AMERICAN COLLEGE of CARDIOLOGY

Balancing Risks and Benefits: Cardiovascular Safety of NSAIDs

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The following are key points from a review on the cardiovascular safety of non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs):

1. There are at least two major isoforms of the cyclooxygenase (COX) enzyme: COX-1 and COX-2. Both isoforms catalyze the conversion of the unsaturated fatty acid into prostaglandin H2, which is further modified by tissue-specific isomerases into bioactive lipids (prostanoids). COX-1 is expressed constitutively in most tissues and regulates normal cellular processes such as platelet aggregation or thrombosis. COX-2 is usually undetectable in most tissues and is expressed in response to induction by inflammatory cytokines. Platelets contain only COX-1, which converts arachidonic acid to thromboxane A2, a potent pro-aggregatory and vasoconstrictive agent.
2. The inhibition of the endogenous COX-1-mediated production of prostaglandins in the gastric mucosal cells increases the risk of gastrointestinal toxicity. It was expected, consequently, that COX-2 selective NSAIDS would possess anti-inflammatory, analgesic, and antipyretic activity, without increasing the risk of gastrointestinal complications.
3. Even before the approval of coxibs, it was anticipated that they could constitute a cardiovascular hazard because the selective COX-2 inhibition would shift the prothrombotic balance on the endothelial surface and favor thrombosis by inhibiting the generation of COX-2-derived vascular prostacyclin while not affecting the COX-1-mediated generation of thromboxane A2.

4. The publication of the APPROVe (Adenomatous Polyp Prevention on Vioxx) trial in 2004 led to withdrawal of rofecoxib from the market. This trial showed that the use of rofecoxib was associated with an increase in thrombotic events. The ACP (Adenoma Prevention with Celecoxib) study showed similarly increased vascular risks associated with Celecoxib use.
5. A meta-analysis of 138 randomized trials comparing the effect of coxibs and traditional NSAIDs on the risk of vascular events demonstrated that coxibs (relative risk, 1.42; 95% confidence interval, 1.13-1.78), as well as high-dose diclofenac (1.63, 1.12-2.37) and ibuprofen (1.51, 0.96-2.37), were associated with a higher risk of vascular events, mainly myocardial infarction (1.86, 1.33-2.59), whereas high-dose naproxen was not (0.92, 0.67-1.26). (Reference: Kearney PM, Baigent C, Godwin J, et al. Do selective cyclo-oxygenate-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomized trials. *BMJ* 2006;332:1302-8.)
6. Naproxen appears to have the least harmful cardiovascular risk profile, also in patients with myocardial infarction or heart failure. There is evidence that the vascular risks of diclofenac are comparable to those of coxibs.
7. There may be an association between NSAID use and development of atrial fibrillation. Subgroups of patients with a particularly high risk of developing atrial fibrillation after initiating NSAID therapy are those with heart failure and chronic kidney disease.
8. Balancing risks and benefits: Some patients may accept a minor absolute risk increase of serious cardiovascular events in order to improve their quality of life.

Clinical Topics: **Arrhythmias and Clinical EP, Dyslipidemia, Heart Failure and Cardiomyopathies, Prevention, Atrial Fibrillation/Supraventricular Arrhythmias, Lipid Metabolism, Acute Heart Failure**

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CURRENT OPINION

Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology

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Introduction

Non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) have been used in clinical practice for more than a century and are among the most widely used drugs worldwide for the treatment of pain, fever, and inflammation.[1,2] For decades, it has been known that many of these drugs can cause fluid retention and elevate blood pressure,[3] thus increasing cardiovascular risk particularly in heart failure patients.[4] However, the main worry in relation to the use of these agents has been gastrointestinal bleeding.[5]

Newer selective COX-2 inhibitors (coxibs) were developed as NSAIDs with reduced gastrointestinal toxicity, but retained analgesic and anti-inflammatory properties. Coxibs were tested in accordance to modern drug development regulations with large numbers of patients included in clinical trials. These trials demonstrated that rofecoxib,[6–8] celecoxib,[9] valdecoxib,[10] and parecoxib[10] increased the risk of cardiovascular complications. As a result, coxibs currently have very limited indications for use. Paradoxically, an older and relatively selective COX-2 inhibitor, diclofenac,[11] continues to be one of the most widely used drugs worldwide and is in most countries sold over the counter.[1] Mixed COX-1/COX-2 inhibitors such as ibuprofen and naproxen are also used widely and, without solid evidence, assumed to be safe. Given the current uncertainty regarding the safety of this class of agents and the rapidly accumulating data on their cardiovascular risks, this review summarizes the current evidence from randomized and observational studies on the cardiovascular safety of non-aspirin NSAIDs and presents a position for their use.

Mechanisms

Non-steroidal anti-inflammatory drugs exhibit their anti-inflammatory effect by inhibiting COX, which is the rate-limiting enzyme in prostaglandin synthesis (*Figure 1*).[12] There are at least two major isoforms of the COX enzyme—COX-1 and COX-2.[12] Both isoforms catalyse the conversion of the unsaturated fatty acid arachidonic acid into prostaglandin H_2,[12] which is further modified by tissue-specific isomerases into bioactive lipids (prostanoids). These prostanoids, including prostaglandins I_2 (prostacyclin), D_2, E_2, $F_{2\alpha}$, and thromboxane A_2, are mediators of a variety of biological effects.[13]

COX-1 is expressed constitutively in most tissues, e.g. myocardium, platelets, parietal cells, and kidney cells.[12] It regulates normal

