

# RHYTHMOS



April 2015 • Volume 10 • No 2 (38)

ISSN: 1792-7919

e-ISSN: 1792-7927

URL: [www.rhythmos.gr](http://www.rhythmos.gr) / <http://rhythmos.info.tn> / <http://www.evangelismos.dom.gr>

*Editor-in-Chief: Antonis S. Manolis, MD*

*Editorial Staff: Spyridon Koulouris, MD, Sokratis Pastromas, MD, Kostas Triantafyllou, MD, Ektor Anninos, MD, Effie Rouska, MD*

## ΡΥΘΜΟΣ

*Διευθυντής Σύνταξης: Αντώνης Σ. Μανώλης*

*Μέλη: Σπυρίδων Κουλούρης, Σωκράτης Παστρωμάς, Κώστας Τριανταφύλλου, Έκτωρ Άννινος, Έφη Ρούσκα*

### EDITORIAL

#### **Adverse Cardiovascular Events with Nonsteroidal Anti-inflammatory Agents**

*Antonis S. Manolis, MD*

Athens University School of Medicine, Athens, Greece

#### ABSTRACT

The extensive use of nonsteroidal anti-inflammatory drugs (NSAIDs), both nonselective and cyclooxygenase-2-specific inhibitors, for the relief of acute and chronic musculoskeletal pain, in addition to gastrointestinal toxicity, confers serious cardiovascular toxicity that affects the overall risk/benefit ratio of this commonly employed therapy. A plethora of studies have provided convincing evidence for a high risk of adverse cardiovascular events associated with NSAIDs related to a number of risk factors, which are herein briefly reviewed and an algorithm is suggested for their safer use. (*Rhythmos* 2015;10(2):21-27)

**Key Words:** nonsteroidal anti-inflammatory drugs; coxibs; osteoarthritis; rheumatoid arthritis; cardiovascular disease; hypertension; myocardial infarction; heart failure

**Abbreviations:** COX = cyclooxygenase; CV = cardiovascular; GI = gastrointestinal; MACE = major adverse cardiac events; MI = myocardial infarction; NSAIDs = non-steroidal anti-inflammatory drugs PPI = proton pump inhibitor

### INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) comprise nonselective and cyclooxygenase (COX)-2-specific inhibitors (Table 1), which are extensively used for the relief of acute and chronic pain associated with several medical conditions, like rheumatoid arthritis and osteoarthritis.<sup>1</sup> Their use will most likely increase as the prevalence of osteoarthritis increases because of increased expected longevity of the population. However, in a plethora of clinical trials, serious adverse cardiovascular (CV) events have been reported with NSAID use,<sup>2-10</sup> which constitutes an issue of public health importance that physicians should be aware of and guided by when prescribing these agents, especially in older individuals<sup>1</sup> who also have an increased prevalence of CV disease, or generally in patients with preexisting medical conditions.<sup>11</sup>

Nonselective NSAIDs, like ibuprofen and naproxen, inhibiting both COX-1 and COX-2, have been available since the seventies, while the newer selective cyclooxygenase-2 (COX-2) inhibitor drugs (the coxibs), like valdecoxib, rofecoxib and celecoxib, were introduced decades later (end of nineties).<sup>12</sup>

With regards to CV adverse effects of NSAIDs, the data are quite worrisome,<sup>2,4,7,10,13</sup> although some studies have produced mixed results.<sup>5,12,14,15</sup> COX-2 inhibitors have been found to induce myocardial infarction (MI) and

strokes, which have led to the withdrawal of rofecoxib and valdecoxib.<sup>3,6</sup> The Alzheimer's Disease Anti-inflammatory Prevention (ADAPT) trial was discontinued, in part because of an excess of CV events noted with naproxen.<sup>16</sup> On the other hand, pooled data from 13 trials with 7718 participants showed that nonselective NSAIDs had no significant effect on CV events (odds ratio-OR 1.3).<sup>12</sup> No significant effect was seen for joint disease trials (OR 0.6) or Alzheimer disease trials (OR 1.6).<sup>12</sup> There was no significant difference in results for naproxen and non-naproxen NSAIDs.

