Impact of NSAIDs on cardiovascular risk and hypertension

Impatto dei FANS sul rischio cardiovascolare e di ipertensione

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications in the world, with more than 20 prescription and non-prescription (over-the-counter) NSAIDs approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency. Although non-narcotic analgesics are generally considered

KEYWORDS
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Summary

Introduction: In recent years, there has been a great deal of evaluation of the cardiovascular (CV) effects of the non-steroidal anti-inflammatory drugs (NSAIDs) and the selective cyclooxygenase-2 (COX-2) inhibitors.

Materials and methods: In this brief review, the focus is on both effects of the NSAIDs and COX-2 inhibitors on blood pressure and CV events. The literature was searched using PubMed for both clinical trials and observational studies reviewing the relations among NSAIDs, blood pressure, and CV events.

Results: Clinical trial results for NSAIDs and COX-2 inhibitors have shown varying levels of destabilization of blood pressure control in treated hypertensive patients as well as variable incident rates of the development of arrhythmias, congestive heart failure, myocardial infarction, and stroke.

Discussion: The non-selective and COX-2 selective NSAIDs can be used with care in selected arthritis patients with hypertension and stable CV disorders (excluding congestive heart failure and moderate to severe kidney dysfunction) when the individual clinical benefit of anti-inflammatory therapy outweighs the CV and gastrointestinal risk.

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safe when used as directed, careful evaluation is warranted in patients with even modest health concerns given their widespread use and accessibility without physician prescription [1]. Recent evidence suggests that at certain doses of the COX-2 selective inhibitors as well as for traditional non-selective NSAIDs, there are increased risks of cardiovascular (CV) events [2,3]. For example, reports of a higher incidence of myocardial infarction (MI) among patients with arthritis taking high doses of the COX-2 selective inhibitor rofecoxib compared to those taking the NSAID naproxen [3—5] began to heighten concerns among rheumatologists since 2001 about the safety of these drugs. Additionally, in 2005, elevated CV event rates were reported in patients with spontaneous adenomatous polyps who were taking high doses of celecoxib compared to placebo [6] and in patients who received parenteral parecoxib followed by oral valdecoxib versus placebo immediately after coronary artery bypass graft surgery [7].

The focus of this brief review is to assess the effects of both nonselective and selective NSAIDs on blood pressure (BP), particularly in patients with hypertension treated with antihypertensive therapies and subsequently, on the impact that the NSAIDs have on CV events from several recent clinical trials for the treatment of arthritis or for cancer prevention as well as from very recent large observational studies.

Pharmacologic effects of cyclooxygenase inhibition on the cardiovascular system

Cyclooxygenases (COX) participate in numerous physiological functions and human pathologic disorders. Cyclooxygenase-1 is the only form of the enzyme in mature platelets and is also expressed in the vascular endothelium, the gastrointestinal epithelium, brain, spinal cord, and kidney. The COX-2 isoform plays an important role in induction of inflammation in response to injury as well as later repair of inflammation. It is noteworthy that COX-2 may be induced by bacterial endotoxins, cytokines, and growth factors and is expressed in atherosclerotic plaques, during angiogenesis, during wound healing and in a variety of epithelial cell cancers [8—10]. In addition, COX-2 is constitutively expressed in the macula densa and renal medullary interstitium [11,12]. One important clinical result of COX-2 inhibition is a reduction in natriuresis and the development of hypertension in susceptible populations. The COX isoenzymes are similar in structure but the substrate—binding channel of COX-2 contains a side pocket that is absent in COX-1. This structural difference has allowed for the design and development of COX inhibitors with side chains that fit within the COX-2 channel but are too large to block COX-1 with equal affinity [13].