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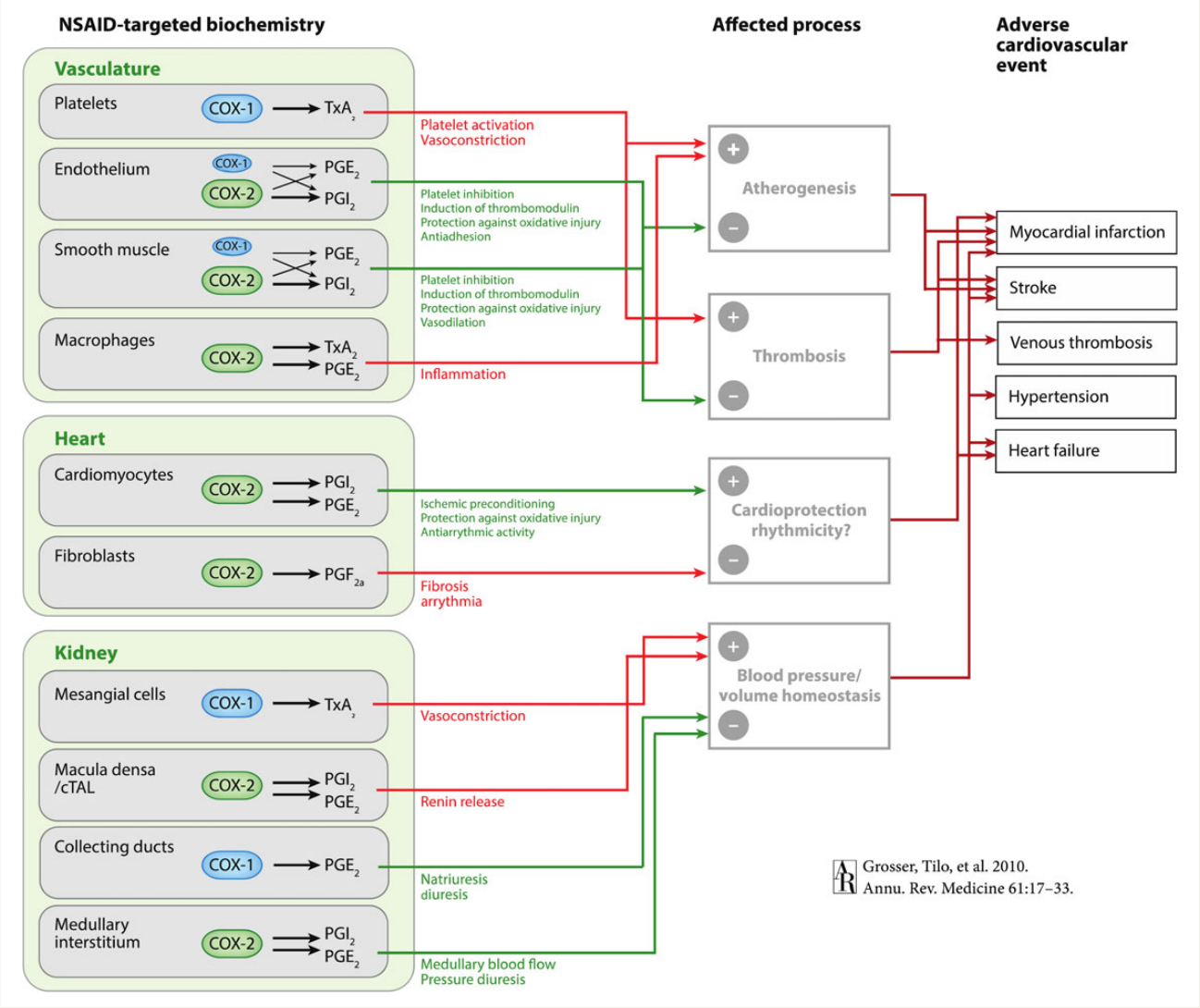

Figure 1 The mechanism underlying the cardiovascular hazard of COX-2 inhibitors.

cellular processes such as platelet aggregation, thrombosis, gastric cytoprotection, and kidney function.[12] COX-1 is stimulated by hormones or growth factors. In contrast, COX-2, usually undetectable in most tissues, is expressed in response to induction by inflammatory cytokines and mitogens, e.g. atherogenesis, rheumatoid arthritis, ischemia, and neoplasms.[12] Also, COX-2 is expressed in normal endothelial cells in response to shear stress.[14] Inhibition of COX-2 is associated with suppression of prostacyclin, which protects the endothelial cells during shear stress,[14] produces vasodilation, inhibits smooth muscle cell proliferation, and interacts with platelets antagonizing aggregation.[13] Platelets contain only COX-1, which converts arachidonic acid to thromboxane A_2—a potent proaggregatory and vasoconstrictive agent.[13]

The inhibition of the endogenous COX-1-mediated production of prostaglandins in the gastric mucosal cells increases the risk of gastrointestinal toxicity (dyspepsia, ulcers, bleeding, and perforation) and limits chronic use of NSAIDs.[5] It was therefore expected that COX-2 selective NSAIDs would possess anti-inflammatory, analgesic, and antipyretic activity, without increasing the risk of gastrointestinal complications.[12] This 'COX-2 hypothesis' provided the rationale for the developing of coxibs, which were first introduced into clinical practice in 1998.[15]

Selectivity for COX-2 represents a continuum, and coxibs can therefore be ranked based on their relative COX-2 vs. COX-1 selectivity as lumiracoxib > rofecoxib > etoricoxib > valdecoxib > parecoxib > celecoxib (*Figure 2*).[15] Among the traditional NSAIDs, some are non-selective or relatively COX-1 selective, while others also have a preference for COX-2 (older COX-2 inhibitors).[11] Importantly, there is an overlap in COX-2 selectivity between the older COX-2 inhibitors and coxibs when comparing the concentration of the drugs required to inhibit COX-1 and COX-2 activity (*Figure 2*).[11] Thus, diclofenac, etodolac, and meloxicam are surprisingly similar to celecoxib with regards to their COX-2 selectivity.[11]

Aspirin has the characteristic analgesic, antipyretic, and anti-inflammatory properties of non-selective NSAIDs.[16] Aspirin is