**Table 1. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**

Non-Selective	Selective COX-2 Inhibitors
<b>Salicylic Acid Derivatives</b> <ul style="list-style-type: none"><li>● Aspirin</li><li>● Sulfasalazine</li></ul>	<ul style="list-style-type: none"><li>● Celecoxib</li><li>● Etoricoxib</li><li>● Lumiracoxib *</li></ul>
<b>Par-aminophenol Derivatives</b> <ul style="list-style-type: none"><li>● Acetaminophen (Paracetamol)</li></ul>	<ul style="list-style-type: none"><li>● Valdecoxib **</li></ul>
<b>Indole and Indene Acetic Acids</b> <ul style="list-style-type: none"><li>● Indomethacin</li><li>● Sulindac</li><li>● Etodolac</li></ul>	<ul style="list-style-type: none"><li>● Rofecoxib **</li><li>● Parecoxib</li></ul>
<b>Heteroaryl Acetic Acids</b> <ul style="list-style-type: none"><li>● Diclofenac</li><li>● Ketorolac</li></ul>	
<b>Arylpropionic Acids</b> <ul style="list-style-type: none"><li>● Ibuprofen</li><li>● Ketoprofen</li><li>● Naproxen</li><li>● Fenoprofen</li><li>● Fluriprofen</li><li>● Loxoprofen</li></ul>	
<b>Anthranilic Acids (Fenamates)</b> <ul style="list-style-type: none"><li>● Mefenamic acid</li></ul>	
<b>Enolic Acids</b> <ul style="list-style-type: none"><li>● Oxicams</li></ul>	
(Piroxicam/Meloxicam)	
<b>Sulfonanilides</b> <ul style="list-style-type: none"><li>● Nimesulide</li></ul>	

\* Not available due to serious hepatotoxicity  
\*\* Rofecoxib and valdecoxib have been withdrawn from the market  
N.B.: Celecoxib is currently the only COX-2 inhibitor available in the United States<sup>17</sup>

The cardiotoxicity associated with use of NSAIDs may be attributed to increase in blood pressure, inhibition of prostacyclin synthesis, oxidative stress, and impaired endothelial function (Table 2). Both selective and nonselective NSAIDs inhibit COX-2-mediated prostaglandin E2 production, thus producing their analgesic and anti-inflammatory effects.<sup>12</sup> Inhibition of COX-1 by nonselective NSAIDs reduces the platelet aggregating factor thromboxane, which may have a cardioprotective effect as has been found with low-dose aspirin. Gastrointestinal (GI) toxicity is mitigated with use of COX-2 inhibitors compared with nonselective NSAIDs

as COX-1-mediated cytoprotection is maintained. On the other hand, COX-2 inhibitors may have an adverse atherothrombotic profile, due to unopposed thromboxane synthesis and platelet aggregation. Furthermore, both nonselective and COX-2-selective NSAIDs have been associated with an increased incidence of hospitalization for congestive heart failure and high blood pressure.<sup>10, 17</sup>

**Table 2. Factors Conferring Cardiovascular Risk by NSAIDs**

- Hypertensive effect or impaired response to antihypertensive therapy (retention of sodium, increased renal vascular constriction, microvascular dysfunction)
- Vascular disruption of COX-2 leading to depressed expression of endothelial nitric oxide synthase and consequent release and function of nitric oxide
- Impaired endothelial function
- Interaction with aspirin (interference with the antiplatelet effects of aspirin)
- Prothrombotic effect of COX-2 inhibition, e.g. decreased production of the vasodilator prostacyclin (which also inhibits platelet activation) with concomitant unimpeded COX-1-mediated production of platelet thromboxane A2
- Disruption of COX-2 dependence of hemodynamic stability and renal function
- Oxidative stress

**NONSELECTIVE NONSTEROIDAL ANTI-INFLAMMATORY DRUGS**

An increase in arterial blood pressure is seen within weeks of starting treatment with a NSAID.<sup>6</sup> However, the magnitude of the hypertensive response varies from drug to drug within this class. For example, naproxen exerts minimal vasopressor effect, whereas blood pressure rises consistently during treatment with diclofenac. The impression is that the blood pressure rise secondary to NSAIDs is dose dependent, but there are few dose-response clinical trials reporting effects on blood pressure. Most studies of the hypertensive response to NSAIDs have focused on the role of the kidneys, because NSAIDs cause sodium retention and interfere with the action of antihypertensive drugs.<sup>6</sup> In general, the available evidence suggests that the increase in CV risk of NSAIDs is commensurate with their hypertensive effect; however, interplay with several other factors may be equally important.