The non-clinical literature has several recent studies demonstrating that removal of prostacyclin leads to both platelet-dependent [14—16] and platelet-independent [17] mechanisms for induction of thrombosis, plaque destabilization, or atherogenesis. In addition, COX-2 is recognized as a key source of prostacyclin under normal laminar flow conditions in the vasculature and has been shown to be cardioprotective in ischemia-reperfusion injury [18]. Thus, some investigators hypothesize that COX-2 inhibition in vascular inflammatory states would lead to a decrease in anti thrombotic prostacyclin made by arachidonate flux and might also provide enhanced leukotriene synthesis along with increased reactive oxygen species and consumption of anti-thrombotic nitric oxide (NO) [19]. Additionally, one study in a rat model showed an association between rofecoxib and its metabolites with marked degradation of aortic elastin through the prevention of cross-linkages, a potential factor for the increased risk of CV events observed with rofecoxib compared to other agents in the NSAID class [20]. In contrast, other studies have demonstrated that COX-2 inhibition improves the vascular endothelial dysfunction that is mediated through reduced NO availability and oxidative stress [21]. Additionally, selective COX-2 inhibition with celecoxib led to reduced tissue factor (TF) expression and activity in human endothelial cells that was mediated by inhibition of c-Jun terminal NH2 kinase phosphorylation [22]. In these three latter studies, the authors suggested that heterogeneity of responses of various inhibitors of COX-2 might lead to different clinical effects, especially in patients with underlying atherosclerotic vascular diseases. However, such conclusions are premature since clinical effects linked to these basic findings have not been studied.

Less is understood about acetaminophen, an indirect COX-2 selective inhibitor, which has been proposed to inhibit prostaglandin production [23], as well as indirectly activate cannabinoid receptors by N-arachidonoyl phenol amine, a metabolite of acetaminophen [24]. There has been speculation that the novel mechanisms of action of acetaminophen could theoretically explain a pressor effect in susceptible individuals.

Nonsteroidal anti-inflammatory drugs in patients with hypertension

Arthritis and hypertension often co-exist in middle-aged and older patients. Thus, co-administration of NSAIDs or COX-2 selective inhibitors with antihypertensive agents has been fairly common in clinical practice [25]. Ten years ago, meta-analyses of NSAID trials showed that many agents within the class (e.g., ibuprofen, indomethacin, and naproxen) could increase mean arterial pressure by as much as 5 to 6 mmHg in hypertensive patients [26,27]. As reported by Grover et al. [28], increases in blood pressure (BP) by NSAIDs of this magnitude are clearly of concern. Using their Cardiovascular Disease Life Expectancy Model, they estimated that if BP control was maintained among 7.3 million treated hypertensive patients receiving NSAIDs or COX-2 inhibitors, 30,000 stroke deaths and 25,000 coronary heart disease deaths would be avoided. Sustained BP elevations in older patients are associated with increases in the risk of both ischemic and hemorrhagic stroke, congestive heart failure, and ischemic cardiac events [29—31]. A relevant example is derived from the VALUE trial [31] where differences of approximately 2 to 4 mmHg in systolic BP control in high cardiovascular risk hypertensive patients resulted in clinically and statistically significant increases in cardiac events in the less-well-controlled group during the first year of the study. From the perspective of treating populations of patients, it has become important to clarify the relative effects of the various NSAIDs and COX-2 selective inhibitors on BP destabilization in patients with hypertension [25].
Effects of NSAIDs that influence blood pressure

Inhibition of COX-2 results in reduction of prostaglandin synthesis and is associated with both anti-natriuretic and vasoconstrictor effects [32–35]. In some patients, these effects have consequences on BP levels and may be of particular relevance in patients with preexisting cardiovascular conditions such as hypertension or congestive heart failure.

Inhibition of COX-2 is associated with reductions in both prostaglandin E₂ (PGE₂) and prostaglandin I₂ (PGI₂ or prostacyclin) [36]. Inhibition of PGE₂ may induce an acute relative reduction in daily urinary sodium excretion of 30–50% [35,36]. Within a few days, patients with normal kidney function will tend to increase sodium excretion in order to maintain homeostasis of sodium balance [36]. However, in patients with chronic kidney disease, this homeostatic process is impaired and, within 1 to 2 weeks of starting NSAID therapy, a considerable amount of salt and water may be retained. This may lead to edema and hypertension and in more severe cases, congestive heart failure [35–39].