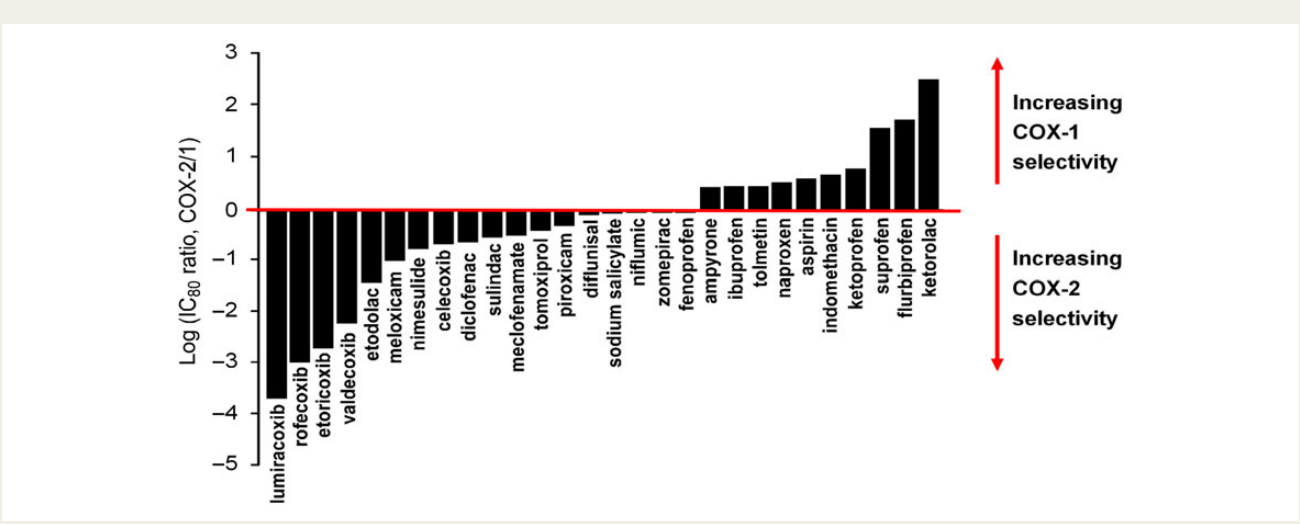

Figure 2 Relative COX selectivity of non-steroidal anti-inflammatory drugs displayed by the concentration of the drugs (IC_{80}) required to inhibit COX-1 and COX-2 activity by 80%.

indicated for pain relief in high doses (≥500 mg). In low doses (75–150 mg), aspirin is not an effective analgesic, but contains its inhibitory effect on platelet aggregation by irreversible blockage of the COX-1 enzyme.[16] Accordingly, the indication for low-dose aspirin (prevention and treatment of occlusive vascular events) differs from that of non-aspirin NSAIDs.[17]

There is no absolute selectivity for one or the other COX isoform. Even highly selective COX-2 inhibitors will also inhibit COX-1 at high enough concentrations (attained selectivity).[15] Attained selectivity for COX-1 varies with the plasma concentration of the COX-2 inhibitor.[18] It is most pronounced when its plasma concentrations are close to peak concentrations and subsides as plasma concentrations drop later in the dosing interval.[18] The importance of the drug potency and plasma half-life can be illustrated by diclofenac. Because diclofenac has a short half-life of 1–2 h, it is prescribed at high doses to produce the drug concentration necessary for effective analgesia throughout the entire dosing interval. As a result, the plasma concentration of diclofenac exceeds greatly that necessary to inhibit COX-2 early in the dosing interval and also inhibits COX-1 coincidently.[15] As the plasma concentration falls with the passage of time, diclofenac continues to inhibit COX-2 completely, whereas its effect on COX-1 subsides gradually. The discordant offset rates of COX isoform inhibition *in vivo* generate a 'window' of COX-2 selectivity.[13] In comparison with other traditional NSAIDs, neither ibuprofen nor naproxen exhibits such a window, because their inhibition of COX-1 exceeds that of COX-2 at all times during the dosing interval.[15]

Another important aspect is haemostasis, which is dependent on the appropriate equilibrium between prostacyclin and thromboxane A_2. Even before the approval of coxibs,[19,20] it was anticipated that they could constitute a cardiovascular hazard because the selective COX-2 inhibition would shift the prothrombotic/antithrombotic balance on the endothelial surfaces and favour thrombosis by inhibiting the generation of COX-2–derived vascular prostacyclin while not affecting the COX-1-mediated generation of thromboxane A_2 (*Figure 1*).[12]

Other factors contributing to the cardiovascular toxicity of COX-2 inhibitors include acceleration of atherogenesis,[21] blood pressure elevation,[22] and risk of heart failure decompensation.[4,23] COX-2-derived prostacyclin also acts as an endogenous antiarrhythmic agent through its inhibition of epicardial sympathetic nerve activity.[24–26] Non-steroidal anti-inflammatory drugs may therefore also elicit proarrhythmic effects that, in addition to its adverse renal effects (e.g. fluid retention, electrolyte disturbances, and blood pressure destabilization), render the patient more susceptible to arrhythmias such as atrial fibrillation (*Figure 1*).[15] The inhibition of the COX-2 up-regulation may be particularly harmful during myocardial ischaemia where thromboxane and prostacyclin are released from the acutely ischaemic myocardium and their balance is related to the risk of arrhythmias[27] and infarct size.[28] A less protective effect of COX-2 up-regulation during myocardial ischaemia may also decrease infarct collagen fibre density in the healing infarct zone, which may lead to greater thinning of the left ventricular wall in the infarct zone, impaired systolic function after MI, and an increased tendency to myocardial rupture.[28]

Evidence from randomized controlled trials

The evidence from major randomized controlled trials regarding the cardiovascular risks associated with use of coxibs is summarized in *Table 1*. The initial evidence for a concern on the cardiovascular safety of NSAIDs arose from safety analyses of large randomized controlled trials. In 2000, the Vioxx Gastrointestinal Outcomes Research (VIGOR) study randomized patients with rheumatoid arthritis to rofecoxib or naproxen and tested the comparative effect on upper gastric events.[8] Rofecoxib use resulted in fewer upper gastric events than naproxen.[8] However, protocol safety analyses showed that rofecoxib users had a 2.4-fold increased risk for the combined outcome of thrombotic cardiovascular events.[29] The Celecoxib Long-term Arthritis Safety Study (CLASS) tested

Table 1 Evidence from major randomized controlled trials on the cardiovascular risks associated with use of coxibs[a]