An initial analysis of the REACH Registry was limited to 23,728 European patients (aged 67.2±9.8 years).<sup>8</sup> A total of 20,588 (86.8%) had established atherothrombotic disease and 3140 (13.2%) had multiple risk factors only. At baseline, 1573 patients (6.6%) received NSAIDs and 15,395 (64.9%) received aspirin. Among the 22,028 (92.8%) with complete 2-year follow-up, 683 (3.2%) died from CV causes, while 395 (1.9%) had MI, 665 (3.1%)

stroke, 1651 (7.6%) cardiac major adverse CV events (MACE) (defined as the composite of CV death, MI or stroke) and 199 (1%) bleeding. NSAID use was independently associated with an increased risk of stroke (odds ratio-OR 1.635;  $p < 0.001$ ), and a trend towards an increased bleeding rate (OR 1.554;  $p = 0.07$ ). No association was found between NSAID use and MI or MACE. The authors concluded that NSAID use in stable patients with established atherothrombotic disease or multiple risk factors is independently associated with a 64% increase in stroke rates at 2 years, whereas no significant effect was observed on CV death or non-fatal MI.

However, a more recent analysis from the same Registry, albeit of the entire registry population, comprising 44,095 patients showed different results about the use of NSAID over 4 years of follow-up.<sup>10</sup> NSAID use was associated with an increased hazard for MI (hazard ratio - HR 1.37;  $P = 0.002$ ), stroke (HR 1.21;  $P = 0.048$ ), heart failure hospitalizations (HR 1.18;  $P = 0.013$ ), and ischemic hospitalizations (HR 1.17;  $P = 0.001$ ) or combined end-points (CV death/MI/ stroke/ ischemic hospitalizations, HR 1.12,  $P = 0.003$ ; CV death/MI/ stroke, HR 1.16,  $P = 0.02$ ). The authors concluded that among patients with stable atherothrombosis, NSAID use was associated with a higher risk of MI, stroke, and hospitalizations for both ischemia and heart failure.

As already mentioned, in another meta-analysis of 13 randomized controlled trials assessing the effect of NSAIDs on CV events in trials of joint disease and Alzheimer's disease, the authors concluded that NSAIDs had no significant effect on CV events or death in the joint disease trials, but an indication for risk was present in trials of Alzheimer's disease.<sup>12</sup> They also stated that there was no significant adverse or cardioprotective effect of naproxen.

#### CYCLOOXYGENASE-2 NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The first observation of NSAID-associated CV risk came from the Vioxx Gastrointestinal Outcomes Research Study (VIGOR), which demonstrated a fivefold difference in the incidence of acute MI between patients treated with rofecoxib 50 mg/day and naproxen 1000 mg/day,<sup>2</sup> and was further corroborated by a meta-analysis of clinical trials of celecoxib and rofecoxib.<sup>18</sup> In addition, a nested case-control study sought to establish if risk was enhanced with rofecoxib at either high or standard doses compared with remote NSAID use or celecoxib use.<sup>3</sup> A total of 1,394,764 people contributed 2,302,029 person years of observation time to the study cohort of NSAID users. Patients received various NSAIDs, including celecoxib ( $n = 40,405$ ), ibuprofen (991,261), naproxen (435,492), and rofecoxib (26,748). From this cohort, 8143 cases of serious coronary

heart disease and 31,496 matched controls were identified. Among the cases, 2210 (27.1%) were fatal. Multivariate odds ratios versus celecoxib were: for rofecoxib (all doses), 1.59 ( $p = 0.015$ ); for rofecoxib  $\leq 25$  mg/day, 1.47 ( $p = 0.054$ ); and for rofecoxib  $> 25$  mg/day, 3.58 ( $p = 0.016$ ). For naproxen versus remote NSAID use the odds ratio was 1.14 ( $p = 0.05$ ). The authors concluded that rofecoxib use increases the risk of serious coronary heart disease compared with celecoxib use, while naproxen use does not protect against serious coronary heart disease.

