	
Non-Hispanic	13
Hispanic	3
Body mass index, kg/m ²	22.6±1.9
Laboratory values	
Total cholesterol, mg/dL	166.9±27.6
Triglycerides, mg/dL	70.9±24.4
LDL, mg/dL	94.7±22.9
HDL, mg/dL	58.1±13.3
Serum creatinine, mg/dL	0.83±0.14
Blood urea nitrogen, mg/dL	13.3±5.3
eGFR, mL/min per 1.73 m ²	110.4±15.9
Systolic blood pressure, mmHg	115.3±8.9
Diastolic blood pressure, mmHg	69.8±9.5
Heart rate, bpm	65.7±9.8

eGFR indicates estimated glomerular filtration rate.

response to the cardiovascular hazard detected in previous randomized controlled trials. Overall, this dosing regimen resulted in an average daily dose of 209±37 mg across all patients in the celecoxib arm.¹⁷ In patients randomized to naproxen treatment in PRECISION, the starting dose was 750 mg/d (375 mg twice per day) with the option to increase to 1000 mg/d (500 mg twice per day) in patients with rheumatoid arthritis, resulting in an average dose of 852±103 mg in the naproxen arm.¹⁷ Although the pharmacological potency of celecoxib measured with isolated COX-2 enzyme or cellular preparations in vitro is higher than that of naproxen,²⁹ here, we demonstrate that 200 mg/d of celecoxib (approximately the average daily dose used in the PRECISION trial) inhibited COX-2 activity in vivo to a lesser degree than 500 mg/d of naproxen (a dose that was 33% lower than the average daily dose used in PRECISION), and this impacted the BP response to NSAID treatment. Our results underscore the importance of considering dose and pharmacoequivalence in vivo in comparisons of safety among drugs of the same class.

Only a small number of clinical trials have prospectively assessed the effects of COX inhibition on BP control. Based on these studies, acute increases of 3 to 5 mmHg in SBP can be expected within 1 to 2 weeks of treatment.^{16,30,31} In our cohort, naproxen treatment for 1 week increased SBP relative to placebo (2.9 [95% CI, 1.8–4.0]

mmHg) to a greater extent than celecoxib treatment (−1.1 [95% CI, −2.2 to −0.04] mmHg) over the final 12-hour dosing interval. This difference is similar to what was observed in PRECISION-ABPM, where the change in SBP from baseline after 4 months of treatment was 1.91±9.796 mmHg among naproxen-treated patients and −0.18±9.400 mmHg among celecoxib-treated patients.¹⁹ We also observed a significant time×treatment effect on SBP for naproxen, but not celecoxib, treatment, which may reflect the longer half-life and duration of COX inhibition with naproxen in addition to differences in potency in vivo. Notably, we observed that the difference in SBP was associated with the degree of COX-2 inhibition on NSAID treatment, consistent with the inhibition of COX-2-mediated prostacyclin formation as the primary mechanism underlying the increased cardiovascular risk associated with NSAID use.

Although naproxen increased SBP to a greater extent than celecoxib in our study cohort, the BP response to NSAID treatment was heterogeneous among individual patients. The effects of COX inhibition on BP control are complex, which may contribute to the variable occurrence of hypertension on NSAIDs.^{10,15,16,32} In the renal cortex, the production of vasodilatory prostaglandin E₂ and prostacyclin maintains the patency of adjacent afferent arterioles,^{16,33} and COX-2 expression in renal medullary interstitial cells plays an important role in the adaptive regulation of BP in response to high-salt diet and dehydration.^{34–36} COX inhibition in these regions of the kidney contributes to the decline in glomerular filtration rate and elevations in BP observed in patients who take NSAIDs. However, dynamic expression of COX-2 in the macula densa system is a component of the tubuloglomerular feedback mechanism, which promotes renin release.^{37–39} Inhibition of COX-2 in these cells would counteract the hypertensive effects of renin-angiotensin system activation. Thus, the effect of NSAID treatment on BP reflects the complex interplay among these regulatory systems. Interestingly, we observed that an individual participant's response was similar to both drugs, suggesting that patient-specific factors may contribute to interindividual heterogeneity in the response to NSAIDs. Future studies are necessary to elucidate the factors that contribute to an individual patient's risk of hypertension and other cardiovascular adverse effects with NSAID treatment.