The NSAIDs and COX-2 selective inhibitors also may impair the systemic and renal vasodilatory benefits of prostacyclin. Loss of this mechanism of vasodilation in the face of numerous vasoconstrictors (e.g., angiotensin 2, catecholamines, and endothelin) may potentially lead to increases in systemic vascular resistance and subsequently to increases in mean arterial pressure. Pharmacologic experiments with NSAIDs have yielded diverse results. Qi et al. [39] used a mouse model to assess the effects of COX-1 and COX-2 on the pressor effect of angiotensin-2 using pharmacologic inhibition or gene knockout of the COX isoenzymes. COX-1 inhibition blunted the pressor effect of angiotensin-2 while COX-2 inhibitors reduced renal medullary blood flow and urine flow and enhanced the pressor effect of angiotensin-2. Hermann et al. [40,41] assessed rofecoxib, celecoxib, diclofenac, and placebo on blood pressure, endothelial function, renal morphology, and protein excretion in salt-sensitive rats and demonstrated that celecoxib, a selective COX-2 inhibitor, but not rofecoxib nor diclofenac reduced glomerular injury and proteinuria as well as improved systolic BP and endothelial function while reducing oxidative stress. Winner et al. [42] showed that several non-selective NSAIDs inhibit the glucuronidation of aldosterone by human kidney microsomes which could theoretically lead to hypertension through enhanced concentrations of aldosterone [43,44].

NSAIDs in patients taking antihypertensive medications

A major focus of clinical research associated with the NSAIDs has been the potential destabilization of BP in hypertensive patients who are receiving renin-angiotensin blocking drugs, beta-blockers, calcium antagonists, or diuretics. In an earlier placebo-controlled trials, high-dose celecoxib (200 mg twice daily) was studied in 178 patients who were on chronic ACE inhibitor therapy [45]. Using ambulatory BP monitoring, we demonstrated that celecoxib was associated with a non-significant increase in 24-hour mean BP of 1.6/1.2 mmHg. Evaluation of the 24-hour BP profiles suggested a transient (1-2 hour) increase in systolic BP following dosing of celecoxib which could be associated with peak inhibition of COX-2. In a smaller trial, Izhar et al. [46] studied the effects of celecoxib and diclofenac on ambulatory BP and glomerular filtration rates in a double-blind crossover study. Mean 24-hour systolic BP was significantly increased by diclofenac (+4.2 mmHg) compared to celecoxib (+0.6 mmHg) and GFR was significantly reduced by diclofenac but not by celecoxib.

A study using the clinic systolic BP as the primary endpoint evaluated the effects of rofecoxib 25 mg/day and celecoxib 200 mg/day in 1,092 osteoarthritis patients on chronic, stable doses of antihypertensive therapies [37]. This trial showed that rofecoxib induced significant increases in systolic BP in patients who were taking ACE inhibitors and beta-blockers but not in those who were taking calcium antagonists. Patients randomly assigned to receive celecoxib did not show a change in systolic BP regardless of the class of antihypertensive therapy. These results support the concept that calcium antagonists do not depend on vascular prostacyclin as part of their mechanism of action or are less affected by accumulation of sodium compared to the other classes of antihypertensives [37,47]. This finding was confirmed in a short-term (3 weeks) placebo-controlled study by Houston et al. [47] in which neither ibuprofen nor naproxen significantly increased mean BP in patients treated with chronic verapamil therapy.

Further evidence of differences among NSAIDs was derived from the CRESCENT trial, a comprehensive randomized, double-blind clinical trial evaluating the effects of NSAIDs in over 400 hypertensives with type 2 diabetes and osteoarthritis who were on ACE inhibitors alone or in combination with other classes of antihypertensive therapy [25]. Treatment with rofecoxib 25 mg daily induced a significant destabilization of 24-hour systolic BP control compared to celecoxib 200 mg daily and naproxen 500 mg twice daily (fig. 1). During the course of the study, significantly more patients developed peripheral edema while taking rofecoxib compared to the other two treatment groups but no patient developed clinically significant kidney dysfunction.