Another meta-analysis comprised 7,462 patients who received celecoxib (200 - 800 mg/day) for 1,268 patient-years who were compared with 4,057 patients treated with placebo for 585 patient-years, as well as 19,773 patients treated with similar dose of celecoxib for 5,651 patient-years who were compared with 13,990 patients treated with nonselective NSAIDs (diclofenac, ibuprofen, naproxen, ketoprofen, and loxoprofen) for 4,386 patient-years.<sup>5</sup> The incidence rates of the combined CV events were not significantly different between patients treated with celecoxib and placebo or between those treated with celecoxib and nonselective NSAIDs. Dose of celecoxib, the use of aspirin, or the presence of CV risk factors did not change these results. The authors concluded that these analyses failed to demonstrate an increased CV risk with celecoxib relative to placebo and demonstrated a comparable rate of CV events with celecoxib treatment compared with nonselective NSAIDs. The authors also acknowledge a major limitation of their analysis, since all but one of the comparator trials did not exceed 1 year of patient follow-up.<sup>5</sup>

#### NONSELECTIVE AND SELECTIVE NSAIDS

A recent Danish study<sup>19</sup> examined the risk of bleeding and CV events among 61,971 patients (mean age, 68) with prior MI taking antithrombotic drugs, who were also prescribed a NSAID. The number of deaths during a median follow-up of 3.5 years was 18,105 (29.2%). A total of 5288 bleeding events (8.5%) and 18,568 CV events (30%) occurred. The crude incidence rates of bleeding (events per 100 person-years) were 4.2 with concomitant NSAID treatment and 2.2 without NSAID treatment, whereas the rates of CV events were 11.2 and 8.3. Multivariate analysis found increased bleeding (hazard ratio-HR, 2.02) and CV risk (HR, 1.40) with NSAID treatment compared with no NSAID treatment. An increased risk of bleeding and CV events was evident with concomitant use of NSAIDs, regardless of antithrombotic treatment, types of NSAIDs, or duration of use. The authors concluded that among patients receiving antithrombotic therapy after MI, the use of NSAIDs was

associated with increased risk of bleeding and excess thrombotic events, even after short-term treatment.

In a post-hoc analysis from the INternational Verapamil Trandolapril STudy (INVEST),<sup>7</sup> which enrolled patients with hypertension and coronary artery disease, at a mean follow-up of 2.7 years, the primary outcome (all-cause death, nonfatal MI or stroke) occurred at a rate of 4.4 events per 100 patient-years in the chronic NSAID group (n=882), vs 3.7 events per 100 patient-years in the non-chronic NSAID group (n=21,691; 14,408 never users and 7286 intermittent users) (HR 1.47;  $P = 0.0003$ ). This was due to an increase in CV mortality (HR 2.26;  $P < 0.0001$ ). The authors concluded that among hypertensive patients with coronary artery disease, chronic self-reported use of NSAIDs was associated with an increased risk of adverse events during long-term follow-up.

A recent Danish analysis<sup>20</sup> of two cohort studies and two case-control studies explored additional (to MI, stroke, heart failure, and hypertension) NSAID-associated CV risks. The authors examined whether use of non-aspirin NSAIDs was associated with risk of MACE after coronary stent implantation, risk of venous thromboembolism, risk of atrial fibrillation, and 30-day stroke mortality. They reported that use of non-aspirin NSAIDs was not associated with MACE following coronary stent implantation, but was associated with an increased risk of venous thromboembolism, atrial fibrillation, and 30-day mortality following ischemic stroke, especially when therapy with selective COX-2 inhibitors was initiated.

The MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long Term) program assessed the relative CV safety of two long-term anti-inflammatory treatments, etoricoxib and diclofenac, in 34,701 patients, 24,913 with osteoarthritis and 9,787 with rheumatoid arthritis.<sup>21</sup> Over an average treatment duration of 18 months, the rates of thrombotic CV events in patients on etoricoxib were similar to those in patients on diclofenac. Another analysis found a continuous linear dose relationship between specific diclofenac doses and the risk of a serious GI or CV event, thus giving credence to guidelines that recommend the use of NSAIDs at the lowest effective dose for the shortest duration.<sup>22-25</sup>

