CLINICAL INVESTIGATION

Emerging therapies in the management of hypertensive patients with osteoarthritis

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Osteoarthritis (OA) constitutes one of the leading causes of pain and disability worldwide. The incidence of OA will likely rise over the next few decades, with a significant impact on healthcare costs. Patients with OA are often affected by a number of cardiovascular comorbidities, including hypertension, which is present in approximately 40% of cases. Cyclooxygenase (COX) inhibitors, both nonselective and selective COX-2 inhibitors, are often used to control pain in these patients. Unfortunately, such drugs may cause a variable degree of blood pressure increase. Because even small increases in blood pressure values may lead to a significant increase in the risk of major cardiovascular events and death, the consequent healthcare concerns have led to the development of the COX-inhibiting nitric oxide donator class of drugs. These new drugs are aimed to improve cardiovascular and gastrointestinal safety profiles, as compared with nonsteroidal anti-inflammatory drugs, through the release of nitric oxide.

Keywords: cardiovascular disease • cyclooxygenase inhibitor • hypertension • nitric oxide donor • osteoarthritis

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Osteoarthritis (OA) is a degenerative joint disease characterized by articular chondrocyte maturation, extracellular matrix degradation, articular cartilage loss and osteophyte formation. OA represents the most common musculoskeletal disease of adults worldwide, as well as the most frequent cause of pain [1]. In addition, OA is second only to ischemic heart disease as a cause of work disability in men aged 50 years and older and accounts for up to 3% of total years of living with disability, making it the eighth leading nonfatal burden of disease worldwide [2], as underscored by disability-adjusted life years (Figure 1). Reported incidence and prevalence rates of OA in specific joints vary widely, due to differences in the case definition of OA [3]. OA may be defined by radiographic criteria alone (radiographic OA), typical symptoms (symptomatic OA), or both. Using radiographic criteria, the distal and proximal interphalangeal joints of the hand have been identified as the joints most commonly affected by OA, but they are the least likely to be symptomatic [4]. By contrast, the knee and hip, which constitute the second and third most common locations of radiographic OA, respectively, are nearly always symptomatic [5]. Prevalence rates for both radiographic OA and, to a lesser extent, symptomatic OA increase with age, and by the age of 65 years it is estimated that approximately 80% of the US population will be affected [6]. Besides age, a number of endogenous (e.g., sex, hereditary, ethnicity) and exogenous (e.g., overweight, macrotrauma, repetitive microtrauma, lifestyle) risk factors are involved in the development of OA, particularly at the level of hand, knee and hip [7,8]. In view of the progressive aging of the population and the growing burden of obesity, the incidence of OA will likely rise over the next few decades. This may result in inflating healthcare costs, since a US community-based analysis of all health services used and charges incurred over a 1-year period estimated that the direct medical costs and charges of patients with OA (US$2654.51 and 663.55/year, respectively) are twice as much as that of patients

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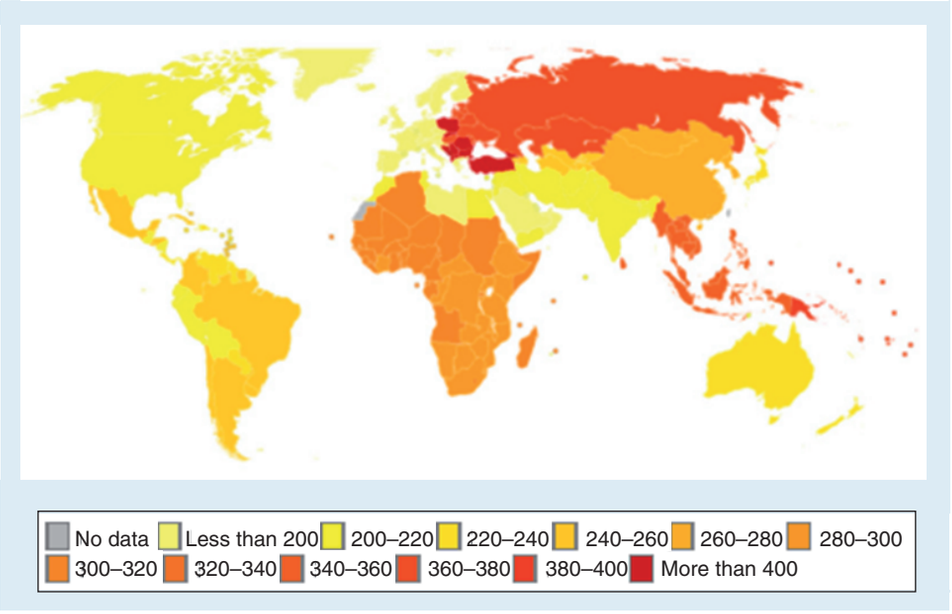

Figure 1. Osteoarthritis world map. Age-standardized disability-adjusted life year rates from osteoarthritis by country (per 100,000 inhabitants).
Data from World Health Organization 2004.

without OA [9]. In addition, a Dutch study estimated that direct and indirect costs attributable to OA in an active population are substantial, with productivity-related costs being predominant [10].

As shown by the Third National Health and Nutrition Examination Survey (NHANES III), OA and hypertension frequently coexist in the same patient. As derived from the Household Adult Questionnaire, OA was present in approximately 21% of the 115.9 million US adults aged 35 years or more, while a concomitant diagnosis of hypertension was present in 40% of these subjects [11].

As reported by NHANES III (Figure 2) [11], other cardiovascular (CV) risk factors including diabetes, hypercholesterolemia and renal impairment are more frequent in patients with OA than in people without OA. The potential impact of this cluster of CV risk factors on overall CV risk and the associated costs of treatment in relation with a given rise in systolic blood pressure (SBP) were estimated using patient-level data from NHANES III of patients with OA and the Framingham equations for risk calculation [12]. Increases in SBP of only 1–5 mmHg are associated with 7100–35,700 additional coronary artery disease and stroke events per year in the USA, with associated costs of US$114–569 million [12]. Therefore, in cases where two different drugs for OA with similar anti-inflammatory efficacy but a different effect on SBP are available, considerations of incremental CV risk may become relevant [12].

Adverse BP effects of the nonsteroidal anti-inflammatory drugs

Cyclooxygenase (COX) is a rate-limiting enzyme that is responsible for the synthesis of prostanoids, through the conversion of arachidonic acid to the labile intermediate PGH2, which is in turn converted into thromboxane A_2 (TxA_2) by thromboxane synthase, prostacyclin (PGI_2) by prostacyclin synthase and into other prostaglandins including PGE_2 and PGD_2 by different isomerases. The COX enzymes are involved in a number of physiological processes and human diseases. The COX-1 isoform is constitutively expressed in most tissues, including the vascular endothelium, brain, spinal cord, kidney and gastroenteric epithelium, as well as in mature platelets. The COX-2 isoform is expressed in atherosclerotic plaques, during angiogenesis and wound healing, in the macula densa and in the renal medullary interstitium [13–15]. The substrate-binding channel of COX-2 contains a side pocket that is absent in COX-1, which has allowed the development of COX inhibitors with side chains that fit within the COX-2 channel but that are too large to block COX-1 with an equivalent affinity. As a consequence, the 'selectivity' of a COX-inhibitor is usually defined by its ratio of affinities to COX-1 and -2. Metabolism of prostaglandins is markedly altered by COX inhibition, which is obtained with two separate classes of drugs, namely, nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors.

■ Studies in healthy & hypertensive subjects

There is general consensus that, in doses that are adequate to reduce inflammation and pain, NSAIDs are a potential cause of BP elevation and/or deterioration of previously achieved BP control [16], in both normotensive and hypertensive individuals [17]. In the latter group, NSAIDs may attenuate the BP-lowering effect of several antihypertensive agents, probably with the only exception of calcium-channel blockers [18–20].