There are limitations to our study. The small sample size limits our ability to comprehensively investigate the factors that contribute to the BP response to NSAIDs. The study cohort included only healthy adults, most of whom were relatively young. Although this limits potential confounding due to effects of age and comorbidities, it precludes interrogation of the influence of these factors on the BP response to NSAID treatment. Prior studies have demonstrated that older individuals (age>65 years) and patients

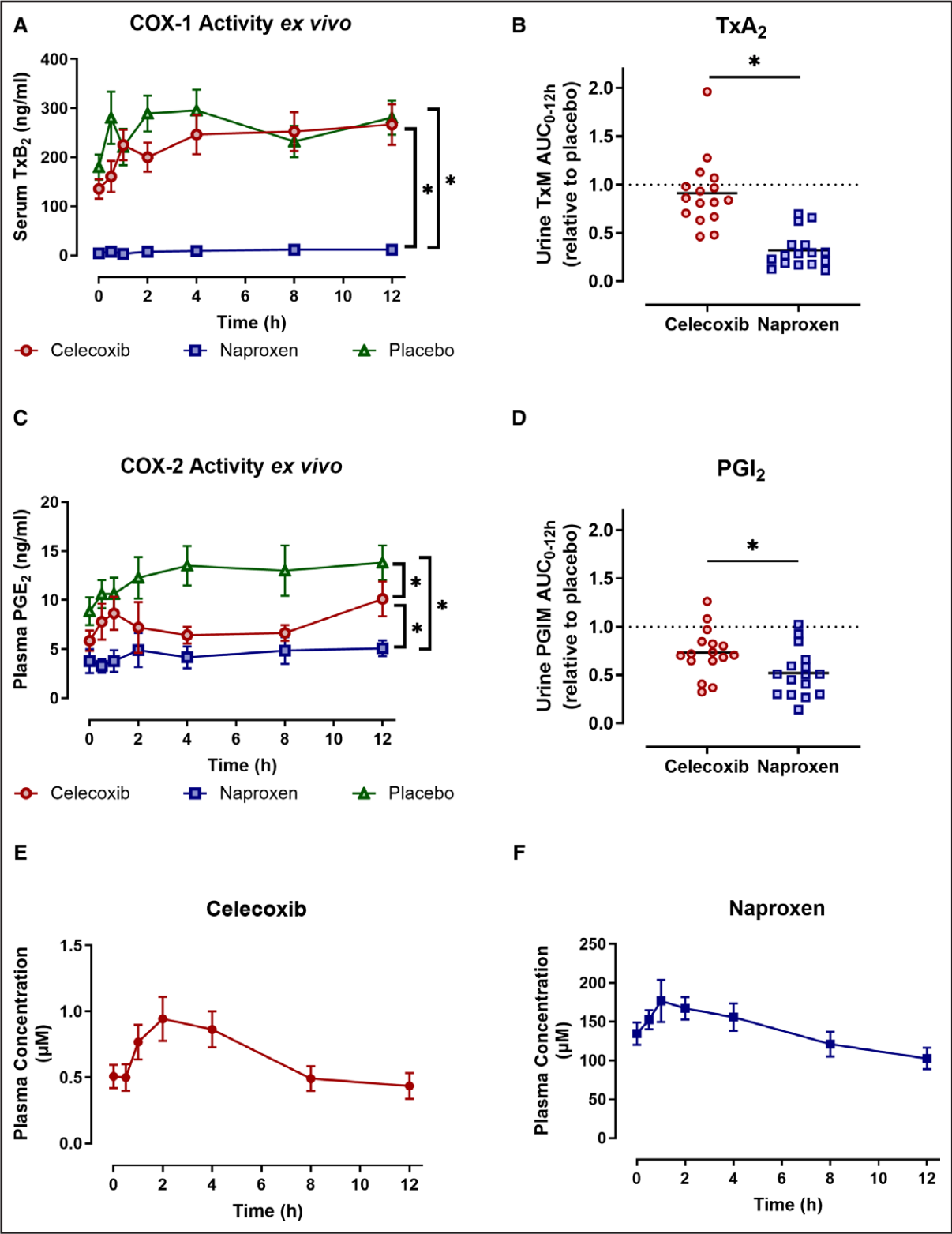


Figure 2. XXX. Comparison of (A) COX (cyclooxygenase)-1 inhibition ex vivo and (B) in vivo, and (C) COX-2 inhibition ex vivo, and (D) in vivo by treatment. Plasma concentrations of (E) celecoxib and (F) naproxen over time. Dosing occurred at 8:00 AM±15 minutes. Data are shown as mean±SEM. *P<0.05.