## BALANCING RISKS AND BENEFITS

NSAID selectivity is a continuous, not a dichotomous, variable, and rather a function of dose, while the risk varies from drug to drug.<sup>23</sup> Diclofenac and celecoxib, for example, have almost equal selectivity. However, a COX-2 inhibitor given at high dose becomes a COX-1 inhibitor. Thus, high doses of COX-2 NSAIDs should be avoided. Most long-term data indicating increased CV risk are derived from trials with selective NSAIDs, but, as

indicated above, an increase in overall CV risk is not confined to COX-2 NSAIDs and may be shared by a number of nonselective NSAIDs for which the data appear equally worrisome.<sup>6, 25</sup>

**NSAID-aspirin interaction.** Clinical trials and observational studies support the hypothesis that nonselective NSAIDs interfere with the antiplatelet effects of aspirin and block its cardioprotective effects. It has been shown that ibuprofen taken 2 hours before an aspirin dose may occupy the site during the entire time that aspirin is available to the platelet for permanent acetylation. The Food and Drug Administration (FDA) has issued a MedWatch that cautioned patients about the potential for ibuprofen to interfere with the CV protective effect of low-dose aspirin.<sup>6</sup> The FDA stated that since there are no data about the effect of other NSAIDs, until proven otherwise, patients should take aspirin 2 hours *before* taking an NSAID. In contrast, selective COX-2 inhibitors do not interfere with the actions of aspirin and preserve its ability to reduce the risk of MI and stroke in high-risk patients. On the other hand, studies to date suggest that aspirin lacks a favorable effect on CV risk in patients who take a selective COX-2 inhibitor. Thus, based on current data, a patient who takes aspirin for secondary prevention should not be prescribed a COX-2 inhibitor.

**Hypertensive and CV Risk.** The impact of NSAIDs in a non-hypertensive patient population is much less than in a hypertensive population, especially patients on angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta-blockers, and perhaps diuretics— but *not* calcium channel blockers. The available evidence suggests that selective and nonselective NSAIDs do not increase CV risk in the absence of a clinically meaningful increase in blood pressure.

Among hypertensive patients on drug therapy, NSAIDs have a much larger effect in elevating the blood pressure<sup>6</sup> or have harmful effects even when blood pressures appears controlled.<sup>7</sup> The biggest changes are seen in patients on ACE inhibitors and beta blockers, because NSAIDs appear to interfere with the action of those drugs. Blood pressure control in patients on calcium channel blockers appears to be unaffected by NSAIDs.

The package-insert labeling on the CV risk of NSAIDs states, “NSAID may cause an increased risk of serious CV thrombotic events, MI, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with CV disease or CV risk factors may be at greater risk. NSAID is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft surgery.”

A NSAID may promote **thrombus formation**. It is important to differentiate between the effects of traditional



NSAIDs and the COX-2s on thrombotic risk and hypertension. Both drug classes increase blood pressure and if untreated over the long term, this increase in blood pressure can contribute to the progression of CV disease, as would the hypertension of any etiology. However, the events that raised concern about the safety of these medications were acute thrombotic events, like MI and stroke. However, these events are not the consequence of hypertension per se. This pathogenic mechanism is consistent with the effects of COX-2 selectivity and dose (i.e., more selective, higher doses), increasing baseline CV risk, and increased duration of treatment on the incidence of acute CV events. Furthermore, NSAIDs make platelets more reactive. The thrombotic event is a plaque rupture. Taking an NSAID, which inhibits prostacyclin, shifts platelet reactivity and increases the likelihood of thrombus formation because the inhibitory effect of prostacyclin is decreased or lost. It should be noted that with an acute MI, the NSAID increases the risk.

**Balancing GI and CV Risk.** If a patient has not responded or does not choose to undertake initial non-pharmacological approaches for the arthritic pain, it is recommended to start with a drug like acetaminophen, which, although not free of risk, may have less identified GI and CV risks. However, acetaminophen does have some hepatic and renal risk. In most guidelines, acetaminophen is a first-line drug.<sup>24,25</sup> Aspirin is not really included in the guidelines, beyond low-dose aspirin, because the GI toxicity of aspirin beyond low doses is higher than that of any of the other NSAIDs. If an NSAID is required, the question arises as to which one should be prescribed. It is here that risk factors for GI tract bleeding become important and probably outweigh CV risk. These drugs are more alike in their CV risk than GI risk. In patients with higher GI risk, the risk/benefit ratio shifts in the direction of the COX-2 inhibitors (Fig. 1). For patients already taking low-dose aspirin, the risk/benefit also shifts in favor of COX-2s, compared to nonselective NSAIDs, with their potential aspirin interaction. It should also be noted that *Helicobacter pylori* eradication reduces the risk of GI complications of NSAIDs.<sup>26</sup>