The average rise in SPB and diastolic blood pressure (DBP) is approximately 2 or 3 mmHg, but it may vary considerably [21]. Normotensive and otherwise healthy subjects who require a short course of NSAIDs usually show only a minor and transient rise in BP [22].

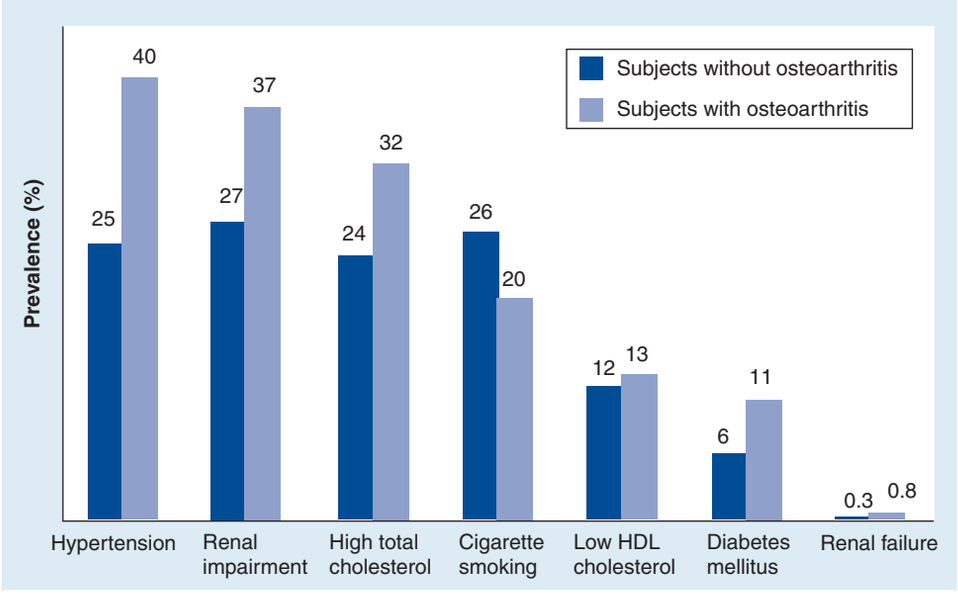

Figure 2. Prevalence of cardiovascular risk factors in subjects with and without osteoarthritis. Renal impairment is defined by the presence of serum creatinine levels over 1.5 mg/dl, while renal failure is defined by serum creatinine levels ≥3.0 mg/dl. Data taken from [11].

In a Medicare elderly population (average age: 79 years), new-onset hypertension affected approximately 22% of subjects not treated with NSAIDs or COX-2 inhibitors, as compared with 21 and 23% in subjects treated with celecoxib or NSAIDs, respectively. On the other hand, the rate of new-onset hypertension rose significantly to 27% among patients treated with rofecoxib [23]. There did not appear to be a clear dose or duration relationship between either COX-2-specific inhibitor and new-onset hypertension. There was no difference in relative risk between low- and high-dose celecoxib or rofecoxib compared with the low- and high-dosage reference groups, or between short- (≤30 days) and long-duration (>30 days) use of celecoxib and the respective reference groups. Long-duration rofecoxib was associated with a slightly higher risk (OR:1.5; 95% CI: 1.0–2.1) than short-duration rofecoxib (OR: 1.1; 95% CI: 0.7–2.0), as compared with nonspecific NSAIDs. Similar trends were seen when rofecoxib use of long duration (OR: 1.6; 95% CI: 1.1–2.2) and short duration (OR: 1.3; 95% CI: 0.8–2.3) were compared with celecoxib. Subjects with concomitant kidney disease or congestive heart failure showed a systematically higher risk of new-onset hypertension [23].

The Nurses Health Study I, in which more than 51,000 nurses were followed for 8 years, showed a gradual increase in the relative risk of developing hypertension with the number of days per month of treatment with conventional NSAIDs (from 11% for 1–4 days per month of treatment up to 52% for ≥22 days/month of treatment, as compared with no treatment with NSAIDs) [24], a finding confirmed by the Nurses Health Study II, in which more than 80,000 nurses were followed for 2 years [25]. Higher average daily doses of NSAIDs were also able to increase the risk of new hypertension, as shown by a pooled analysis of both the Nurses Health studies (Figure 3) [26]. The latter also removed the potential objection that headache may have confounded the relation between NSAID use and BP increase, thanks to secondary analyses restricting the study populations to those women who did not report headache as an indication for analgesic use [26].

Hypertensive subjects with long-term exposure to NSAIDs may experience a greater, although variable, degree of BP elevation, as compared with healthy normotensive subjects. Increases up to 10.3/6.6 mmHg (SBP/DBP) [19] or up to 12/5 mmHg [20] have been reported in individual studies.

Pope *et al.* performed a meta-analysis of 1324 subjects, mostly hypertensives (92%), for a total of 54 studies [27]. Mean BP increased by 3.3 mmHg in the hypertensive subjects treated with NSAIDs, as compared with 1.1 mmHg in the normotensive patients. In hypertensives, mean BP raised by 2.9 mmHg with piroxicam, 4.8 mmHg with indomethacin and 6.1 mmHg with naproxen. However, this meta-analysis excluded the subjects more prone to develop a BP increase with NSAIDs, for example, the elderly and patients with congestive heart failure or renal failure [27]. An additional limitation is the relatively small number of subjects included in the reviewed studies.

In another meta-analysis of 66 trials enrolling 771 relatively young subjects (mean age: 47.6 years), NSAIDs increased BP values of approximately 5.0 mmHg [28]. Piroxicam, indomethacin and ibuprofen caused the greater rise in BP. Remarkably, the antihypertensive effects of beta-blockers was blunted to a greater extent than that of vasodilators and diuretics by NSAIDs [28].

■ Evidence from comparative clinical trials & meta-analysis

The impact on BP of different COX-2 inhibitors, as compared with traditional NSAIDs, has been evaluated by a number of controlled trials. One of those studies is the Celecoxib Rofecoxib Efficacy and Safety in Comorbidities Evaluation (CRESCENT) study that

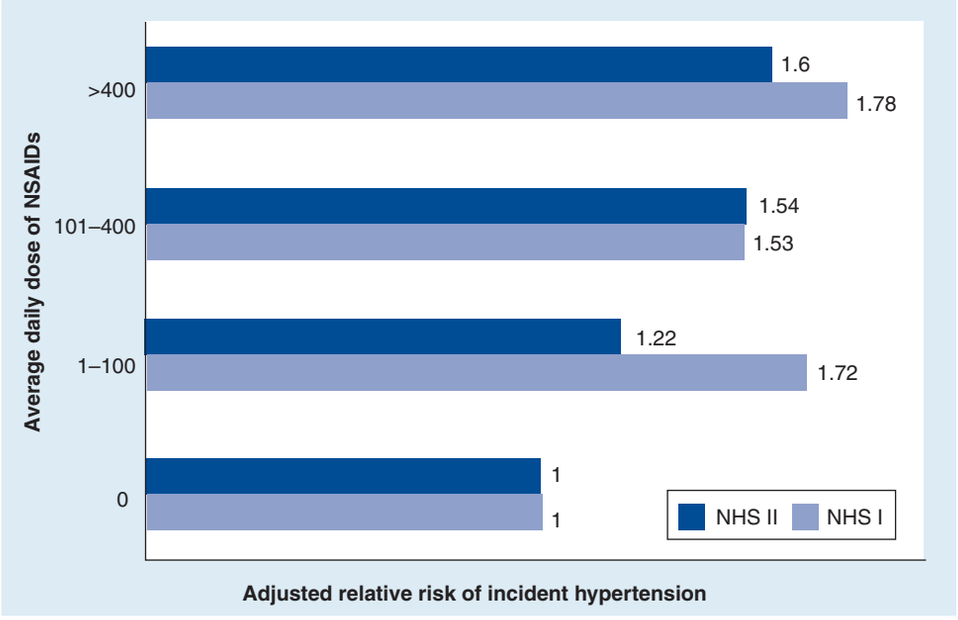

Figure 3. Adjusted relative risk of incident hypertension with increasing average daily dose of traditional non-steroidal anti-inflammatory drugs in the two Nurses Health studies [26].

was carried out in 404 hypertensive diabetics with concomitant OA, randomized to celecoxib 200 mg once daily, rofecoxib 25 mg once daily or naproxen 500 mg twice daily. 24-h ambulatory BP was performed at entry and after 6 and 12 weeks of treatment. The three drugs were equally effective in reducing OA symptoms. Rofecoxib, but not celecoxib and naproxen, induced a significant increase in 24-h SBP. Furthermore, all treatments deteriorated BP control, although such an effect was more pronounced with rofecoxib [29].

