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Cardiovascular effects and safety of (non-aspirin) NSAIDs

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Abstract | Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective, widely used analgesics. For the past 2 decades, considerable attention has been focused on their cardiovascular safety. After early studies indicating an association between NSAID use and increased risks of heart failure and elevated blood pressure, subsequent studies found a link between NSAID use and an increased risk of thrombotic events. Selective cyclooxygenase 2 (COX2) inhibitors (also known as coxibs) have been associated with the greatest risk of adverse vascular effects but concern also relates to non-selective NSAIDs, especially those with strong COX2 inhibition such as diclofenac. Although NSAID use is discouraged in patients with cardiovascular disease, pain-relief medication is often required and, in the absence of analgesics that are at least as effective but safer, NSAIDs are frequently prescribed. Furthermore, non-prescription use of NSAIDs, even among people with underlying cardiovascular risks, is largely unsupervised and varies widely between countries. As concern mounts about the disadvantages of alternatives to NSAIDs (such as opioids) for pain management, the use of NSAIDs is likely to rise. Given that the pharmaceutical development pipeline lacks new analgesics, health-care professionals, patients and medicine regulatory authorities are focused on optimizing the safe use of NSAIDs. In this Review, we summarize the current evidence on the cardiovascular safety of NSAIDs and present an approach for their use in the context of holistic pain management.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used globally to relieve pain but, for more than a decade, the cardiovascular safety of the commonly used NSAIDs (celecoxib, diclofenac, ibuprofen and naproxen) has attracted considerable attention. Meta-analyses of both randomized and observational data report cardiovascular risks associated with NSAID use[1,2], and specialist cardiology groups have cautioned against the use of these drugs[3,4]. Medicine regulatory authorities, including the FDA and the European Medicines Agency, have issued both class and individual NSAID warnings[5,6]. Nevertheless, NSAIDs are still often used by patients with cardiovascular disease or who are at high risk of cardiovascular events. For example, in Denmark, over a period of 13 years, 46% of patients with previous myocardial infarction (MI) were prescribed NSAIDs[7,8].

Even with short-term use of <7 days, NSAIDs have been associated with an increased risk of thrombotic cardiovascular events[9]. When co-prescribed with antithrombotics for patients with cardiovascular disease, the short-term use of NSAIDs has been associated with a substantial independent risk of bleeding[10,11]. These risks are of considerable public-health concern, especially among older patients, given that the prevalence of both heart disease and chronic painful conditions increases with age and that the population is ageing in several parts of the world. Moreover, in many countries, some NSAIDs (most commonly ibuprofen but also diclofenac, mefenamic acid and naproxen) are available 'over the counter' without prescription in pharmacies and retail outlets, including online outlets, with various restrictions on the quantities that can be purchased and often with no requirement for the retailer to provide professional advice to consumers. No systematic data are available on the cardiovascular risks for users of over-the-counter NSAIDs or on the outcomes experienced by this group.

Increasing concern about the disadvantages of alternative analgesics to NSAIDs, such as opioids, also suggests that NSAID use will rise in the future. Combined with a pharmaceutical development pipeline that lacks new analgesics, health-care professionals, patients and medicine regulatory authorities need to optimize the safe use of NSAIDs. This need is particularly relevant to groups with a high baseline risk such as patients with or at risk of cardiovascular disease.

In this Review, we consider the cardiovascular safety of NSAIDs. We begin by outlining the biological mechanisms of NSAID-associated benefits and harms. We then summarize the evidence on their cardiovascular risks and discuss information on outcomes when NSAIDs

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Key points

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with increased cardiovascular risk but are often still used for pain management.
- Even with short-term use (<7 days), NSAIDs have been associated with an increased risk of thrombotic cardiovascular events.
- Ageing populations, concern about the disadvantages of alternative analgesics (such as opioids) and a sparse analgesic drug development pipeline all suggest that NSAID use will rise in the future.
- Non-pharmacological measures (physiotherapy, exercise and weight management) are feasible options for many patients to achieve pain control while minimizing pharmacological analgesic needs, with additional benefits in terms of cardiovascular risk management and wellbeing.

are taken concomitantly with antithrombotic drugs intended to reduce cardiovascular risks. Next, we consider NSAID use in the context of the alternative analgesics available, the advice issued by specialist groups and the analgesic development pipeline. We conclude by suggesting a holistic approach to pain management, aiming to minimize NSAID use, and choosing the lowest-risk options from a cardiovascular perspective according to our interpretation of the evidence.

Biological mechanisms of NSAID effects

NSAIDs inhibit the cyclooxygenase (COX) enzymes, which are involved in the production of prostaglandins[12–16]. The two major COX isoenzymes are COX1 (also known as prostaglandin G/H synthase 1) and COX2 (also known as prostaglandin G/H synthase 2), both of which form prostaglandin H_2 from arachidonic acid. Prostaglandin H_2 is further catalysed by prostaglandin synthases and isomerases to produce bioactive lipids (prostanoids) such as thromboxane A_2, prostaglandin D_2, prostaglandin E_2, prostaglandin F_2 and prostacyclin (also known as prostaglandin I_2), which influence immune, cardiovascular, gastrointestinal, renovascular, pulmonary, central nervous system and reproductive functions[3,15] (FIG. 1).