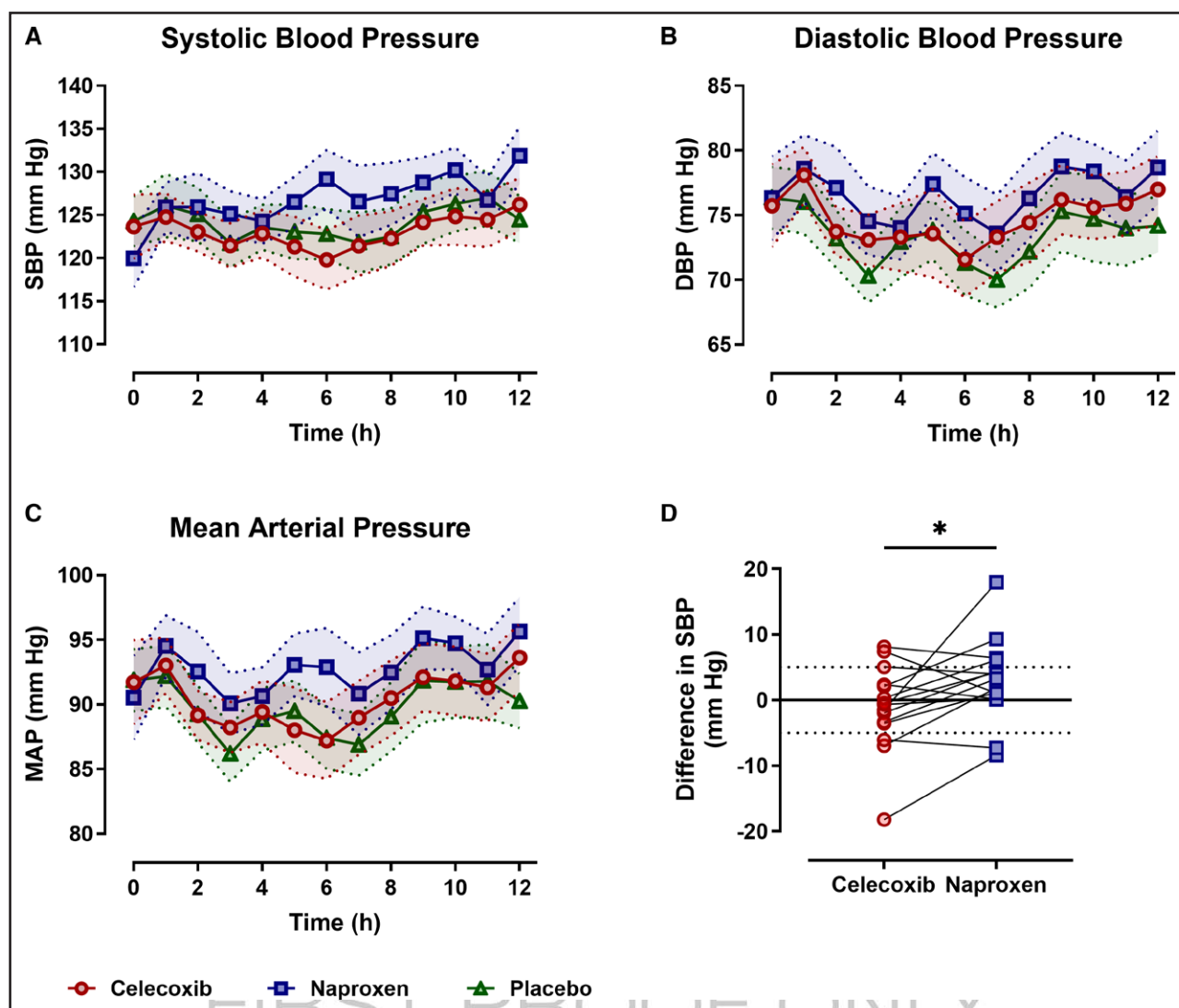


Figure 3. XXX.