Based on these clinical effects noted above, NSAIDs should be used with caution in hypertensive patients who are taking ACE inhibitors, angiotensin receptor blockers, or beta-blockers, as well as in patients who have diabetes or mild kidney disease. Of particular concern is that some patients are susceptible to the development of congestive heart failure. Data from population based cohort studies have demonstrated that patients who are prescribed NSAIDs and some COX-2 inhibitors develop substantial increased relative risks of hospitalization for heart failure compared to non-users of NSAIDs [48]. Thus, hypertensive patients, especially those with a history of left ventricular hypertrophy and diastolic dysfunction should be seen relatively soon (e.g., 1-3 weeks) after anti-inflammatory therapy is initiated.

Recent advances in the development of newer classes of anti-inflammatory agents that potentially have less BP destabilization are under investigation. A new study using an integrated safety analysis of 3 large osteoarthritis clinical trials characterized the effects of naproxen, a nitric oxide-donating cyclooxygenase inhibitor, on blood pressure after 13 weeks of therapy with naproxen, naproxen or
placebo, and included a subgroup taking renin-angiotensin system inhibitors [49]. The key finding of the study demonstrated that naproxcinod had BP effects similar to that of placebo, and changes from baseline in the naproxcinod 750 mg treated patients were significantly less than the changes in patients treated with naproxen 500 mg (equipotent to naproxcinod 750 mg) with similar efficacy for pain control in the entire study group, as well as in patients treated with RAS inhibitors (table 1).

Cardiovascular events in clinical arthritis trials

Cardiovascular event rates among users of NSAIDs have been evaluated in various types of study design. The initial studies that first examined CV events in arthritis populations were the VIGOR [3] and CLASS studies [2,50]. These two studies remain important with regard to outcomes as

| Group comparisons                              | Mean difference | (95% confidence intervals) | p value |
|------------------------------------------------|-----------------|----------------------------|---------|
| Systolic blood pressure                        |                 |                            |         |
| Naproxcinod 750 mg vs naproxen 500 mg          | —6.5 mmHg       | (—11.4, —1.5)              | 0.011   |
| Naproxcinod 375 mg vs naproxen 500 mg          | —4.2 mmHg       | (—9.1, 0.8)                | 0.096   |
| Naproxcinod 750 mg vs placebo                  | —0.4 mmHg       | (—5.4, 4.5)                | 0.864   |
| Naproxcinod 375 mg vs placebo                  | 1.9 mmHg        | (—3.1, 6.8)                | 0.462   |
| Naproxen 500 mg vs placebo                     | 6.1 mmHg        | (0.8, 11.3)                | 0.024   |
| Diastolic blood pressure                       |                 |                            |         |
| Naproxcinod 750 mg vs naproxen 500 mg          | —3.1 mmHg       | (—6.5, 0.3)                | 0.071   |
| Naproxcinod 375 mg vs naproxen 500 mg          | —1.3 mmHg       | (—4.7, 2.1)                | 0.445   |
| Naproxcinod 750 mg vs placebo                  | —1.0 mmHg       | (—4.4, 2.4)                | 0.578   |
| Naproxcinod 375 mg vs placebo                  | 0.9 mmHg        | (—2.6, 4.3)                | 0.623   |
| Naproxen 500 mg vs placebo                     | 2.2 mmHg        | (—1.4, 5.8)                | 0.236   |