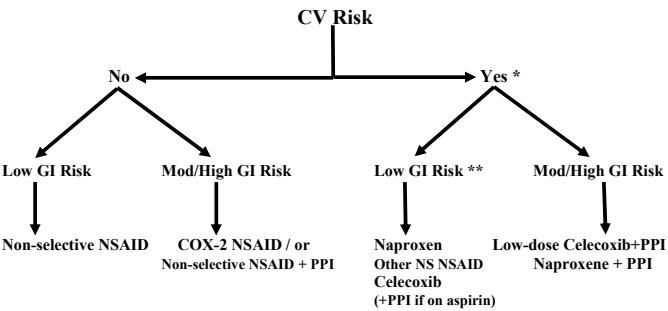
Also one should remember that risks with NSAIDs include hypertension and edema, but the *biggest* risk has always been GI bleeding. The quoted rate is up to 50,000 deaths per year related to GI bleeding, with 10,000 preventable deaths! If one could reduce those in half with a strategy of using either a proton pump inhibitor (PPI) with a nonselective NSAID or a COX-2 inhibitor, then one would have considerably improved morbidity and mortality in this patient population. Indeed, rheumatologists worry more about complications of the GI tract than the heart.

Thus, GI bleeding is a major concern for patients taking NSAIDs. However, some clinicians are concerned that the GI safety advantage of COX-2-selective drugs is offset by an increase in CV risk. The GI safety advantage of 50 mg of rofecoxib compared to 500 mg bid naproxen in the VIGOR trial *was* offset by a similar increase in CV events. A similar increase in CV events was not seen in the CLASS (Celecoxib Long-Term Arthritis Safety Study) trial in patients using 800 mg of celecoxib compared to usual doses of ibuprofen or diclofenac.<sup>27</sup> Both these trials were powered for GI events, and unfortunately, there are no published randomized controlled trials with COX-2 inhibitors powered for CV end points. In a large observational study of approximately 1.4 million patients in the California Kaiser-Permanente system, use of more than 25 mg of rofecoxib was associated with an increased CV risk of about 300%, approximately the equivalent of the CV risk of cigarette smoking.<sup>3</sup> However, a similar risk was not seen in this study with lower doses of rofecoxib and there was no observed increase in risk with celecoxib compared to nonusers of NSAIDs. A major discussion in rheumatology apparently is whether to prescribe a COX-2 inhibitor in patients with increased GI risk or a non-selective NSAID plus a PPI and whether patients will be compliant. In the absence of a tablet combining a PPI plus a NSAID, a COX-2 inhibitor has an advantage based on patient compliance with use of a single drug instead of two. The risk of GI bleeding on an NSAID plus a PPI regimen is about the same as a COX-2 inhibitor alone. In elderly patients with a prior history of GI bleeding who are on low dose aspirin, celecoxib plus a PPI is another alternative.

**NSAID Agent Selection.** It is important that cardiologists, who are not among those physicians frequently prescribing NSAIDs, have a particular responsibility to be apprised of current information and data relevant to the CV risks of NSAIDs, especially when these agents are administered to patients receiving low-dose aspirin for cardioprotection.<sup>28</sup> Moreover, every physician prescribing these agents should carefully weigh the benefits and risks of the use of NSAIDs from a CV and GI perspective by thoughtfully synthesizing the evidence for CV safety and prudently making decisions for individual patients (Fig. 1).<sup>17</sup>

According with a recent meta-analysis of data on the relative risk of CV events with individual NSAIDs listed on the Essential Medicines Lists (EMLs) of several countries, 3 drugs (rofecoxib, diclofenac, etoricoxib) had consistently highest CV risk compared with nonuse.<sup>9</sup> Naproxen was associated with a low risk. Diclofenac was listed on 74 national EMLs, naproxen on 27. Rofecoxib use was not documented in any country, since its withdrawal. Diclofenac and etoricoxib accounted for one-

third of total NSAID usage. Diclofenac was by far the most commonly used NSAID. The authors concluded that listing of NSAIDs on national EMLs should take into account the associated CV risk, and since diclofenac has a risk very similar to rofecoxib, it should be withdrawn from the market and removed from EMLs.