Author, acronym, journal, year	Design, setting, period, and population	Exposures and outcomes (primary/secondary)	Results (95% CI) and limitations
Farkouh *et al.*[37] The TARGET study *Ann Rheum Dis* 2007	RCT (double-blinded, active controls) 29 countries (849 centres) 2001–2002 OA patients ($n = 18\,325$)	Lumiracoxib (400 mg/d) vs. ibuprofen (800 mg t.i.d.) (sub-study 1) or naproxen (500 mg b.i.d.) (sub-study 2) MACE (MI, stroke, CV death)/HF	In high-risk patients using aspirin (75–100 mg/d), MACE risk was higher for ibuprofen (2.14%) vs. lumiracoxib (0.25%) ($P = 0.038$), but similar for naproxen (1.58%) and lumiracoxib (1.48%). In high-risk patients not using aspirin, MACE risk was lower for naproxen (0%) than lumiracoxib (1.57%) ($P = 0.027$), but not ibuprofen vs. lumiracoxib (0.92 vs. 0.80%). Heart failure risk was higher for ibuprofen than lumiracoxib (1.28 vs. 0.14%; $P = 0.031$), but similar for naproxen and lumiracoxib. *Post hoc* analysis, not placebo controlled, stratification on aspirin/CV risk not pre-planned
ADAPT group[36] The ADAPT study *PLoS Clin Trials* 2006	RCT (double-blinded, active, and placebo controls) US (6 centres) 2001–2004 AD patients ≥70 years ($n = 2528$)	Celecoxib (200 mg b.i.d.) or naproxen (220 mg b.i.d.) vs. placebo MACE (MI, stroke, CV death, HF, and TCI)	3-year risk of MACE in the celecoxib, naproxen, and placebo-treated groups were 5.54% (28/717), 8.25% (40/713), and 5.68% (37/1070). Hazard ratio for MACE was 1.10 (0.67–1.79) for celecoxib and 1.63 (1.04–2.55) for naproxen compared with placebo Few events.
Cannon *et al.*[35] The MEDAL study *Lancet* 2006	Pooled analysis of three double-blinded RCTs (MEDAL, EDGE, EDGE II) 46 countries (1380 centres) 2002–2006 OA or RA patients ($n = 34\,701$)	Etoricoxib (60 or 90 mg/d) vs. diclofenac (150 mg/d) MACE (thrombotic CV events)/GI events	MACE rate per 100 PY was 1.24 for etoricoxib and 1.30 diclofenac (HR 0.95, 0.81–1.11). Upper GI event rate was lower with etoricoxib vs. diclofenac (0.67 vs. 0.97; HR 0.69, 0.57–0.83), but similar for complicated upper GI events (0.30 vs. 0.32) Not placebo-controlled
Nussmeier *et al.*[58] *Anesthesiology* 2006	RCT 14 countries (113 centres) 2002–2003	Patients undergoing major orthopaedic, abdominal, gynaecologic, or non-cardiac thoracic surgery ($n = 1062$) Parecoxib/valdecoxib vs. placebo MACE (CV, renal, surgical-wound, and GI events)	MACE rate was not different for parecoxib/valdecoxib (2.7%) vs. placebo (3.2%, $P = 0.58$), including CV thromboembolic events (1.0% in each group; $P = 1.0$) Few events
Nussmeier *et al.*[10] *N Engl J Med* 2005	RCT 27 countries (175 centres) 2003–2004	Elective, primary CABG patients ($n = 1671$) Parecoxib/valdecoxib vs. placebo/valdecoxib vs. placebo Adverse events (CV, renal, surgical-wound, GI events), MACE (MI, cardiac arrest, stroke, PE)	When compared with the group given placebo alone, both the parecoxib/valdecoxib and placebo/valdecoxib groups had increased rate of adverse events (7.4% in each of these two groups vs. 4.0% in the placebo group; RR for each comparison was 1.9, 1.1–3.2). Relative risk for MACE was 3.7 (1.0–13.5) for the group with parecoxib/valdecoxib compared with placebo (2.0 vs. 0.5%). Few events
Solomon SD *et al.*[34] The APC study *N Engl J Med* 2005	RCT (double-blinded, placebo-controlled) US, UK, Australia, Canada (91 centres) 1999–2002 Colorectal neoplasia patients ($n = 2035$)	Celecoxib (200 or 400 mg b.i.d.) vs. placebo MACE (MI, stroke, CV death, HF)	Risk of MACE was 1% for placebo, 2.3% for 200 mg celecoxib b.i.d. (HR 2.3, 0.9–5.5), and 3.4% for 400 mg celecoxib b.i.d. (HR 3.4, 1.4–7.8) Few events, not powered for safety
Bresalier *et al.*[7] The APPROVe study *N Engl J Med* 2005	RCT (double-blinded, placebo-controlled) 29 countries (108 centres) 2000–2001 Colorectal adenoma patients ($n = 2586$)	Rofecoxib (25 mg/d) vs. placebo MACE (MI, unstable angina, cardiac death, ischaemic stroke, TCI, peripheral arterial thrombosis, DVT, pulmonary embolism)	Rate of MACE was 1.50 for rofecoxib and 0.78 for placebo per 100 PY, yielding HRs of 1.92 (1.19–3.11) for MACE, 2.80 (1.44–5.45) for cardiac events, and 2.32 (0.89–6.74) for cerebrovascular events. All-cause and CV death rates were similar Relatively few events

Continued

Table 1 *Continued*

Author, acronym, journal, year	Design, setting, period, and population	Exposures and outcomes (primary/secondary)	Results (95% CI) and limitations
Silverstein *et al.*[30] The CLASS study *JAMA* 2000	RCT (double-blinded, active controls) USA and Canada (386 centres) 1998–2000 OA or RA patients (≥18 years) ($n = 8059$)	Celecoxib (400 mg b.i.d.) vs. ibuprofen (800 mg t.i.d.) or diclofenac (75 mg b.i.d.) GI events/MACE (MI, stroke, death)	No difference in risk of GI events[31] or MACE (0.9% for celecoxib vs. 1.0% for ibuprofen/diclofenac)[29] Few events, not powered for safety, not placebo-controlled
Bombardier *et al.*[8] The VIGOR trial *N Engl J Med* 2000	RCT (double-blinded, active control) 22 countries (301 centres) 1999 RA patients ($n = 8076$)	Rofecoxib (50 mg/d) vs. naproxen (500 mg b.i.d.) GI events/MI, MACE (thrombotic CV events)	GI event rate was 2.1 for rofecoxib vs. 4.5 for naproxen per 100 PY (HR 0.5, 0.3–0.6). Corresponding MI risk was 0.4 vs. 0.1%. The MI rate was 5-fold increased for rofecoxib (20 vs. 4 events),[15,86] yielding an HR for MACE of 2.38 (1.39–4.00)[29] Few events, not powered for safety, not placebo controlled