Adapted from White WB, et al. Am J Cardiol 2009;104(6):840-5.
supra-therapeutic doses of COX-2 selective inhibitors were compared with maximal therapeutic NSAID doses in their target treatment population of osteoarthritis and/or rheumatoid arthritis. Findings were dissimilar for VIGOR and CLASS as absolute CV event rates were substantially higher with rofecoxib 50 mg daily than with naproxen 500 mg twice daily in the VIGOR trial [3], whereas in CLASS, rates were similar for celecoxib 800 mg daily, ibuprofen 2,400 mg daily, and diclofenac 150 mg daily [50]. The CV event rates in 2 meta-analyses of celecoxib and various NSAIDs [51,52] in the osteoarthritis and rheumatoid arthritis populations confirmed that there were similar rates of Anti-Platelet Trialists’ Collaboration (APTC) [53] adjudicated endpoints. Findings from a third COX-2 inhibitor trial [54], the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), were similar to those in CLASS but the cumulative incidence of APTC events in TARGET was quite low and did not differ between lumiracoxib and naproxen or ibuprofen. There were no placebo or non-inflammatory treatment arms in VIGOR, CLASS or TARGET since all of these patients suffered from arthritis and would not have tolerated a long-term trial without an active treatment. The CV event rates in the arthritis trials range from 0.7% in the TARGET [54] treatment arms to about 1% in the CLASS treatment arms [50] and pooled analyses of clinical trials for celecoxib [51] to approximately 2% in the rofecoxib arm in VIGOR [3]. Limitations of these trials include lack of power typically required for elucidating CV risk in a definitive fashion and a maximal treatment exposure of 15 months. In addition, VIGOR excluded patients taking low-dose acetaminophen acid while in CLASS and TARGET this was allowed if prescribed at baseline by the patient’s personal physician. Nevertheless, these controlled clinical trial data demonstrate that supratherapeutic doses of celecoxib and maximal doses of lumiracoxib have CV risk similar to that of the non-selective NSAIDs.

In comparison, the Multinational Etoricoxib andDiclofenac Arthritis Long-term (MEDAL) [55] program was a combined analysis of three randomized, double blinded, controlled trials comparing etoricoxib (60 or 90 mg daily) and diclofenac (150 mg daily) taken for 18 months in patients with arthritis. With long-term use of these drugs, the rates of thrombotic cardiovascular events in patients with arthritis on etoricoxib were shown to be similar to those in patients on diclofenac, yielding event rates of 1.24 and 1.30 per 100 patient-years with a hazard ratio of 0.95 (95% CI 0.81–1.11) for etoricoxib compared with diclofenac. Etoricoxib was associated with a significantly lower risk for adverse upper gastrointestinal events, such as ulcer, bleeding or perforation, with event rates of 0.67 vs 0.97 per 100 patient-years on diclofenac (hazard ratio 0.69; 95% CI 0.57–0.83). Although the MEDAL program was the first clinical program designed to assess non-inferiority for thrombotic cardiovascular events between a COX-2 selective and a traditional NSAID, the results observed cannot be extrapolated to other selective and nonselective NSAIDs [55].

Effects of acetaminophen on blood pressure

Surprisingly, there has been very little assessment of the cardiovascular effects of acetaminophen (or paracetamol), one of the most widely used pain analgesics in the world. Recently, Sudano et al. [56] demonstrated for the first time that acetaminophen induces a significant increase in ambulatory BP (mean systolic pressures from 122.4 ± 11.9 to 125.3 ± 12.0 mmHg, p = 0.02, and diastolic pressures from 73.6 ± 9.7 to 75.4 ± 7.9 mmHg, p = 0.02) vs placebo in patients with coronary artery disease, thus casting doubt that acetaminophen has an entirely ‘benign’ cardiovascular profile. The study was a randomized, double-blinded, placebo-controlled crossover study evaluating the effects of acetaminophen (1 g three times daily) administered for 2 weeks on ambulatory blood pressure, a variety of serum biomarkers, and platelet and vascular function in 33 patients with known coronary artery disease. Results of the various biomarkers and functional assessments studied in the trial were inconclusive [56,57]. As exposure to acetaminophen was limited to only 2 weeks and subjects had no pain indication results of the trial may not necessarily reflect the effects of the agent in a more typical clinical situation [56]. In fact, one concern is that longer-term use of acetaminophen might induce more substantial increases in BP than was observed in the study [57].