**Figure 1.** A suggested algorithm for use of NSAIDs. COX = cyclooxygenase; CV = cardiovascular; GI = gastrointestinal; Mod = moderate; NS = non-selective; NSAID = non-steroidal anti-inflammatory drug; PPI = proton pump inhibitor.

\* The American Heart Association<sup>25</sup> suggests a stepped-care approach to pharmacological therapy for the management of musculoskeletal symptoms in patients with known CV disease or risk factors, focusing on agents with the lowest reported risk of CV events (acetaminophen, aspirin, tramadol, narcotic analgesics, nonacetylated salicylates) and then progressing toward other agents associated with increasing levels of CV risk, that is, *non-COX-2-selective NSAIDs* → *NSAIDs with some COX-2 activity* → *COX-2-selective NSAIDs*.

\*\* *Ibuprofen is contraindicated when on aspirin.*

**N.B.:** NSAIDs should be taken at the lowest effective dose for the shortest possible time to minimize both CV and GI risks.

The loss of prostaglandins has important homeostatic CV effects. When a selective or nonselective NSAID is given, a variety of prostaglandins are inhibited in the joint tissues, in the kidneys, and in blood vessels in a dose-dependent manner. When high doses of certain drugs are given to susceptible patients, CV risk can increase.

Because risk has been established for many selective COX-2 inhibitors but not for most nonselective NSAIDs, many clinicians prescribe a nonselective NSAID preferentially to patients who have 1 or more cardiac risk factors. However, there are no data suggesting that most nonselective NSAIDs carry less risk than most selective COX-2 inhibitors, regardless whether there is underlying hypertension or dyslipidemia. For patients with multiple underlying cardiac risk factors receiving low-dose aspirin, the evidence indicates that clinicians should prescribe a selective COX-2 inhibitor. In high-risk patients, it is critical to preserve the cardioprotective effects of aspirin, and this can be achieved only with a selective COX-2

inhibitor. Furthermore, there appears to be a dose effect of celecoxib in terms of CV risk, so at reasonably low doses, it may be relatively safe.

Thus, if an anti-inflammatory drug is needed for the treatment of arthritis, the current evidence suggests that either naproxen or a low dose of celecoxib (200 mg daily) has no measurable CV risk. The 2 drugs that appear to carry the *highest* CV risk are rofecoxib (selective COX-2 inhibitor) and diclofenac (nonselective NSAID). The evidence with diclofenac is particularly worrisome. Diclofenac causes increased blood pressure and increased CV risk in both clinical trials and epidemiological studies.

Current recommendations also indicate that NSAIDs should be taken at the lowest effective dose for the shortest possible time to minimize both CV and GI risks.<sup>22, 23</sup> Caution should be particularly exercised in prescribing COX-1 and 2 inhibitors for musculoskeletal disorders in patients who already suffer from GI or CV conditions.

Most recently, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) issued a warning of an increased risk of CV events in patients who take high doses of ibuprofen. The Committee states that there is a small increase in the risk of MI and stroke with ibuprofen when taken at doses of 2400 mg/day or higher ([http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2015/04/news\\_detail\\_002306.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/04/news_detail_002306.jsp&mid=WC0b01ac058004d5c1)). The risk, according to the committee, is similar to the risk observed with other NSAIDs, such as COX-2 inhibitors and diclofenac. However, the EMA had earlier stated that there was a consistent but small increase in the risk of CV side effects with diclofenac compared with other NSAIDs ([http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2013/06/news\\_detail\\_001830.jsp&mid=WC0b01ac058001d126](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001830.jsp&mid=WC0b01ac058001d126)).

A very large prospective randomized NSAID study will be reporting long-awaited CV safety results in the next year.<sup>29</sup> The PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen) trial has randomized approximately 24,000 patients with symptomatic rheumatoid arthritis or osteoarthritis and at high risk for or with established CV disease to 1 of 3 available NSAIDs (celecoxib, ibuprofen or naproxen).