In a comparative study between celecoxib and rofecoxib involving over 1000 subjects with hypertension and OA concomitantly treated with fixed doses of antihypertensive drugs, significantly more patients in the rofecoxib group compared with the celecoxib group developed increased SBP (change >20 mmHg plus absolute value ≥140 mmHg) at any time point (14.9 vs 6.9%; $p < 0.01$), in patients treated with angiotensin-converting enzyme inhibitors (ACEIs) and beta-blockers, whereas those on calcium-channel antagonists or diuretic monotherapy receiving either celecoxib or rofecoxib showed no significant increases in BP [30].

In a recent meta-analysis, Chan *et al.* investigated all published COX-2 inhibitor trials, including patients with comorbidities other than arthritis, to ascertain BP response to COX-2 inhibitors and how they may differ from placebo and nonselective NSAIDs [31]. A total of 130,405 individuals from 51 trials were included. The large majority of these patients (113,027; 87%) were affected by OA. In the arthritis studies, the relative risk (RR) of developing hypertension associated with COX-2 inhibitors compared with placebo and nonselective NSAIDs were 1.47 (95% CI: 1.07–2.02; $p < 0.05$) and 1.53 (95% CI: 1.31–1.78; $p < 0.01$), respectively [31]. However, a major limitation of this meta-analysis was that BP was often not a prespecified end point, and hypertension was not clearly defined in many of the included studies.

BP increase & the risk of cardiovascular disease in patients treated with NSAIDs

There is general consensus on the existence of a direct, continuous and graded relationship between BP levels, beginning from values as low as 115/75 mmHg, and the risk of CV disease, which appears highly consistent across different age groups. This has been demonstrated by Lewington *et al.* in a meta-analysis involving approximately 1 million individuals enrolled in 61 observational studies [32]. Two limitations of this meta-analysis were the inclusion of generally uncomplicated subjects without prior CV disease, and the single BP measurement for each individual patient [32].

Meta-regression analyses of intervention studies conducted in patients with increased CV risk or high BP demonstrated a clear association between the degree of BP reduction and the size of the outcome benefit [33]. For example, a 5 mmHg reduction in BP was associated with a 25% lower risk of major CV events [34]. Interestingly, the beneficial outcome associated with BP reduction appeared to occur quite rapidly. This was also underscored by the Valsartan Antihypertensive Long-term Use Evaluation (VALUE), trial wherein 15,245 patients aged 50 years or older with treated or untreated hypertension and high risk of cardiac events were randomized to either valsartan or amlodipine. A small difference in SBP (3.8 mmHg) in favor of the amlodipine group, as compared with the valsartan group, allowed a significant reduction of the incidence of CV events to be achieved during the first 3 months of the trial [35]. Over the following months this difference in SBP progressively disappeared, along with the outcome differences between the two groups [35].

Recently, the *Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica* (CardioSis), which randomly allocated 1111 treated, nondiabetic hypertensives with SBP at least 150 mmHg to a goal SBP of less than 140 mmHg (usual control) or less than

130 mmHg (tight control) [36], suggested that even small reductions in BP (3.8/1.5 mmHg) may be associated with a lower risk of major clinical events during a relatively short follow-up (2 years).

Even if NSAIDs and COX-2 inhibitors could also lead to an increased risk of CV events through a number of alternative mechanisms (see section 'Other mechanisms involved in the cardiovascular toxicity of traditional NSAIDs and COX-2 inhibitors'), small increases in BP values may clearly play an important role, as observed in various randomized controlled trials. For example, in the Vioxx GI Outcomes Research (VIGOR) study, rofecoxib more than doubled the risk of serious CV events, as compared with naproxen. A 3-mmHg higher increase in SBP was observed with rofecoxib compared with naproxen (4.6 vs 1.6 mmHg, respectively) [37,38].

Similarly, in the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial, a comparative study between rofecoxib and placebo in 2586 patients with history of colorectal adenomas, a 1.92 higher risk of major CV events was observed in the rofecoxib group ($p = 0.008$). A 3.9 mmHg difference in achieved SBP (+3.4 mmHg with rofecoxib and -0.5 mmHg with placebo) was also observed [39].

Finally, in a nonprespecified *post hoc* analysis of individual patient data from two celecoxib trials, the Adenoma Prevention with Celecoxib (APC) trial and the Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial, celecoxib 200 or 400 mg twice daily or 400 mg once daily showed a nearly twofold increased CV risk. This study raised the possibility of a direct association between the rise in SBP (2–5 mmHg) with celecoxib and the increased incidence of CV end points [40].

On the other hand, the large Therapeutic Arthritis Research and Gastrointestinal Event (TARGET) study, enrolling 18,325 patients with OA and high CV risk, randomized to lumiracoxib 400 mg once daily, naproxen 500 mg twice daily, or ibuprofen 800 mg three-times daily, did not show any difference in the primary CV end point (a composite of nonfatal and silent myocardial infarction, stroke or CV death) between the three groups. The lack of difference could partly be explained by the fact that lumiracoxib induced a small-to-null increase in systolic and diastolic BP (+0.4 and -0.1 mmHg, respectively) from baseline values, as compared with the other NSAIDs, including ibuprofen (+2.1 and +0.5 mmHg, respectively). In other words, the difference in achieved BP between groups was lower than 2/1 mmHg (SBP/DBP) [41].

A recent AHA Scientific Statement expressed concerns about the potential implications of BP rise induced by traditional NSAIDs or COX-2 inhibitors, suggesting BP and renal function should be monitored in subjects taking these drugs, particularly in the presence of coexisting hypertension, renal disease and heart failure [42].

The ongoing Prospective of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial [43], enrolling over 20,000 patients with OA or rheumatoid arthritis, will be the first large-scale trial to exclusively study patients with CV disease or those at high risk for CV disease taking NSAIDs or COX-2 inhibitors. The primary end point is the composite of CV death, nonfatal myocardial infarction or nonfatal stroke. This will be the first study of COX-2 inhibitors to compare a CV primary end point across three NSAIDs. The expectation is that the celecoxib-treated group will have fewer patients with BP elevations than the naproxen-treated group, but no special precautions are currently planned to restrict titration of antihypertensive drugs or standardize BP readings with regard to quality or duration between drug administration and measurement [44]. PRECISION is likely to have many more CV events than those summarized in the largest worldwide meta-analysis on this topic [45], so it should add greatly to our knowledge about the relationship between COX-2 inhibitors, BP changes and CV risk, helping to clarify an ongoing dilemma in clinical practice [43].

Mechanisms of the BP-raising effect

Experimental and clinical evidence strongly suggests that NSAIDs and COX-2 inhibitors may trigger vasoconstriction and a marked antinatriuretic effect [46–49], therefore increasing BP values, even if the exact underlying mechanisms are not completely understood.