Observational studies that have assessed the cardiovascular risk of NSAIDs

Cardiovascular event rates in patients taking NSAIDs have been evaluated in numerous observational studies during the past decade. One well-known limitation of observational studies are that they are all generally retrospective and used either nested case-control or cohort analyses based on drug use in a database. Therefore, they will always pose some methodological concerns related to confounding, selection bias, and lack of information on non-prescription drugs, smoking status and aspirin use. However, the magnitude of the populations studied and the number of CV events analyzed enhance their scientific and clinical value. Many observational studies utilize similar methods but do vary greatly with regards to sample size, number of events, and duration of exposure.

The largest observational cohort study was performed using a database of Kaiser Permanente in northern California. Using a case-control design, Graham et al. [58] studied approximately 1.4 million people, who were observed for 2 years. Nonusers (including those who were remote users) of NSAIDs served as controls, and nonfatal myocardial infarction and sudden cardiac death associated with the use of various NSAIDs and COX-2 selective agents were then compared. Most of the non-selective NSAIDs increased the relative risk of a cardiac event compared with the control group. High doses (> 25 mg daily) of rofecoxib were associated with a particularly elevated risk of myocardial infarction and sudden death, whereas celecoxib was not.

An analysis of the risk of cardiac events including death in patients who had had a previous acute myocardial infarction was performed by Gislason et al. [59] in Denmark. In a cohort of about 60,000 patients, the use of the non-selective NSAIDs ibuprofen and diclofenac was fairly common (11-17%) while only 4-5% received either celecoxib or rofecoxib. In this analysis, the duration of exposure to the NSAIDs was usually under 90 days. Using a Cox proportional hazards analysis for
hazard ratios of death and re-hospitalization for MI, they reported a significant increased risk with any use of a nonselective NSAID and the selective COX-2 inhibitors. As was observed in the study by Graham et al. [58], the risk of cardiac events appeared to be increased with higher doses of the NSAIDs.

McGettigan et al. [60] pooled all of the NSAID observational studies from cohort and case-control studies. As shown in fig. 2A-D, some NSAIDs increased the risk of cardiovascular events (primarily acute myocardial infarction) compared to non-users of NSAIDs, whereas others did not increase the risk of cardiovascular events. Most notably were the increased CV event rates on rofecoxib and diclofenac and the lack of an increase in CV event rates on celecoxib and naproxen [60].

An observational study by Chan et al. [61] evaluated the effects of acetaminophen on potential cardiovascular events. The study was a prospective cohort of nearly 71,000 women between 44 and 69 years of age who had 2,041 confirmed CV events during 12 years of observation. Compared to non-users of NSAIDs or acetaminophen, women with frequent consumption of acetaminophen (> 22 days per month) had about the same increased risk of a CV event (RR 1.35; 95% CI 1.14—1.59) as women who took frequent NSAIDs (RR 1.44; 95% CI 1.27—1.65). The mechanism for increased CV events in women taking acetaminophen is unknown but the authors speculated that increases in blood pressure, inhibition of prostaglandin synthesis, and impaired endothelial function could all play a role.