From the above discussion, it becomes clear that we are in dire need to develop new and effective NSAID formulations to minimize the safety and tolerability concerns associated with currently available NSAIDs, yet maintain efficacy in management of inflammation and pain.<sup>30</sup>

## REFERENCES

- Pilotto A, Sancarlo D, Addante F, Scarcelli C, Franceschi M. Non-steroidal anti-inflammatory drug use in the elderly. *Surg Oncol* 2010;19:167-172.
- 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* 2000;343:1520-1528.
- Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet* 2005;365:475-481.
- Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;352:1071-1080.
- White WB, West CR, Borer JS, et al. Risk of cardiovascular events in patients receiving celecoxib: a meta-analysis of randomized clinical trials. *Am J Cardiol* 2007;99:91-98.
- Friedewald VE, Jr., Bennett JS, Packer M, Roberts WC and Williams GW. The editor's roundtable: nonsteroidal antiinflammatory drugs and cardiovascular risk. *Am J Cardiol* 2008;102:1046-1055.
- Bavry AA, Khaliq A, Gong Y, et al. Harmful effects of NSAIDs among patients with hypertension and coronary artery disease. *Am J Med* 2011;124:614-620.
- Barthelemy O, Limbourg T, Collet JP, et al. Impact of non-steroidal anti-inflammatory drugs (NSAIDs) on cardiovascular outcomes in patients with stable atherothrombosis or multiple risk factors. *Int J Cardiol* 2013;163:266-271.
- McGettigan P and Henry D. Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries. *PLoS Med* 2013;10:e1001388.
- Kohli P, Steg PG, Cannon CP, et al. NSAID use and association with cardiovascular outcomes in outpatients with stable atherothrombotic disease. *Am J Med* 2014;127:53-60.e51.
- Huang WF, Hsiao FY, Wen YW, Tsai YW. Cardiovascular events associated with the use of four nonselective NSAIDs (etodolac, nabumetone, ibuprofen, or naproxen) versus a cyclooxygenase-2 inhibitor (celecoxib): a population-based analysis in Taiwanese adults. *Clin Ther* 2006;28:1827-1836.
- Salpeter SR, Gregor P, Ormiston TM, et al. Meta-analysis: cardiovascular events associated with nonsteroidal anti-inflammatory drugs. *Am J Med* 2006;119:552-559.
- Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092-1102.
- White WB, Faich G, Borer JS and Makuch RW. Cardiovascular thrombotic events in arthritis trials of the cyclooxygenase-2 inhibitor celecoxib. *Am J Cardiol* 2003;92:411-418.
- Lee TA, Bartle B and Weiss KB. Impact of NSAIDs on mortality and the effect of preexisting coronary artery disease in US veterans. *Am J Med* 2007;120:98.e99-16.
- ADAPT Research Group. Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT). *PLoS Clin Trials* 2006;1:e33.
- Scheiman JM. Balancing risks and benefits of cyclooxygenase-2 selective nonsteroidal anti-inflammatory drugs. *Gastroenterol Clin North Am* 2009;38:305-314.
- Mukherjee D, Nissen SE and Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001;286:954-959.
- Schjerning Olsen AM, Gislason GH, McGettigan P, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. *JAMA* 2015;313:805-814.
- Schmidt M. Cardiovascular risks associated with non-aspirin non-steroidal anti-inflammatory drug use. *Dan Med J* 2015;62.
- Cannon CP, Curtis SP, FitzGerald GA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006;368:1771-81.
- Odom DM, Mladsi DM, Saag KG, et al. Relationship between diclofenac dose and risk of gastrointestinal and cardiovascular events: meta-regression based on two systematic literature reviews. *Clin Ther* 2014;36:906-917.
- Patrono C, Baigent C. Nonsteroidal anti-inflammatory drugs and the heart. *Circulation* 2014;129:907-916.
- Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)* 2012;64:465-474.
- Antman EM, Bennett JS, Daugherty A, et al. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. *Circulation* 2007;115:1634-1642.
- Jones R, Rubin G, Berenbaum F and Scheiman J. Gastrointestinal and cardiovascular risks of nonsteroidal anti-inflammatory drugs. *Am J Med* 2008;121:464-474.
- Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000;284:1247-1255.
- Farkouh ME and Greenberg BP. An evidence-based review of the cardiovascular risks of nonsteroidal anti-inflammatory drugs. *Am J Cardiol* 2009;103:1227-1237.
- 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* 2009;157:606-612.
- McCarberg B, Gibofsky A. Need to develop new nonsteroidal anti-inflammatory drug formulations. *Clin Ther* 2012;34:1954-1963.