COX inhibition exerted by NSAIDs leads to the systematic reduction of a number of prostaglandins with vasodilating effect, such as PGE_2 and PGI_2. At the kidney level such inhibition causes a drop in the renal blood flow, with reduced glomerular filtration rate and consequent azotemia and creatinine increase [49]. Inhibition of prostaglandins may also trigger an increase in chloride absorption, with consequent sodium retention, edema and hypertension, as well as a reduction of renin and aldosterone, with consequent potassium retention and hyperkalemia. Finally, prostaglandin reduction increases the effect of antidiuretic hormone, which contributes to water retention and hyponatremia [49].

Renal adverse effects are relatively rare in young and healthy people, in whom the kidneys are usually able to compensate for the hydrosaline retention induced by NSAIDs. Although acute COX inhibition may reduce the urinary sodium excretion by 30% or more [48], in the presence of sustained COX inhibition and normal kidney function, sodium and water homeostasis is usually preserved, without any rise in the BP [50]. By contrast, patients with reduced kidney function, as well as elderly people and subjects with congestive heart failure, may experience considerable hydrosaline retention, leading

to a rise in BP in just a few weeks [23,51]. Luckily, nephrotoxicity is usually largely reversible after discontinuation of NSAIDs [52].

In one study, the average risk of coronary heart failure was approximately 60% higher in NSAID users, as compared with nonusers [53]. Among the different NSAIDs, the risk was highest for indomethacin and lowest for diclofenac [53].

Prostacyclin may exert an important vasodilatory effect, counteracting the vasoconstriction triggered, for example, by angiotensin II and endothelin. As a consequence, PGI_2 inhibition by NSAIDs and COX-2 inhibitors may induce systemic vasoconstriction and increased peripheral vascular resistance, explaining part of the increase in BP.

Other mechanisms involved in the CV toxicity of traditional NSAIDs & COX-2 inhibitors

Even if BP increase plays a major role in determining the increased risk of major CV events in patients treated with traditional NSAIDs and COX-2 inhibitors, additional mechanisms are likely to be involved. For example, evidence from meta-analyses of randomized controlled trials [54] or observational studies [55] suggests that COX-2 inhibitors may cause a higher risk of arterial thrombotic events, such as myocardial infarctions, compared with nonusers. The sudden voluntary withdrawal of rofecoxib (Vioxx®), a 'selective' COX-2 inhibitor, by Merck & Co on September 30, 2004 as a result of its adverse CV effects, raised the question as to whether this toxicity is a class effect [56]. COX-1 and -2 are the isoenzymes involved in the production of various eicosanoids from arachidonic acid. Those eicosanoids include TxA_2 and PGI_2, which have critical roles in blood vessel function. While TxA_2 is a potent vasoconstrictor and is a promoter of platelet aggregation, PGI2 is a vasodilator and an inhibitor of platelet aggregation. It is also believed that COX-2 is the enzyme mainly responsible for the production of PGI_2 while COX-1 plays a more central role in the biosynthesis of TxA_2. Therefore, selective inhibition of COX-2 could change the balance between the production of PGI_2 and TxA_2, shifting it towards higher levels of the latter compound and increasing the risk of vasospasm, thromboembolism and CV events (i.e., myocardial infarction) [57].

Although the level of thrombotic risk may vary between individual NSAIDs and COX-2 inhibitors, it appears to be relatively small, especially for patients without other risk factors. COX-2 inhibitors increase the risk of atherothrombosis by approximately three events per 1000 people/year (compared with placebo). Diclofenac 150 mg once daily has a thrombotic risk profile similar to etoricoxib. Ibuprofen may have a small thrombotic risk at high doses (i.e., 2400 mg/day), but at lower doses (i.e., ≤1200 mg/day) epidemiological data do not suggest an increased risk of myocardial infarction.

Finally, naproxen 1000 mg once daily has a lower thrombotic risk than selective inhibitors of COX-2, and overall, epidemiological data do not suggest an increased risk of myocardial infarction [58,101,102]. Because NO has various CV effects, including platelet inhibition, naproxcinod could theoretically allow an even more favorable thrombogenic risk profile, but this hypothesis has not been confirmed by a comparative study, in which naproxcinod (375 and 750 mg twice daily) and naproxen (250 and 500 mg twice daily) were administered for 12 consecutive days. All dose regimens inhibited serum thromboxane B2 (TxB2) concentrations. The extent of inhibition was both dose- and concentration-dependent with the twice daily regimens. Notably, there was no statistically significant difference in serum TxB2 between equimolar doses of naproxcinod and naproxen. In addition, equimolar doses of naproxcinod and naproxen also elicited comparable effects on arachidonic acid and collagen-induced platelet aggregation, with no apparent effect on ADP-induced aggregation [103].

Naproxcinod: the first COX-inhibiting NO donator

The COX-inhibiting NO donator (CINOD) class has been developed for the treatment of patients with OA with the aim of improving the CV and gastrointestinal safety profile, as compared with NSAIDs. This is due to the release of NO [59–62], which also enhances the blood flow in the gastric mucosa, with consequent increased mucous production, reduced healing time and a final effect of gastroprotection [61].

The pharmacokinetics of CINODs is not completely understood. In particular, it is unclear whether CINODs are cleaved before intestinal absorption, or whether they are absorbed intact and subsequently metabolized, possibly in the liver. The exact mechanisms of NO release also require further investigation, since CINODs are able to release NO in biological fluids, but not in inert media [61], reasonably in line with the need of biological enzymes in the process of NO release *in vivo*.

Naproxcinod is the first CINOD with analgesic, anti-inflammatory, antipyretic and NO-donating properties that has been investigated in a large clinical trial [63]. It is made up of the traditional NSAID naproxen covalently bound to the NO-donating moiety butanediol mononitrate [64]. The molecular structures of naproxen and naproxcinod are shown in Figure 4. The molecule of naproxcinod is cleaved to produce naproxen and the NO-donating moiety. Plasma bioavailability of naproxen is reduced by approximately 15–20% after administration of naproxcinod, as compared with equimolar doses of naproxen [65], and the gastrointestinal uptake of naproxen is also slower [62]. After cleavage from naproxcinod, naproxen retains its inhibitory activity on COX-1 and -2, while NO released from the moiety may exert

its favorable biologic effects on the CV system (Box 1). It is well established that NO produced by endothelial cells is able to induce vasodilation and inhibition of both platelet aggregation and vascular smooth muscle proliferation [66,67]. In addition, NO regulates interactions between leukocytes and the blood vessel wall, therefore constituting an important homeostatic regulator in the vasculature, the absence of which plays a role in a number of different pathological conditions, such as hypertension and vasospasm [67,68]. In the gastroenteric mucosa, NO contributes to preserve gastric mucosal integrity by increasing blood flow and mucous production [69].

Naproxcinod demonstrated similar efficacy to naproxen in animal models of OA [62]. Investigations in rodents showed a dose-related inhibition of COX-1 after both single and repeated administration [70].

Naproxcinod lowered BP in rats with spontaneous hypertension or with hypertension induced by NG-nitro-L-arginine methyl ester (L-NAME) [71] and was able to protect isolated rabbit hearts in ischemia–reperfusion models [72], most likely as a consequence of the sustained NO release. In a two-kidney, one-clip rat model of renovascular hypertension, induced by a partial occlusion of the renal artery, naproxcinod significantly reduced BP as compared with both naproxen and vehicle [73].

While naproxen did not cause any change in NO, dose–response studies provided convincing evidence that naproxcinod may effectively release NO *in vivo* [74]. In line with these findings, progressively higher doses of naproxcinod have been shown to increase the levels of the second messenger cGMP, the specific signaling pathway of NO [75].