Comparison of (A) systolic blood pressure (SBP), (B) diastolic blood pressure (DBP), and (C) mean arterial pressure (MAP) over a 12-hour dosing interval by treatment. Data are shown as mean \pm SEM. D, Change in SBP relative to placebo with celecoxib and naproxen treatment. Dosing occurred at 8:00 AM \pm 15 minutes. * $P < 0.05$.

with hypertension have greater elevations in BP with NSAID treatment.⁴⁰ NSAIDs also can decrease the efficacy of antihypertensive drugs and given the role of renal COX-2 in the activation of the renin-angiotensin-aldosterone system,^{37–39,41,42} perhaps particularly for renin-angiotensin-aldosterone system inhibitors. Thus, we would hypothesize that the degree of BP elevation would be greater in patients with these cardiovascular risk factors. Although quantification of urinary prostanoid metabolites provides a measurement of the degree of COX inhibition systemically in vivo, we are unable to determine the tissue source of these metabolites. This study observed acute changes in BP following 7 days of treatment and linked them to COX-2 inhibition. Different mechanisms may contribute to more steady BP increases over time, observed in long-duration clinical trials.⁴³ Finally, we compared

only 1 dose level of naproxen and celecoxib, which limits our ability to extrapolate our results to higher doses or other NSAIDs. Despite these limitations, our results provide mechanistic insight into the outcome of PRECISION.

In conclusion, our results demonstrate that naproxen 500 mg/d inhibits COX-2 activity to a greater degree than celecoxib 200 mg/d, and the degree of COX-2 inhibition is associated with the BP response to NSAID treatment. While PRECISION concluded noninferiority of celecoxib compared with naproxen with regard to cardiovascular risk, this is based on a comparison of doses that are not equipotent. Future studies should consider the pharmacokinetic and pharmacodynamic properties of the drugs, as well as patient-specific risk factors when seeking to compare the cardiovascular risk associated with the use of specific NSAIDs.