**Prevention trials with COX Inhibitors**

Placebo-controlled COX-2 inhibitor trials in non-arthritis populations raised concern regarding CV safety—in fact, the safety data were published prior to their efficacy findings. In the first published trial, the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial [6], the composite cardiovascular event rate for CV death, nonfatal MI, and nonfatal stroke was 1.50 events/100 patient-years for rofecoxib 25 mg daily versus 0.78 events/100 patient-years for placebo; in the Adenoma Prevention with Celecoxib (APC) trial [62,63], the combined composite CV event rate of CV death, nonfatal MI and stroke plus hospitalized heart failure was approximately 0.4 events/100 patient-years for placebo, 0.86 events/100 patient-years for celecoxib 400 mg daily, and 1.27 events/100 patients-years for celecoxib 800 mg daily. Finally, in the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) [64] trial, the estimated rates of adjudicated CV events (MI, stroke, congestive heart failure) were 0.72 events/100 patient-years for placebo.
and 0.94 events/100 patient-years for celecoxib 400 mg daily. As shown in table 2, event numbers were low in these colonic polyp trials and would not typically be considered definitive by standards of preventive cardiology clinical trials. In addition to the polyp trials, a study entitled, Alzheimer’s Disease Anti-Inflammatory Prevention Trial (ADAPT) evaluated the effects of naproxen and celecoxib versus placebo for the primary prevention of Alzheimer’s dementia. The ADAPT trial was terminated prematurely as a result of interim data analysis suggesting increased CV disease and stroke risk in the low dose naproxen group (220 mg twice daily) compared to placebo; of note, the risk on celecoxib was similar to placebo [65]. The implications of the findings from the APPROVe, APC, PreSAP and ADAPT trials relate primarily to disease prevention and not necessarily for the chronic treatment of arthritis pain and inflammation.

Conclusions

The data that have accumulated in the past 5-7 years underscore the importance of analyzing the risks and benefits of traditional NSAIDs and COX-2 selective inhibitors when making decisions for the management of chronic arthritis pain and inflammation. Since the majority of patients with moderate to severe arthritis who might benefit from NSAID or COX-2 therapy are likely to be elderly they are also at high risk for gastrointestinal and CV adverse events. Additionally, many of these patients are likely to be taking low-dose aspirin and could be using available over-the-counter NSAIDs for pain as well. Selecting a combination of therapies that provide relief from arthritis-related symptoms, minimizes CV risk, and preserves the gastrointestinal mucosa is complex. The data accumulated thus far suggest that certain NSAIDs and COX-2 inhibitors might induce small absolute increases in CV events compared to placebo or non-users of the NSAIDs. There was also evidence that rofecoxib in supra-therapeutic doses increased CV events relative to naproxen but this finding has not been proven with direct clinical trials comparing celecoxib, etoricoxib, or lumiracoxib versus other NSAIDs. Other important factors to consider for patient safety include the potential interference of proprionic acid NSAIDs, (e.g., ibuprofen or naproxen), with the antiplatelet effects of aspirin, direct effects of non-selective NSAIDs and of COX-2 selective inhibitors on fluid retention and blood pressure, differences between these agents with regard to associated gastrointestinal adverse event rates, and the utility of co-administration of anti-inflammatory therapies with gastro-protective agents such as proton pump inhibitors when patients require cardio-protective doses of aspirin. Recent developments for potentially improving safety of NSAIDs has included the development of new classes of anti-inflammatory and analgesic agents, such as COX-inhibiting nitric oxide donators [64] and selective E prostanoid receptor antagonists [66,67]. These agents appear to induce less blood pressure destabilization particularly in patients on antihypertensive therapies.

Conflict of interest statement

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### Table 2

Cardiovascular events’ (adjudicated) from COX-2 inhibitor colonic polyp prevention trials.

| Name of trial   | N     | COX-2 inhibitor          | Placebo events/N (rate/100 pt-years) | COX-2 inhibitor events/N (rate/100 pt-years) |
|-----------------|-------|--------------------------|-------------------------------------|-------------------------------------------|
| APPROVe         | 2,586 | Rofecoxib (25 mg)        | 26/1,299 (0.78)                     | 46/1,287 (1.50)**                      |
| APC             | 2,035 | Celecoxib (200 mg bid)   | 7/676 (0.40)                        | 18/683 (0.86)                         |
| PreSAP          | 1,561 | Celecoxib (400 mg qd)    | 12/628 (0.72)                       | 23/933 (0.94)                        |

** Significant compared to the placebo rate.

APPROVe = The Adenomatous Polyp Prevention on Vioxx trial; APC = The Adenoma Prevention with Celecoxib trial; PreSAP = The Prevention of Colorectal Sporadic Adenomatous Polyps trial; QD = once daily; BID = twice daily.

Events include cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and the development of congestive heart failure.
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