In animal models, naproxcinod caused less gastrointestinal damage as compared with equimolar doses of naproxen [71,76]. In a model of arthritic rats, naproxcinod reduced the degree of injury of gastric mucosa by approximately 70% when compared with equimolar doses of naproxen [77]. In a human study, this drug improved gastrointestinal tolerability and caused fewer gastroduodenal erosions as compared with naproxen [78].

Naproxcinod showed a similar potency to equimolar doses of naproxen in a series of randomized, double-blind, placebo-controlled studies conducted in patients with OA at different sites [64,79,80]. The dose of naproxcinod 750 mg twice daily showed the best balance between efficacy and safety [80].

Finally, animal studies provided solid evidence of the gastroprotective effects of naproxcinod, which were partly confirmed in human studies. In a study conducted in 31 healthy volunteers, the number of gastroduodenal erosions was 11.5 with naproxen and only 4.1 with naproxcinod ($p < 0.01$) [78]. In a multicenter study, naproxcinod significantly decreased the numbers of erosions and ulcers in stomach and stomach/duodenum combined as compared with naproxen [79]. The incidence of a Lanza score over 2, an overall measure of gastroduodenal damage, was significantly higher with naproxen than with naproxcinod (43.7 vs 32.2%; $p < 0.001$) (Figure 5) [79]. A subsequent randomized, double-blind, crossover study, consisting of two 12-day treatment periods and employing six sequences, aimed to compare the effects on the gastroduodenal mucosa of healthy volunteers of different doses and dosing regimens of naproxcinod (at that time coded AZD3582), as compared with equimolar doses of naproxen. The groups were: naproxcinod 750 mg once daily versus 375 mg twice daily (n = 25); naproxcinod 375 mg twice daily versus 750 mg twice daily (n = 25); and naproxen 250 mg twice daily versus 500 mg twice daily (n = 25). Gastroduodenal tract damage was similar with naproxcinod 375 and 750 mg twice daily (mean number of erosions and ulcers ± SD: 2.88 ± 3.95 versus 3.08 ± 2.80, respectively; p = 0.824; one ulcer counted as ten erosions), while gastroduodenal toxicity was

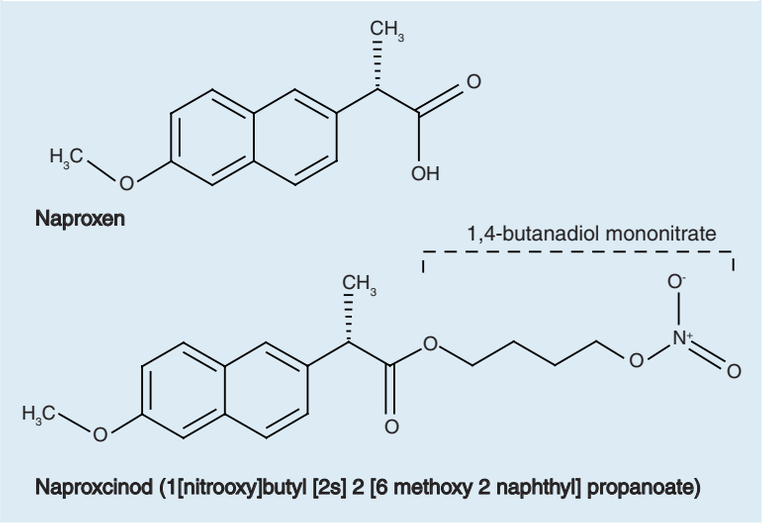

Figure 4. Naproxen and naproxcinod.

Box 1. Main biological effects of naproxcinod, mediated by cylooxygenase inhibition and nitric oxide release.

Cyclooxygenase-mediated effects
■ Inhibition of prostaglandin synthesis
■ Anti-inflammatory activity
■ Gastroenteric damaging effects
NO-mediated effects
■ Vasodilation
■ Inhibition of platelet aggregation
■ Inhibition of smooth cells proliferations
■ Modulation of the interactions between leukocytes and blood vessel walls
■ Increased blood flow in the gastric mucosa
■ Increased mucous production

significantly lower with naproxcinod 375 mg twice daily than with naproxen 250 mg twice daily (2.88 ± 3.95 vs 6.16 ± 9.36; p < 0.05), and with naproxcinod 750 mg twice daily vs naproxen 500 mg twice daily (3.08 ± 2.80 versus 6.68 ± 6.97; p < 0.05). The authors concluded that naproxcinod has an improved gastroduodenal safety profile compared with equimolar doses of naproxen [81]. Naproxcinod was generally well tolerated, with only a small number of potential NO mechanism-based events at the higher dose, particularly dizziness. The latter has also been reported with other NSAIDs [82].

BP in clinical studies

In a recent clinical study, 916 subjects with OA of the knee were randomized to either naproxcinod 375 and 750 mg twice daily, naproxen 500 mg twice daily or placebo. Mean duration of follow-up was 13 weeks. After 13 weeks of treatment, SBP fell by 2.9 and 0.8 mmHg more with naproxcinod than with naproxen (95% CI: -5.2 to -0.6; p = 0.015) or placebo (95% CI: -3.3 to 1.6; p = 0.505), respectively [63]. In a subgroup of 207 patients concomitantly treated with ACEIs or angiotensin-receptor blockers, alone or with diuretics, naproxcinod 750 mg reduced SBP of 6.5 mmHg more than naproxen 500 mg. Approximately 22% of patients treated with naproxen 500 mg experienced a SBP increase of more than 10 mmHg, as compared with 14% of naproxcinod 750 mg (p = 0.04) [63]. Naproxcinod showed effects on BP similar to that of placebo.

A prespecified pooled analysis of the three naproxcinod Phase III trials in patients with OA of the hip or knee included 2734 patients assigned to naproxcinod (375 and 750 mg twice daily), naproxen 500 mg twice daily or placebo and followed for 13 weeks [83]. The main end point was the change in SBP from baseline to week 13. There was no treatment-by-study interaction [84]. Of the patients (mean age: 61 years), 49% had a prior diagnosis of hypertension (per medical history, but not uncontrolled at the time of inclusion as it was an exclusion criterion). Baseline SBP did not differ between the groups. Naproxcinod 750 mg twice daily allowed an additional 1.78 mmHg lowering of SBP, as compared with naproxen 500 mg twice daily (p = 0.0059), while the comparison with placebo showed a substantial similarity (difference: 0.37 mmHg; p = 0.2753). By contrast, SBP was significantly higher by 1.42 mmHg with naproxen 500 mg twice daily compared with placebo (p = 0.0160) [83]. Again, naproxcinod showed a similar effect to placebo on SBP, while naproxen increased it significantly.

The BP effects of naproxcinod, as assessed by 24-h ambulatory BP monitoring, have been recently evaluated by two separate studies. In the first of them, a double-blind, crossover study, 121 hypertensives not previously treated with NSAIDs or COX-2 inhibitors were assigned to naproxcinod 750 mg twice daily and naproxen 500 mg twice daily in random order for 2 weeks each, with a 2-week placebo period interposed between each of the two active treatment periods. A 24-h ambulatory BP monitoring was performed at the start and the end of each active treatment period. Naproxcinod allowed patients to achieve lower SBP and DBP values, as compared with naproxen, with most of the advantage of naproxcinod over naproxen observed in the first 8 h after oral intake [85]. Further long-term trials are needed to elucidate the clinical significance of these observations.