Medline search: NSAIDs OR selective cyclooxygenase inhibitor AND cardiovascular risk. Filter: Clinical Trial: 7 relevant papers/161 hits = 7 in total.
AD, Alzheimer's disease; b.i.d., bis in die (twice daily); CV, cardiovascular; DVT, deep venous thrombosis; GI, gastrointestinal; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; PE, pulmonary embolism; PY, person-years; t.i.d., ter in die (3 times a day); RA, rheumatoid arthritis; RCT, randomized controlled trial; TCI, transient ischaemic attack.
[a]Major trials were arbitrarily defined as trials with >1000 participants.

the gastrointestinal toxicity of celecoxib compared with the traditional NSAIDs ibuprofen and diclofenac.[30] Re-analyses of CLASS found no difference in gastrointestinal toxicity[31] and a similar cardiovascular event rate for the three drugs (0.9% for celecoxib vs. 1.0% for ibuprofen/diclofenac).[30] A pooled analysis of VIGOR and CLASS shortly after the studies were published found that compared with a matched non-treatment group, celecoxib and rofecoxib carried an increased cardiovascular risk.[29] This initiated the concern for unforeseen cardiovascular side effects of coxibs and in 2004, the manufacturer withdrew rofecoxib from the market after the publication of the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial.[6,7,32,33] This placebo-controlled randomized trial found that the use of rofecoxib was associated with an increase in thrombotic events, which primarily reflected a greater number of myocardial infarctions and ischaemic cerebrovascular events.[7] Since this trial, *post hoc* analyses of additional trials have been published. The Adenoma Prevention with Celecoxib (APC) study showed similarly increased vascular risks associated with celecoxib use.[34] A pooled analysis of the APC and the Prevention of Spontaneous Adenomatous Polyps study showed a dose-dependent increase in cardiovascular risk and blood pressure associated with celecoxib treatment.[9] In 2006, the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) study compared etoricoxib with diclofenac (i.e. newer vs. older COX-2 inhibitors) and found no difference in rates of thrombotic cardiovascular events.[35] The same year the Randomized, Controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) showed that naproxen carried an increased risk of cardiovascular and cerebrovascular disease in elderly patients with dementia.[36] The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) in 2007 showed no difference in cardiovascular risk between lumiracoxib and ibuprofen or naproxen.[37] To date, only one trial has specifically investigated the pain relieving effect of valdecoxib compared with placebo in patients undergoing bypass surgery.[10] This study was stopped early due to an increased cardiovascular event rate in the valdecoxib group compared with the placebo group (relative risk (RR) = 3.7, 95% confidence interval (CI): 1.0–13.5%).

When evaluating the complete body of evidence derived from the randomized trials on coxibs, it is evident that relatively few major trials have been conducted and most of these were not designed specifically to answer whether coxibs carry an increased thromboembolic risk. The *post hoc* analyses from the various trials are not unanimous, but they raise a clear warning sign concerning the cardiovascular risk associated with use of selective COX-2 inhibitors in general. Several meta-analyses have summarized the randomized data available (see Supplementary material online, *Table S1*). As with all meta-analyses, they should be interpreted cautiously as they are inherently limited by the data from which they are derived. Thus, the major randomized trials have tested different coxibs and used different types of traditional NSAIDs or placebo as control groups. Moreover, most randomized trials were conducted in different patient populations, age groups, and treatment settings.

Kearney *et al.*[38] conducted the first large meta-analysis of 138 randomized trials comparing the effect of coxibs and traditional NSAIDs on the risk of vascular events ($n = 145\,373$ participants).[38] The meta-analysis concluded that coxibs (RR = 1.42, 95% CI: 1.13–1.78), as well as high-dose diclofenac (1.63, 1.12–2.37) and ibuprofen (1.51, 0.96–2.37), were associated with a higher risk of vascular events, mainly myocardial infarction (1.86, 1.33–2.59), whereas high-dose naproxen was not (0.92, 0.67–1.26).[38] Similarly results were reported by Trelle *et al.*[39] in a meta-analysis of 31 large-scale randomized trials ($n = 116\,429$). Here, the safety profiles of individual NSAIDs varied considerably depending on the outcome, but naproxen seemed least harmful and not associated with myocardial infarction (0.82, 0.37–1.67) or cardiovascular death (0.98, 0.41–2.37).[39]