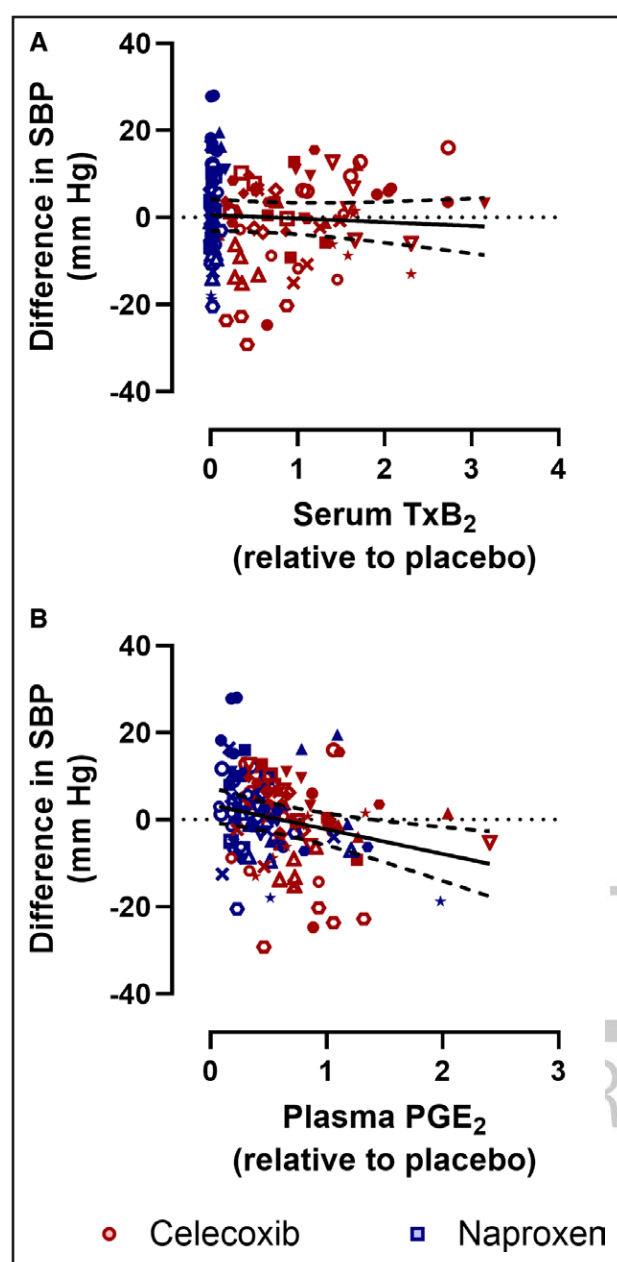


Figure 4. Relationship between degree of COX (cyclooxygenase)-1 and COX-2 inhibition ex vivo and change in systolic blood pressure (SBP) relative to placebo at each time point for naproxen (blue) and celecoxib (red). Repeated measurements in the same participant are indicated by the same symbol. PGE₂ indicates prostaglandin E₂.

PERSPECTIVES

1. Naproxen 250 mg twice a day inhibited COX-2 activity to a greater degree than celecoxib 100 mg twice a day.
2. The degree of COX-2 inhibition was associated with the increase in systolic BP with NSAID treatment relative to placebo.
3. Dose and its pharmacological potency achieved in vivo should be considered when evaluating the

relative cardiovascular safety of COX-2-selective versus nonselective NSAIDs.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. National Academies of Sciences Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse. Pain management and the opioid epidemic: balancing societal and individual benefits and risks of prescription opioid use. In: Phillips JK, Ford MA, Bonnie RJ, eds. *Pain Management and the Intersection of Pain and Opioid Use Disorder*. National Academies Press (US); 2017.
2. Grosser T, Woolf CJ, FitzGerald GA. Time for nonaddictive relief of pain. *Science*. 2017;355:1026–1027. doi: 10.1126/science.aan0088
3. Stagnitti MN. Trends in outpatient prescription analgesics utilization and expenditures for the U.S. civilian noninstitutionalized population, 1996 and 2006. Statistical brief #235. *Medical Expenditure Panel Survey*. Agency for Healthcare Research and Quality; 2009.
4. Zhou Y, Boudreau DM, Freedman AN. Trends in the use of aspirin and non-steroidal anti-inflammatory drugs in the general U.S. population. *Pharmacoepidemiol Drug Saf*. 2014;23:43–50. doi: 10.1002/pds.3463
5. Gorski T, Cadore EL, Pinto SS, da Silva EM, Correa CS, Beltrami FG, Kruei LF. Use of NSAIDs in triathletes: prevalence, level of awareness and reasons for use. *Br J Sports Med*. 2011;45:85–90. doi: 10.1136/bjsm.2009.062166
6. Kuster M, Renner B, Oppel P, Niederweis U, Brune K. Consumption of analgesics before a marathon and the incidence of cardiovascular, gastrointestinal and renal problems: a cohort study. *BMJ Open*. 2013;3:e002090. doi: 10.1136/bmjopen-2012-002090
7. Walker LA, Zambraski EJ, Williams RF. Widespread use of prescription non-steroidal anti-inflammatory drugs among U.S. Army active duty soldiers. *Mil Med*. 2017;182:e1709–e1712. doi: 10.7205/MILMED-D-16-00183
8. Institute of Medicine (U.S.). Committee on advancing pain research care and education. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. 2011. doi: 10.17226/13172
9. Keshwani S, Smith SM, Brown J, Lo-Ciganic WH, Yang S, Smolinski NE, Hincapie-Castillo JM. Trends in prescribing of non-steroidal anti-inflammatory medications in the US ambulatory care setting from 2006 to 2016. *J Pain*. 2023;24:1994–2002. doi: 10.1016/j.jpain.2023.06.008
10. Grosser T, Yu Y, FitzGerald GA. Emotion recollected in tranquillity: lessons learned from the COX-2 saga. *Annu Rev Med*. 2010;61:17–33. doi: 10.1146/annurev-med-011209-153129