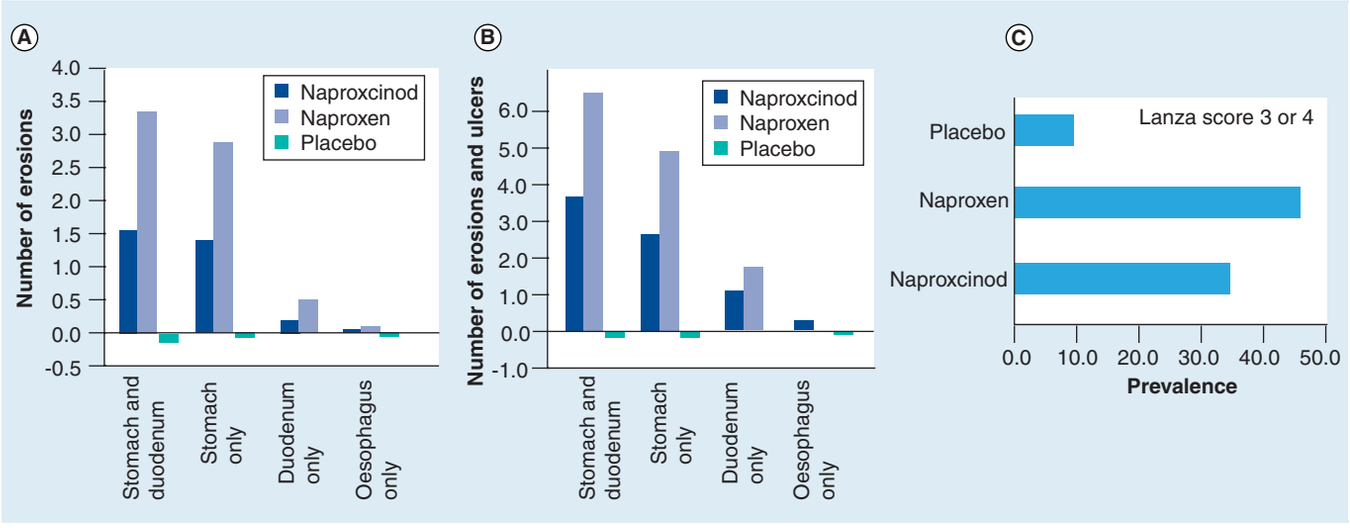

Figure 5. Secondary endoscopic end points. (A) Erosions only, **(B)** erosions and ulcers, **(C)** Lanza score 3 or 4 after 6 weeks of follow-up in patients with hip or knee osteoarthritis treated with naproxcinod, naproxen or placebo. Ten erosions were considered to represent one ulcer [82].

In the second trial, 118 patients with OA (hip or knee) and controlled essential hypertension were randomly assigned to naproxcinod 375 mg twice daily or naproxen 250 mg twice daily. Both treatments were force-titrated to the next highest dose at 3-week intervals (naproxcinod 750 and 1125 mg twice daily; naproxen 500 and 750 mg twice daily). A 24-h ambulatory BP monitor study was carried out at baseline and at the end of each period. Average 24-h SBP, the primary end point of the study, was 3.8 mmHg lower in patients treated with naproxcinod [86], once again indicating that NO release is able to avoid the increase in BP commonly seen with conventional NSAIDs. The overall study difference in SBP between naproxen and naproxcinod was statistically significant (p = 0.0198).

Future perspective

The development of the CINOD class aimed to improve the CV and gastrointestinal safety profiles, as compared with NSAIDs, through the release of NO. Naproxcinod, the first CINOD tested in large intervention trials, is not only able to enhance the gastric blood flow and the mucous production, with a final effect of gastroprotection, but also to prevent BP increases, both in normotensive and hypertensive patients, as compared with naproxen. Therefore, naproxcinod is a possible candidate to become a valuable alternative to NSAIDs and COX-2 inhibitors in the treatment of patients with OA. Further long-term trials are needed to fully elucidate the clinical relevance of naproxcinod in reducing BP values and CV events.

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Executive summary

- A large number of patients with osteoarthritis (OA; ~40%) are affected by hypertension.
- Many of these subjects take non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX)-2 inhibitors to control pain, and these drugs are known to destabilize blood pressure (BP) control by reducing the BP-lowering effect of a number of antihypertensive agents (including acetycholine esterase-inhibitors, angiotensin-receptor blockers and beta-blockers).
- Because of this, it is possible to observe a rise in BP values, with an expected rise in the risk of major cardiovascular complications and death.
- Other mechanisms may also contribute to the increased risk of cardiovascular complications observed with traditional NSAIDs and COX-2 inhibitors.
- COX-inhibiting nitric oxide donators (CINODs) have been designed to overcome the adverse effects arising from chronic NSAIDs administration. In fact, CINODs are able to combine the COX-mediated anti-inflammatory activity of the NSAID component with the systemic vasodilatation and potential gastrointestinal protection induced by the nitric oxide component.
- Naproxcinod, the first CINOD tested in patients with OA, may induce fewer BP effects compared to equimolar doses of naproxen.

Bibliography

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Anandacoomarasamy A, March L. Current evidence for osteoarthritis treatments. *Ther. Adv. Musculoskel. Dis.* 2, 17–28 (2010).

2 Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bull. World Health Organ.* 81, 646–656 (2003).

3 Kopec JA, Rahman MM, Berthelot JM *et al.* Descriptive epidemiology of osteoarthritis in British Columbia, Canada. *J. Rheumatol.* 34, 386–393 (2007).

4 Dahaghin S, Bierma-Zeinstra SM, Ginai AZ, Pols HA, Hazes JM, Koes BW. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). *Ann. Rheum. Dis.* 64, 682–687 (2005).

5 Horvath G, Koroknai G, Acs B, Than P, Bellyei A, Illes T. Prevalence of radiographic primary hip and knee osteoarthritis in a representative Central European population. *Int. Orthop.* DOI: 10.1007/s00264-010-1069-6 (2010) (Epub ahead of print).

6 Lawrence RC, Hochberg MC, Kelsey JL *et al.* Estimates of the prevalence of selected arthritic and musculoskeletal diseases in the United States. *J. Rheumatol.* 16, 427–441 (1989).

7 Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. *Am. J. Sports Med.* 35, 1756–1769 (2007).

8 Michael JW, Schluter-Brust KU, Eysel P. The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. *Dtsch Arztebl. Int.* 107, 152–162 (2010).

9 Gabriel SE, Crowson CS, Campion ME, O'Fallon WM. Direct medical costs unique to people with arthritis. *J. Rheumatol.* 24, 719–725 (1997).

10 Rabenda V, Manette C, Lemmens R, Mariani AM, Struvay N, Reginster JY. Direct and indirect costs attributable to osteoarthritis in active subjects. *J. Rheumatol.* 33, 1152–1158 (2006).

11 Singh G, Miller JD, Lee FH, Pettitt D, Russell MW. Prevalence of cardiovascular disease risk factors among US adults with self-reported osteoarthritis: data from the Third National Health and Nutrition Examination Survey. *Am. J. Manag. Care* 8, S383–S391 (2002).

▪ **Third National Health and Nutrition Examination Survey (NHANES) III showed that osteoarthritis is present in approximately 21% of US adults aged 35 years or more, and that a concomitant hypertension is evident in approximately 40% of these subjects.**

12 Singh G, Miller JD, Huse DM, Pettitt D, D'Agostino RB, Russell MW. Consequences of increased systolic blood pressure in patients with osteoarthritis and rheumatoid arthritis. *J. Rheumatol.* 30, 714–719 (2003).

13 Kiefer W, Dannhardt G. Novel insights and therapeutical applications in the field of inhibitors of COX-2. *Curr. Med. Chem.* 11, 3147–3161 (2004).

14 Hao CM, Breyer MD. Hypertension and cyclooxygenase-2 inhibitors: target: the renal medulla. *Hypertension* 44, 396–397 (2004).

15 Harris RC, Zhang MZ, Cheng HF. Cyclooxygenase-2 and the renal renin–angiotensin system. *Acta Physiol. Scand.* 181, 543–547 (2004).

16 Williams B, Poulter NR, Brown MJ *et al.* Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J. Hum. Hypertens.* 18, 139–185 (2004).

17 Warner TD, Mitchell JA. COX-2 selectivity alone does not define the cardiovascular risks associated with non-steroidal anti-inflammatory drugs. *Lancet* 371, 270–273 (2008).