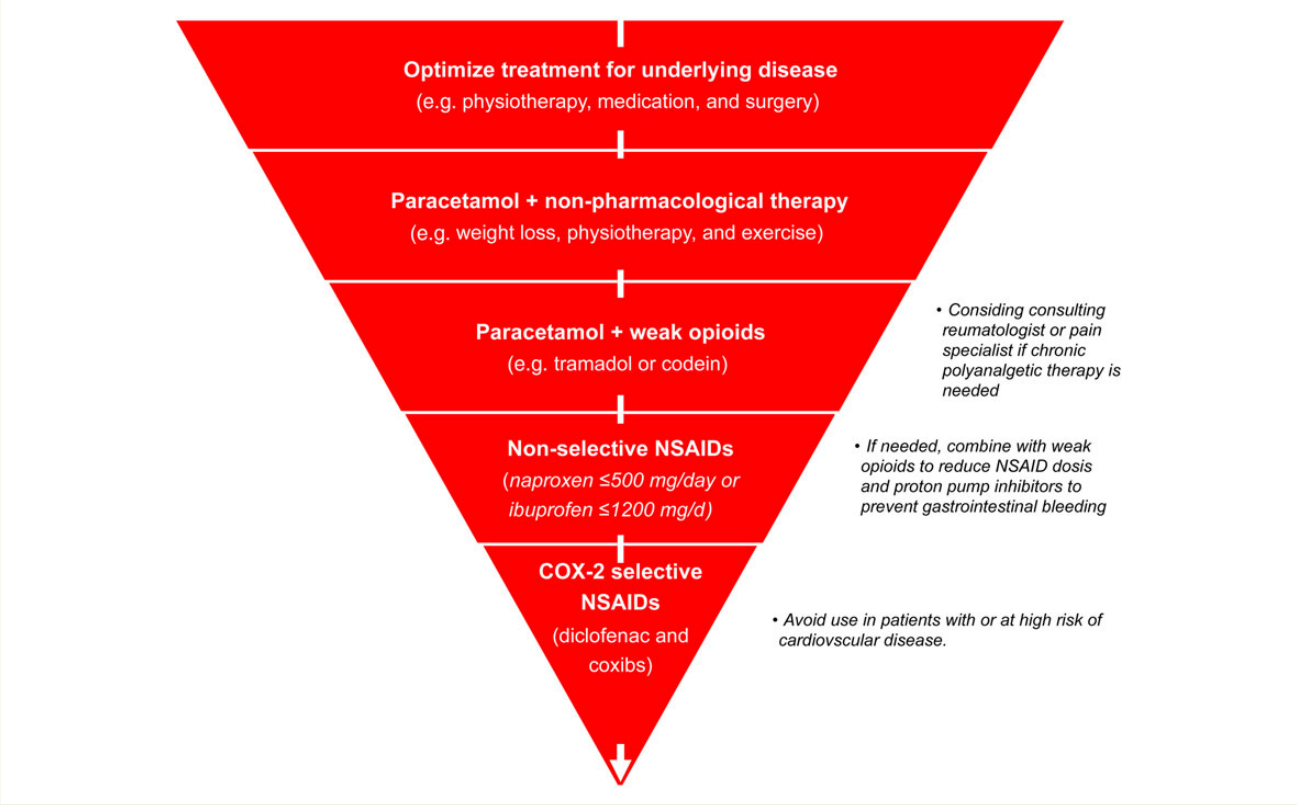

Figure 3 Stepwise approach to pharmacological treatment of musculoskeletal pain in patients with or at high risk of cardiovascular disease.

In the largest meta-analysis to date, the Coxib and traditional NSAID Trialists Collaboration summarized data from 280 placebo-controlled ($n = 124\,513$) and 474 active-controlled trials ($n = 229\,296$).[40] The study concluded that the vascular risks of diclofenac (RR = 1.41, 95% CI: 1.12–1.78), and possibly high-dose ibuprofen (1.44, 0.89–2.33), were comparable with coxibs (1.37, 1.14–1.66).[40] The increased vascular risk was driven by an increased rate of major coronary events and were independent of baseline characteristics, including cardiovascular risk.[40] In contrast, naproxen did not increase the risk of major vascular events (0.93, 0.69–1.27).[40] Finally, all non-aspirin NSAIDs roughly doubled the risk of heart failure.[40]

Evidence from observational studies

Numerous observational studies have investigated adverse cardiovascular effects of non-aspirin NSAID therapy. Results of such studies should be interpreted with caution due to their non-randomized design. A particular concern is confounding by indication, i.e. that the adverse effects can be difficult to distinguish from those associated with the underlying disease for which the drug was prescribed. The value of these studies is primarily comparisons of drugs used for similar indications. Also, while the randomized trials only have examined cardiovascular risks associated with NSAIDs in high doses and sometimes atypical settings,[40] observational studies have investigated NSAID use in typical doses in community settings. This is important as it remains unclear from the trial data whether the apparent increased vascular risk associated with high-dose ibuprofen (2400 mg daily) persists in lower doses.[40]

The results of available meta-analyses of observational studies are shown in Supplementary material online, *Table S1*. The largest meta-analysis, by McGettigan *et al.*,[41] included data from 21 cohort studies with >2.7 million exposed individuals and 30 case–control with a total of 184 946 cardiovascular events. Among the most extensively studied drugs, the highest overall cardiovascular risk was observed for rofecoxib (RR = 1.45, 95% CI: 1.33–1.59) and diclofenac (1.40, 1.27–1.55) and the lowest for ibuprofen (1.18, 1.11–1.25) and naproxen (1.09, 1.02–1.16).[41] The risk was elevated even with low doses of rofecoxib (1.37, 1.20–1.57), celecoxib (1.26, 1.09–1.47), and diclofenac (1.22, 1.12–1.33), and rose in each case with the use of higher doses.[41] For ibuprofen, a cardiovascular risk was seen only with the use of higher doses (>1200 mg/day).[41] Naproxen was risk-neutral at all doses, and had also a lower risk when compared directly with ibuprofen (0.92, 0.87–0.99).[41]

Meta-analyses of both randomized trials and observational studies support that the increased vascular risk associated with non-aspirin NSAID use is independent of baseline characteristics, including baseline vascular risk.[40,41] However, to guide clinical decision-making, we elaborate below on the evidence relating to important sub-groups of patients, i.e. patients with myocardial infarction or heart failure, patients undergoing cardiac and non-cardiac surgery, and patients receiving antithrombotic treatment. Finally, the emerging evidence of an NSAID-associated risk of atrial

fibrillation will be discussed. The design and results of the studies conducted in each of these patient sub-groups is summarized in Supplementary material online, *Table S2*.

Evidence on non-steroidal anti-inflammatory drug use in patients with myocardial infarction and heart failure

While all non-aspirin NSAIDs roughly double the risk of heart failure, they also increase the risk of adverse events in heart failure patients,[4] including recurrent admission for myocardial infarction and dose-related excess mortality risk.[42] These adverse effects are presumable due to a combination of thromboembolic properties[43] and adverse renal effect which may worsen heart failure.[22]

Similar to the overall reports, these risks appear highest for coxibs and diclofenac and lowest for naproxen.[42] There is mechanistic evidence that naproxen (as well as ibuprofen) may reduce the irreversible antiplatelet effect of aspirin by interfering with aspirin acetylation of the COX-1-binding site on platelets, or by providing insufficient COX-1 inhibition during the dosing cycle.[44,45] However, naproxen still appears to have the least harmful cardiovascular risk profile, also in patients with myocardial infarction or heart failure.[42,46]

Previously, use of NSAIDs was thought to be risk-neutral in short treatment periods and in low doses.[47] However, cumulating evidence suggests that there is no safe-treatment window.[10,40,48,49] After myocardial infarction, the risk of death and rehospitalization for myocardial infarction seem independent of treatment duration[48] and the time elapsed since debut of myocardial infarction.[46] For diclofenac, the increased vascular risk appear to start immediately after treatment initiation and persist thereafter.[48]

Only few studies have been conducted in the sub-group of patients with coronary stents.[50–52,53] The randomized COREA-TAXUS ($n = 274$)[50,51] and Mini-COREA ($n = 909$)[52] trial followed patients after paclitaxel-eluting stent implantation. These studies did not find an increased vascular risk associated with adjunctive use of celecoxib for 6 months after stent implantation.[50,51] However, due to their underpowered design, larger trials are needed assess the NSAID-associated cardiovascular risks in this patient group.