11. Krum H, Swergold G, Gamaitoni A, Peloso PM, Smugar SS, Curtis SP, Brater DC, Wang H, Kaur A, Laine L, et al. Blood pressure and cardiovascular outcomes in patients taking nonsteroidal antiinflammatory drugs. *Cardiovasc Ther*. 2012;30:342–350. doi: 10.1111/j.1755-5922.2011.00283.x
12. Smyth EM, Grosser T, Wang M, Yu Y, FitzGerald GA. Prostanoids in health and disease. *J Lipid Res*. 2009;50(Suppl):S423–S428. doi: 10.1194/jlr.R800094-JLR200
13. Cheng Y, Austin SC, Rocca B, Koller BH, Coffman TM, Grosser T, Lawson JA, FitzGerald GA. Role of prostacyclin in the cardiovascular response to thromboxane A_2 . *Science*. 2002;296:539–541. doi: 10.1126/science.1068711
14. Yu Y, Ricciotti E, Scalia R, Tang SY, Grant G, Yu Z, Landesberg G, Crichton I, Wu W, Pure E, et al. Vascular COX-2 modulates blood pressure and thrombosis in mice. *Sci Transl Med*. 2012;4:132ra154. doi: 10.1126/scitranslmed.3003787
15. Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. *J Clin Invest*. 2006;116:4–15. doi: 10.1172/JCI27291
16. Catella-Lawson F, McAdam B, Morrison BW, Kapoor S, Kujubu D, Antes L, Lasseter KC, Qian H, Gertz BJ, FitzGerald GA. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. *J Pharmacol Exp Ther*. 1999;289:735–741.
17. Nissen SE, Yeomans ND, Solomon DH, Luscher TF, Libby P, Husni ME, Graham DY, Borer JS, Wisniewski LM, Wolski KE, et al; PRECISION Trial Investigators. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med*. 2016;375:2519–2529. doi: 10.1056/NEJMoa1611593
18. Obeid S, Libby P, Husni E, Wang Q, Wisniewski LM, Davey DA, Wolski KE, Xia F, Bao W, Walker C, et al. Cardiorenal risk of celecoxib compared with naproxen or ibuprofen in arthritis patients: insights from the PRECISION trial. *Eur Heart J Cardiovasc Pharmacother*. 2022;8:611–621. doi: 10.1093/ehjcvp/pvab015
19. Ruschitzka F, Borer JS, Krum H, Flammer AJ, Yeomans ND, Libby P, Luscher TF, Solomon DH, Husni ME, Graham DY, et al. Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement) Trial. *Eur Heart J*. 2017;38:3282–3292. doi: 10.1093/eurheartj/ehx508
20. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377–381. doi: 10.1016/j.jbi.2008.08.010
21. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J, et al; REDCap Consortium. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208. doi: 10.1016/j.jbi.2019.103208
22. Patrignani P, Filabozzi P, Patrono C. Selective cumulative inhibition of platelet thromboxane production by low-dose aspirin in healthy subjects. *J Clin Invest*. 1982;69:1366–1372. doi: 10.1172/jci110576
23. Panara MR, Renda G, Sciuilli MG, Santini G, Di Giamberardino M, Rotondo MT, Tacconelli S, Seta F, Patrono C, Patrignani P. Dose-dependent inhibition of platelet cyclooxygenase-1 and monocyte cyclooxygenase-2 by meloxicam in healthy subjects. *J Pharmacol Exp Ther*. 1999;290:276–280.
24. Li X, Fries S, Li R, Lawson JA, Probert KJ, Diamond SL, Blair IA, FitzGerald GA, Grosser T. Differential impairment of aspirin-dependent platelet cyclooxygenase acetylation by nonsteroidal antiinflammatory drugs. *Proc Natl Acad Sci USA*. 2014;111:16830–16835. doi: 10.1073/pnas.1406997111
25. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, Crews DC, Doria A, Estrella MM, Froissart M, et al; Chronic Kidney Disease Epidemiology Collaboration. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med*. 2021;385:1737–1749. doi: 10.1056/NEJMoa2102953
26. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw*. 2015;67:1–48.
27. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA; American Heart Association. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. *Circulation*. 2007;115:1634–1642. doi: 10.1161/CIRCULATIONAHA.106.181424
28. Grosser T, Ricciotti E, FitzGerald GA. The cardiovascular pharmacology of nonsteroidal anti-inflammatory drugs. *Trends Pharmacol Sci*. 2017;38:733–748. doi: 10.1016/j.tips.2017.05.008
29. Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc Natl Acad Sci USA*. 1999;96:7563–7568. doi: 10.1073/pnas.96.13.7563
30. Whelton A, Fort JG, Puma JA, Normandin D, Bello AE, Verburg KM; SUCCESS VI Study Group. Cyclooxygenase-2-specific inhibitors and cardio-renal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. *Am J Ther*. 2001;8:85–95. doi: 10.1097/00045391-200103000-00003
31. Whelton A, White WB, Bello AE, Puma JA, Fort JG; SUCCESS-VII Investigators. Effects of celecoxib and rofecoxib on blood pressure and edema in patients ≥ 65 years of age with systemic hypertension and osteoarthritis. *Am J Cardiol*. 2002;90:959–963. doi: 10.1016/s0002-9149(02)02661-9
32. Snowden S, Nelson R. The effects of nonsteroidal anti-inflammatory drugs on blood pressure in hypertensive patients. *Cardiol Rev*. 2011;19:184–191. doi: 10.1097/CRD.0b013e31821ddc4
33. Terragno NA, Terragno DA, McGiff JC. Contribution of prostaglandins to the renal circulation in conscious, anesthetized, and laparotomized dogs. *Circ Res*. 1977;40:590–595. doi: 10.1161/01.res.40.6.590
34. Perazella MA, Tray K. Selective cyclooxygenase-2 inhibitors: a pattern of nephrotoxicity similar to traditional nonsteroidal anti-inflammatory drugs. *Am J Med*. 2001;111:64–67. doi: 10.1016/s0002-9343(01)00757-4
35. Qi Z, Hao CM, Langenbach RI, Breyer RM, Redha R, Morrow JD, Breyer MD. Opposite effects of cyclooxygenase-1 and -2 activity on the pressor response to angiotensin II. *J Clin Invest*. 2002;110:61–69. doi: 10.1172/JCI14752
36. Zewde T, Mattson DL. Inhibition of cyclooxygenase-2 in the rat renal medulla leads to sodium-sensitive hypertension. *Hypertension*. 2004;44:424–428. doi: 10.1161/01.HYP.0000140924.91479.03
37. FitzGerald GA, Hossmann V, Hummerich W, Konrads A. The renin-kallikrein-prostaglandin system: plasma active and inactive renin and urinary kallikrein during prostacyclin infusion in man. *Prostaglandins Med*. 1980;5:445–456. doi: 10.1016/0161-4630(80)90068-3
38. Petri-Peterdi J, Komlosi P, Fuson AL, Guan Y, Schneider A, Qi Z, Redha R, Rosivall L, Breyer MD, Bell PD. Luminal NaCl delivery regulates basolateral PGE₂ release from macula densa cells. *J Clin Invest*. 2003;112:76–82. doi: 10.1172/JCI18018
39. Stichtenoth DO, Marhauer V, Tsikas D, Gutzki FM, Frolich JC. Effects of specific COX-2-inhibition on renin release and renal and systemic prostanoid synthesis in healthy volunteers. *Kidney Int*. 2005;68:2197–2207. doi: 10.1111/j.1523-1755.2005.00676.x
40. Krum H, Swergold G, Curtis SP, Kaur A, Wang H, Smugar SS, Weir MR, Laine L, Brater DC, Cannon CP. Factors associated with blood pressure changes in patients receiving diclofenac or etoricoxib: results from the MEDAL study. *J Hypertens*. 2009;27:886–893. doi: 10.1097/HJH.0b013e328325d831
41. Xu C, Yang G, Fu Z, Chen Y, Xie S, Wang F, Yang T. Na⁺-retaining action of COX-2 (cyclooxygenase-2)/EP₁ pathway in the collecting duct via activation of intrarenal renin-angiotensin-aldosterone system and epithelial sodium channel. *Hypertension*. 2022;79:1190–1202. doi: 10.1161/HYPERTENSIONAHA.121.17245
42. Yang T, Endo Y, Huang YG, Smart A, Briggs JP, Schnermann J. Renin expression in COX-2-knockout mice on normal or low-salt diets. *Am J Physiol Renal Physiol*. 2000;279:F819–F825. doi: 10.1152/ajprenal.2000.279.5.F819
43. Becker MC, Wang TH, Wisniewski L, Wolski K, Libby P, Luscher TF, Borer JS, Mascette AM, Husni ME, Solomon DH, et al; PRECISION Investigators. Rationale, design, and governance of Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen (PRECISION), a cardiovascular end point trial of nonsteroidal antiinflammatory agents in patients with arthritis. *Am Heart J*. 2009;157:606–612. doi: 10.1016/j.ahj.2008.12.014