18 Polonia J, Boaventura I, Gama G *et al.* Influence of non-steroidal anti-inflammatory drugs on renal function and 24h ambulatory blood pressure-reducing effects of enalapril and nifedipine gastrointestinal therapeutic system in hypertensive patients. *J. Hypertens.* 13, 925–931 (1995).

19 Morgan TO, Anderson AI. Interaction of indometacin with felodipine and enalapril. *J. Hypertens.* 1(Suppl. 3), S334–S338 (1993).

20 Morgan TO, Anderson AI, MacInnis RJ. ACE inhibitors, beta-blockers, calcium blockers, and diuretics for the control of systolic hypertension. *Am. J. Hypertens* 14, 241–247 (2001).

21 Grover SA, Coupal L, Zowall H. Treating osteoarthritis with cyclooxygenase-2-specific inhibitors: what are the benefits of avoiding blood pressure destabilization? *Hypertension* 45, 92–97 (2005).

22 Kurth T, Hennekens CH, Sturmer T *et al.* Analgesic use and risk of subsequent hypertension in apparently healthy men. *Arch. Intern. Med.* 165, 1903–1909 (2005).

23 Solomon DH, Schneeweiss S, Levin R, Avorn J. Relationship between COX-2 specific inhibitors and hypertension. *Hypertension* 44, 140–145 (2004).

24 Dedier J, Stampfer MJ, Hankinson SE, Willett WC, Speizer FE, Curhan GC. Nonnarcotic analgesic use and the risk of hypertension in US women. *Hypertension* 40, 604–608 (2002).

25 Curhan GC, Willett WC, Rosner B, Stampfer MJ. Frequency of analgesic use and risk of hypertension in younger women. *Arch. Intern. Med.* 162, 2204–2208 (2002).

26 Forman JP, Stampfer MJ, Curhan GC. Non-narcotic analgesic dose and risk of incident hypertension in US women. *Hypertension* 46, 500–507 (2005).

▪ **This pooled analysis of both Nurses Health studies showed that higher daily doses of nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of new hypertension, and also removed the potential objection that headache may have confounded the relationship between NSAID use and blood presure (BP) increase, evident in both Nurses Health trials.**

27 Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. *Arch. Intern. Med.* 153, 477–484 (1993).

28 Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann. Intern. Med.* 121, 289–300 (1994).

29 Sowers JR, White WB, Pitt B *et al.* The Effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and Type 2 diabetes mellitus. *Arch. Intern. Med.* 165, 161–168 (2005).

30 Whelton A, White WB, Bello AE, Puma JA, Fort JG. Effects of celecoxib and rofecoxib on blood pressure and edema in patients > or =65 years of age with systemic hypertension and osteoarthritis. *Am. J. Cardiol.* 90, 959–963 (2002).

31 Chan CC, Reid CM, Aw TJ, Liew D, Haas SJ, Krum H. Do COX-2 inhibitors raise blood pressure more than nonselective NSAIDs and placebo? An updated meta-analysis. *J. Hypertens.* 27, 2332–2341 (2009).

▪▪ **This large meta-analysis showed that patients with osteoarthritis taking cyclooxygenase (COX)-2 inhibitors shared a higher risk of developing hypertension, as compared with placebo or nonselective NSAIDs.**

32 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 360, 1903–1913 (2002).

▪▪ **This huge meta-analyis involved approximately 1 million individuals enrolled in 61 observational studies, and demonstrated the existence of a direct, continuous and graded relationship between BP values, beginning from values as low as 115/75 mmHg, and the risk of cardiovascular (CV) disease.**

33 Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet* 358, 1305–1315 (2001).

34 Staessen JA, Li Y, Thijs L, Wang JG. Blood pressure reduction and cardiovascular prevention: an update including the 2003–2004 secondary prevention trials. *Hypertens. Res.* 28, 385–407 (2005).

35 Julius S, Kjeldsen SE, Weber M *et al.* Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 363, 2022–2031 (2004).

36 Verdecchia P, Staessen JA, Angeli F *et al.* Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. *Lancet* 374, 525–533 (2009).

37 Bombardier C, Laine L, Reicin A *et al.* Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N. Engl. J. Med.* 343, 1520–1528 (2000).

38 White WB. Cardiovascular effects of the cyclooxygenase inhibitors. *Hypertension* 49, 408–418 (2007).

39 Bresalier RS, Sandler RS, Quan H *et al.* Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N. Engl. J. Med.* 352, 1092–1102 (2005).

40 Solomon SD, Pfeffer MA, McMurray JJ *et al.* Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. *Circulation* 114, 1028–1035 (2006).

41 Farkouh ME, Kirshner H, Harrington RA *et al.* Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet* 364, 675–684 (2004).

▪ **The large TARGET study, enrolling 18,325 patients with osteoarthritis and high CV risk, did not show any difference in the primary CV end point (a composite of nonfatal and silent myocardial infarction, stroke or CV death) between lumiracoxib, naproxen or ibuprofen.**

42 Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. *Circulation* 115, 1634–1642 (2007).

43 Becker MC, Wang TH, Wisniewski L *et al.* 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.* 157, 606–612 (2009).

■■ **The ongoing PRECISION trial is the first trial to study patients at high CV risk taking NSAIDs or COX-2 inhibitors, and it will greatly help to clarify the relationship between COX-2 inhibitors, BP changes and CV risk.**

44 Elliott W. Do the blood pressure effects of nonsteroidal antiinflammatory drugs influence cardiovascular mortwice dailyity and mortality? *Curr. Hypertens. Rep.* 12, 258–266 (2010).

45 Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 332, 1302–1308 (2006).

46 Morgan TO, Anderson A, Bertram D. Effect of indomethacin on blood pressure in elderly people with essential hypertension well controlled on amlodipine or enalapril. *Am. J. Hypertens.* 13, 1161–1167 (2000).

47 Simon LS, Smolen JS, Abramson SB *et al.* Controversies in COX-2 selective inhibition. *J. Rheumatol.* 29, 1501–1510 (2002).

48 Brater DC. Effects of nonsteroidal anti-inflammatory drugs on renal function: focus on cyclooxygenase-2-selective inhibition. *Am. J. Med.* 107, 65S–70S (1999).

49 Whelton A. Renal and related cardiovascular effects of conventional and COX-2-specific NSAIDs and non-NSAID analgesics. *Am. J. Ther.* 7, 63–74 (2000).

50 Whelton A, Schulman G, Wallemark C *et al.* Effects of celecoxib and naproxen on renal function in the elderly. *Arch. Intern. Med.* 160, 1465–1470 (2000).

51 Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. *Am. J. Med.* 106, 13S–24S (1999).

52 Wilson SL, Poulter NR. The effect of non-steroidal anti-inflammatory drugs and other commonly used non-narcotic analgesics on blood pressure level in adults. *J. Hypertens.* 24, 1457–1469 (2006).

53 Garcia Rodriguez LA, Hernandez-Diaz S. Nonsteroidal antiinflammatory drugs as a trigger of clinical heart failure. *Epidemiology* 14, 240–246 (2003).

54 Caldwell B, Aldington S, Weatherall M, Shirtcliffe P, Beasley R. Risk of cardiovascular events and celecoxib: a systematic review and meta-analysis. *J. R. Soc. Med.* 99, 132–140 (2006).

55 McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 296, 1633–1644 (2006).

56 Couzin J. Drug safety. Withdrawal of Vioxx casts a shadow over COX-2 inhibitors. *Science* 306, 384–385 (2004).

57 Tabrizchi R. Risk of cardiovascular events and cyclooxygenase-2 inhibitors. *Vasc. Health Risk Manag.* 2, 95–96 (2006).