Evidence on non-steroidal anti-inflammatory drug use in patients undergoing cardiac and non-cardiac surgery

As the perioperative use of NSAIDs is common and cardiac complications are the most common causes of morbidity and mortality after surgery,[54] the cardiovascular safety of NSAIDs following surgery is of major clinical importance (see Supplementary material online, *Tables S1* and *S2*). With regard to cardiac surgery, a randomized trial ($n = 1671$) showed that short-term use of coxibs (intravenous parecoxib for at least 3 days, followed by valdecoxib until day 10) were associated with an increased risk of cardiovascular events after coronary artery bypass grafting compared with standard care plus placebo (RR = 3.7, 95% CI: 1.0–13.5).[10] Sternal wound infections were another complication associated with coxib use after cardiac surgery.[55] Examining the use of traditional NSAIDs, a meta-analysis of 20 randomized trials with a total of 1065 patients undergoing cardiothoracic surgery did not show a significant increase of myocardial infarction when adding traditional NSAIDs for pain management of cardiothoracic surgery.[56] Also, a small randomized trial ($n = 98$) found naproxen to be an effective adjunct for optimization of pain control, with no apparent increase in other complications.[57] The low sample sizes of the cardiac surgery trials warrants caution when interpreting the results.[56,57] Still, together with the risk-neutral effect reported in other patient groups,[40,41] the results of these trials indicate that naproxen may be the safest non-aspirin NSAID to use following cardiac surgery.

With regard to non-cardiac surgery, a randomized trial found that parecoxib and valdecoxib did not increase thromboembolic events in patients undergoing non-cardiac surgery.[58] These results were also supported by a subsequent meta-analysis of 32 randomized trial that did not find an increased cardiovascular risk when comparing parecoxib/valdecoxib to placebo.[59] However, the study results were imprecise due to a limited number of events.[58,59] A single-centre observational study with >10 000 patients undergoing arthroplasty found no association between NSAID use and post-operative myocardial infarction.[60] In contrast, another meta-analysis of three randomized trials including 2604 major surgery patients detected a 2.3-fold increase of major cardiovascular events in the group with COX-2 inhibitors.[61] Recent ESC/ESA guidelines on non-cardiac surgery recommend to avoid NSAIDs and in particular COX-2 inhibitors in patients with ischaemic heart disease or prior stroke.[62]

Evidence on non-steroidal anti-inflammatory drug use in combination with antithrombotic treatment

Antithrombotic treatment is one of the cornerstones of the management of patients with cardiovascular disease, and lowers the risk of thrombosis and mortality. Invariably, bleeding risk is increased with antithrombotic treatment and especially with combination therapies,[63,64] but less is known about the risks of co-administering non-aspirin NSAID and antithrombotic agents.

Assessing bleeding risk in patients with atrial fibrillation, a cohort of >150 000 atrial fibrillation patients (using aspirin, oral anticoagulant therapy, aspirin+oral anticoagulant therapy, or no antithrombotic treatment) found that use of non-aspirin NSAIDs was associated with increased absolute risks for serious bleeding across all antithrombotic regimens.[65] At 3 months, the absolute risk for serious bleeding within 14 days of NSAID exposure was 1.9 events per 1000 patients higher than patients without NSAID exposure.[65] For patients on oral anticoagulant therapy, the corresponding absolute risk difference associated with NSAID therapy was 2.5 per 1000 patients.[65] Increased risk for serious bleeding was present for all

types of non-aspirin NSAIDs with incremental risk with larger doses.[65] Patients with atrial fibrillation using NSAIDs also had an increased risk of thromboembolism (HR = 1.36, 1.27–1.45). In patients with venous thromboembolism, a study showed a 1.8-fold increased risk for clinically relevant bleeding and 2.4-fold increased risk for major bleeding in patients co-administered non-aspirin NSAIDs and anticoagulation with rivaroxaban or enoxaparin-vitamin K antagonist.[66] Coadministrating antithrombotic treatment with all types of non-aspirin NSAIDs has also been shown to increase the bleeding risk in patients with myocardial infarction (HR = 2.02, 95% CI: 1.81–2.26).[67] Importantly, <1 week of non-aspirin NSAID treatment increased the bleeding risk.[67]

Evidence on non-steroidal anti-inflammatory drug use in relation to atrial fibrillation

The role of COX inhibition in atrial fibrillation occurrence has only more recently gained attention. Initially, a meta-analysis of 114 clinical trials reported that use of rofecoxib was associated with an increased risk of cardiac arrhythmia (RR = 2.90, 95% CI: 1.07–7.88), but too few events were available to study atrial fibrillation separately (see Supplementary material online, *Table S1*).[68] Subsequently, several observational studies examined the NSAID-associated risk for atrial fibrillation (see Supplementary material online, *Table S2*).[68–73] These data have been summarized in a recent meta-analysis with >400 000 cases of atrial fibrillation (see Supplementary material online, *Table S1*).[74] Compared with non-users, users of non-aspirin NSAIDs had a 1.2-fold increased risk of atrial fibrillation, increasing to 1.5-fold among new users.[74] COX-2 inhibitors, particularly diclofenac, were associated with higher risks than non-selective NSAIDs.[73,74] Sub-groups of patients with a particular high risk of developing atrial fibrillation after initiating NSAID therapy were patients with heart failure (RR = 1.82, 95% CI: 1.42–2.32) and chronic kidney disease (1.58, 1.34–1.85).[73,74]

Regulatory considerations

The European Medicines Agency (EMA) and the Food and Drug Administration have continuously reviewed the cardiovascular safety of non-aspirin NSAIDs since the withdrawal of rofecoxib in 2004.[6,7] When concerns also arose for celecoxib,[29] it prompted a class review by EMA of the cardiovascular safety for all COX-2 inhibitors. This regulatory process concluded that coxibs were associated with a dose and duration-dependent increased risk of cardiovascular events. The EMA review was widened to include data related to traditional NSAIDs, and in 2006 EMA concluded that although the benefits of non-aspirin NSAIDs for treatments for arthritis and other painful conditions outweighed their risks, they should be used at *the lowest effective dose for the shortest possible duration*.[47] Thus, the overall benefit–risk balance remained positive for short-term use.[47] However, the agency emphasized that there was a potential increase in the risk for thrombotic events especially when these drugs were used in high doses and for long-term treatment.[47] The EMA review resulted in an update of the product information of the different NSAIDs to reflect available evidence at the time.[75] Importantly, the EMA noted specifically at the time that diclofenac, particularly at high dose, may be associated with an increased risk of arterial thrombotic events.[47]

As recommended by the EMA, the European Commission subsequently funded an independent research project under the Seventh Framework Programme—'safety of non-steroidal anti-inflammatory drugs' (SOS)—to assess and compare the risk of cardiovascular and gastrointestinal events in users of NSAIDs and coxibs.[76] The findings from the SOS project (see Supplementary material online, *Table S1*), together with additional observational studies and meta-analyses led to the updated 2012 EMA report on the cardiovascular risks of NSAIDs.[75] Here, the EMA concluded that the existing prescribing information for ibuprofen and naproxen reflected the known level of cardiovascular and other risks for these drugs.[75] However, EMA noted that although small risks cannot be excluded, naproxen seem associated with a lower cardiovascular risk than COX-2 inhibitors and other traditional NSAIDs.[75] Conversely, ibuprofen and diclofenac, especially if administered at high doses, may be associated with an increased risk of thrombotic events.[75] On diclofenac, the EMA concluded that the evidence consistently pointed towards a less favourable cardiovascular risk profile compared with naproxen and ibuprofen, and risks similar to that of coxibs.[77]

Public health impact

The prevalence of non-aspirin NSAID use is high in Western countries.[1] Danish data estimate that 15% of the population redeem at least one prescription of non-aspirin NSAIDs each year,[2] increasing to >60% over a 10-year period.[78] This high overall use is a concern as these drugs are associated with risk of myocardial infarction and death also in the otherwise healthy general population.[79] Moreover in contrast to guideline recommendations,[80] a surprisingly large proportion (~35%) of patients with myocardial infarction or chronic heart failure receive non-aspirin NSAIDs after discharge from hospital.[42,43] Despite the increasing evidence implying that the cardiovascular risks associated with diclofenac are comparable with that of coxibs, diclofenac remains among one of the most sold drugs worldwide.[1] Although the absolute risks may be relative low, the high prevalence of NSAID use makes their impact on cardiovascular disease burden a great concern. Supporting this view, the EMA stated that although diclofenac rarely exceed a 2-fold increased risk for cardiovascular events compared with no use, its cardiovascular side effect profile are likely to have a public health impact.[75] The Coxib and traditional NSAID Trialists Collaboration has estimated that among 1000 individuals allocated coxibs or diclofenac for a year, 3 more will experience a major vascular events compared with placebo, among which one will be fatal.[40] Considering instead 1000 high-risk patients (including aspirin users) treated with coxibs or diclofenac for a year, the extra number of individuals likely to experience a major vascular event increases to seven or eight, among which two will be fatal.[40]

Balancing benefits and risks

Treatment of pain and inflammation may in many cases be worthwhile in spite of the risk imposed by the therapeutic agent. Thus, some patients may accept a minor absolute risk increase of serious

cardiovascular events in order to improve their quality of life. These tradeoffs are by nature complex and choosing between different NSAIDs to a large extent also involve balancing the risk of cardiovascular and gastrointestinal complications.[81] Increasing COX-1 selectivity is in general associated with augmented gastrointestinal risk, but COX-2 inhibitors also increase the risk relative to placebo (1.8-fold for coxibs, 1.9-fold for diclofenac, 4.0-fold for ibuprofen, and 4.2-fold for naproxen).[40] Based on patient's gastrointestinal risk,[81] the need for concomitant proton pump inhibitor use to prevent gastrointestinal bleeding should always be considered.[81–83] Whether or not the patient accepts the predicted risks in return for relief of their symptoms should be a major consideration when initiating NSAID therapy. When differentiating between different NSAIDs, it is important to be aware that there is no evidence to support that diclofenac is superior for pain relief than less hazardous NSAIDs. In contrast, there is level 1a evidence that the vascular risks of diclofenac are comparable with coxibs.[40,84] Similar level of evidence favour naproxen ≤500 mg/day as the agent with the least harmful cardiovascular risk profile and level 2a evidence supports that ibuprofen ≤1200 mg/day is also a safe alternative.[41,84] Although the relative vascular risks associated with coxibs and diclofenac are independent of baseline vascular risk,[40] patients with cardiovascular disease or risk factors (such as hypertension, hyperlipidaemia, diabetes mellitus, or smoking) still have a higher absolute incidence of thromboembolic events due to their increased baseline risk.[85] As a practical guide for clinicians, *Figure 3* shows a stepwise approach to the pharmacological treatment of musculoskeletal pain in patients with or at high risk of cardiovascular disease.

Conclusions

To summarize the existing evidence on the cardiovascular risks associated with non-aspirin NSAID use, the ESC working group for Cardiovascular Pharmacotherapy holds the following positions regarding the use of non-aspirin NSAIDs:

- Prescription of non-aspirin NSAIDs requires in each particular case a careful evaluation of the risk of cardiovascular complications and bleeding.
- Non-aspirin NSAIDs should only be sold over the counter when measures are put in place to ensure that their use is accompanied by an appropriate warning of their frequent cardiovascular complications.
- Non-aspirin NSAIDs should in general not be used in patients with established or at high risk of cardiovascular disease.
- When prescribing traditional NSAIDs, older selective COX-2 inhibitors such as diclofenac, should be avoided, as no available data demonstrate a therapeutic superiority compared with other agents that justify their use in view of their associated cardiovascular risks.

Authors' contributions

C.T.-P. handled funding and supervision. C.T.-P. and M.S. conceived and designed the research. M.S. drafted the manuscript. All authors made critical revision of the manuscript for key intellectual content.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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