58 MHRA. NSAIDs and coxibs: balancing of cardiovascular and gastrointestinal risks. *Drug Safety Update* 1, 13 (2007).

59 Wallace JL, Ignarro LJ, Fiorucci S. Potential cardioprotective actions of no-releasing aspirin. *Nat. Rev. Drug Discov.* 1, 375–382 (2002).

60 Fiorucci S, Santucci L, Distrutti E. NSAIDs, coxibs, CINOD and H2S-releasing NSAIDs: what lies beyond the horizon. *Dig. Liver Dis.* 39, 1043–1051 (2007).

61 Fiorucci S. Prevention of nonsteroidal anti-inflammatory drug-induced ulcer: looking to the future. *Gastroenterol. Clin. North Am.* 38, 315–332 (2009).

62 Wallace JL, Viappiani S, Bolla M. Cyclooxygenase-inhibiting nitric oxide donators for osteoarthritis. *Trends Pharmacol. Sci.* 30, 112–117 (2009).

63 White WB, Schnitzer TJ, Fleming R, Duquesroix B, Beekman M. Effects of the cyclooxygenase inhibiting nitric oxide donator naproxcinod versus naproxen on systemic blood pressure in patients with osteoarthritis. *Am. J. Cardiol.* 104, 840–845 (2009).

64 Schnitzer TJ, Kivitz AJ, Lipetz RS, Sanders N, Hee A. Comparison of the COX-inhibiting nitric oxide donator AZD3582 and rofecoxib in treating the signs and symptoms of Osteoarthritis of the knee. *Arthritis Rheum.* 53, 827–837 (2005).

65 Fagerholm U, Bjornsson MA. Clinical pharmacokinetics of the cyclooxygenase inhibiting nitric oxide donator (CINOD) AZD3582. *J. Pharm. Pharmacol.* 57, 1539–1554 (2005).

66 Rees DD, Palmer RM, Moncada S. Role of endothelium-derived nitric oxide in the regulation of blood pressure. *Proc. Natl Acad. Sci. USA* 86, 3375–3378 (1989).

67 Moncada S, Higgs EA. The discovery of nitric oxide and its role in vascular biology. *Br. J. Pharmacol.* 147(Suppl. 1), S193–S201 (2006).

68 Giles TD. Aspects of nitric oxide in health and disease: a focus on hypertension and cardiovascular disease. *J. Clin. Hypertens. (Greenwich)* 8, 2–16 (2006).

69 Wallace JL. Cooperative modulation of gastrointestinal mucosal defence by prostaglandins and nitric oxide. *Clin. Invest. Med.* 19, 346–351 (1996).

70 Muscara MN, McKnight W, Asfaha S, Wallace JL. Wound collagen deposition in rats: effects of an NO-NSAID and a selective COX-2 inhibitor. *Br. J. Pharmacol.* 129, 681–686 (2000).

71 Muscara MN, McKnight W, Del Soldato P, Wallace JL. Effect of a nitric oxide-releasing naproxen derivative on hypertension and gastric damage induced by chronic nitric oxide inhibition in the rat. *Life Sci.* 62, PL235–PL240 (1998).

72 Rossoni G, Manfredi B, Del Soldato P, Berti F. The nitric oxide-releasing naproxen derivative displays cardioprotection in perfused rabbit heart submitted to ischemia–reperfusion. *J. Pharmacol. Exp. Ther.* 310, 555–562 (2004).

73 Muscara MN, McKnight W, Lovren F, Triggle CR, Cirino G, Wallace JL. Antihypertensive properties of a nitric oxide-releasing naproxen derivative in two-kidney, one-clip rats. *Am. J. Physiol. Heart Circ. Physiol.* 279, H528–H535 (2000).

74 Rossoni G, Manfredi B, De Gennaro Colonna V *et al.* Nitric oxide and prostacyclin pathways: an integrated mechanism that limits myocardial infarction progression in anaesthetized rats. *Pharmacol. Res.* 53, 359–366 (2006).

75 Berndt G, Grosser N, Hoogstraate J, Schroder H. A common pathway of nitric oxide release from AZD3582 and glyceryl trinitrate. *Eur. J. Pharm. Sci.* 21, 331–335 (2004).

76 Davies NM, Roseth AG, Appleyard CB *et al.* NO-naproxen vs. naproxen: ulcerogenic, analgesic and anti-inflammatory effects. *Aliment. Pharmacol. Ther.* 11, 69–79 (1997).

77 Fiorucci S, Di Lorenzo A, Renga B, Farneti S, Morelli A, Cirino G. Nitric oxide (NO)-releasing naproxen (HCT-3012 [(*S*)-6-methoxy-alpha-methyl-2-naphthaleneacetic Acid 4-(nitrooxy)butyl ester]) interactions with aspirin in gastric mucosa of arthritic rats reveal a role for aspirin-triggered lipoxin, prostaglandins, and NO in gastric protection. *J. Pharmacol. Exp. Ther.* 311, 1264–1271 (2004).

78 Hawkey CJ, Jones JI, Atherton CT *et al.* Gastrointestinal safety of AZD3582, a cyclooxygenase inhibiting nitric oxide donator: proof of concept study in humans. *Gut* 52, 1537–1542 (2003).

79 Lohmander LS, McKeith D, Svensson O *et al.* A randomised, placebo controlled, comparative trial of the gastrointestinal safety and efficacy of AZD3582 versus naproxen in osteoarthritis. *Ann. Rheum. Dis.* 64, 449–456 (2005).

80 Karlsson J, Pivodic A, Aguirre D, Schnitzer TJ. Efficacy, safety, and tolerability of the cyclooxygenase-inhibiting nitric oxide donator naproxcinod in treating osteoarthritis of the hip or knee. *J. Rheumatol.* 36, 1290–1297 (2009).

81 Wilder-Smith CH, Jonzon B, Fornstedt-Wallin B, Hedman A, Karlsson P. Dose–effect comparisons of the CINOD AZD3582 and naproxen on upper gastrointestinal tract mucosal injury in healthy subjects. *Scand. J. Gastroenterol.* 41, 264–273 (2006).

82 Singh G, Fort JG, Goldstein JL *et al.* Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I Study. *Am. J. Med.* 119, 255–266 (2006).

83 White WB, Schnitzer TJ, Djian J, Frayssinet H, Duquesroix B, Weber M. The nitric oxide donator naproxcinod has blood pressure effects similar to placebo in patients with osteoarthritis. *J. Clin. Hypertens.* 28, e441 (2010) (Abstract).

84 Hedges LV. Meta-analysis. *J. Educ. Behav. Stat.* 17, 279–296 (1992).

85 Townsend R, Bittar N, Rosen J *et al.* The 24-hour blood pressure profile of naproxcinod, a first-in-class cyclooxygenase inhibiting nitric oxide donator, compared with naproxen in stable hypertensive subjects *Circulation* 116, II-609 (2007) (Abstract).

86 Townsend R, Backris GL, Erdy G *et al.* A 12-week, double-blind, randomised, forced tritration, parallel-group study to assess the effects of naproxcinod and naproxen on arterial blood pressure as measured by ABPM in osteoarthritis patients with controlled essential hypertension. *J. Hypertens.* 27(Suppl. 4), S7 (2009) (Abstract 1B4).

Websites

101 National Prescribing Centre. Cardiovascular and gastrointestinal safety of NSAIDs. MeRec Extra. www.npc.co.uk/ebt/merec/cardio/cdrisk/resources/merec_extra_no30.pdf

102 MHRA. Safety of selective and non-selective non-steroidal anti-inflammatory drugs. www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2025036&RevisionSelectionMethod=LatestReleased

103 NicOx. FDA's Joint Meeting of the Arthritis Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee. Briefing Document 12 May 2010: naproxcinod 375 mg capsules for relief of the signs and symptoms of osteoarthritis. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM211468.pdf