The COX isoenzymes are present in various tissues throughout the human body and influence haemostasis via different prostanoids[17,18]. COX1 in platelets and in myocardial, parietal and kidney cells regulates processes such as platelet aggregation, thrombosis, gastric cytoprotection and kidney function. COX1 is upregulated in response to inflammatory cytokines and mitogens in situations such as atherogenesis, rheumatoid arthritis, ischaemia and neoplasms. COX2 is expressed in normal endothelial cells in response to shear stress and its inhibition leads to suppression of the production of protective prostacyclin. Other vascular benefits of prostacyclin include vasodilatation and the inhibition of both smooth muscle cell proliferation and platelet aggregation.

Pharmacologically, the 'selective' COX2 inhibitors (also known as coxibs), such as celecoxib and rofecoxib (withdrawn worldwide in 2004 but examined in many NSAID studies), are characterized by selective inhibition of COX2, whereas the non-selective NSAIDs, such as diclofenac, ibuprofen and naproxen, inhibit both COX isoenzymes. The selective COX2 inhibitors were intended to lower the rates of gastrointestinal adverse events (upper gastrointestinal bleeding) but are associated with excess cardiovascular risk[19]. The coxibs can be ranked on the basis of their selectivity for COX2 versus COX1 inhibition: rofecoxib > etoricoxib > valdecoxib > parecoxib > celecoxib[20]. Other NSAIDs include non-selective COX inhibitors, such as ibuprofen and naproxen, and those with some selectivity for COX2 while also inhibiting COX1, such as diclofenac, etodolac and meloxicam (which have a selectivity for COX2 that is similar to that of celecoxib)[21].

Vascular endothelial cells express both COX1 and COX2, whereas platelets express only COX1 and have an important role in cardiovascular haemostasis. Platelet COX1 produces thromboxane A_2, which stimulates platelet aggregation and vasoconstriction, and increases vascular and cardiac remodelling. COX2 mediates the synthesis of prostacyclin, a potent vasodilator that also inhibits platelet function and promotes renal sodium excretion. One of the proposed mechanisms for the cardiovascular risk of NSAIDs is the observed shift in the prothrombotic–antithrombotic balance on endothelial surfaces towards thrombosis[3,13,15].

An association between the degree of COX2 inhibition and the risk of thrombosis has also been observed[3,13,22]. The simplified hypothesis has been that the more COX2 inhibition that an NSAID exerts relative to COX1 inhibition, the higher the risk of cardiovascular events. However, this theory of balanced versus unbalanced COX inhibition is debated because non-selective NSAIDs have also been associated with increased cardiovascular risk. Other mechanisms might explain the harmful effects of NSAIDs; for example, prostacyclin has been found to act as a restraint on many prothrombotic stimuli, including ADP, adrenaline, collagen, serotonin, thrombin and thromboxane A_2 (REFS[15,21]).

When considering the cardiovascular risks associated with NSAIDs, the factors that are highly relevant to patients and prescribers are the nature of the risks, who is (most) at risk, whether all NSAIDs have the same risks and whether a 'safe' window of time exists for NSAID use. Relevant information has arisen mainly from epidemiological studies and is discussed below. Randomized studies specifically designed to examine the cardiovascular safety of NSAID treatment are scarce, but these are also discussed, if available.

NSAIDs and myocardial infarction

The biological explanation for the NSAID-associated risk of MI has primarily emphasized the prothromboembolic effects described above, but NSAIDs have also been found to influence renal function and the regulation of fluid balance, causing fluid retention and worsening of heart failure, all of which contribute to the risk of MI[23] (FIG. 2). Furthermore, NSAIDs have been found to interact with antihypertensive drugs, such as angiotensin-converting enzyme inhibitors[24], through mechanisms related to the inhibition of prostaglandin synthesis, which interferes with the renal vasculature and the regulation of blood pressure. Moreover, NSAIDs can increase serum aldosterone levels, leading to sodium retention and hypertension[25,26].

Individual observational studies and meta-analyses of data from multiple studies have examined the

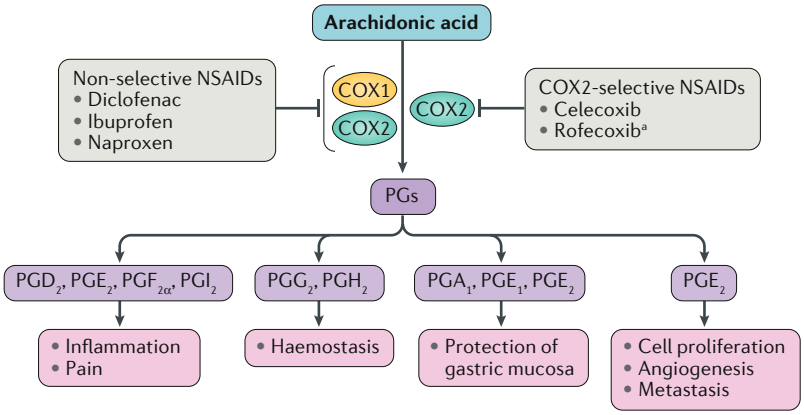

Fig. 1 | **Mechanism of action of NSAIDs.** Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclooxygenase isoenzymes COX1 and COX2 with varying degrees of specificity for the COX2 isoform. As a result, the conversion of arachidonic acid to prostaglandins (PGs) is inhibited. The main effects of PGs throughout the body are listed. [a]Withdrawn from the market.

NSAID-associated risk of MI in broad populations of users, adjusting for identified cardiovascular risk factors, and have shown that, compared with non-use, NSAID use increases the risk of MI[1,27,28]. Studies in which patients are stratified according to cardiovascular risk or which focus specifically on patients with established cardiovascular risk report similar estimates of the relative risk of MI with NSAID use[29,30]. Both selective and non-selective NSAIDs have been associated with increased risks of cardiovascular morbidity and cardiovascular death[27–31]. Naproxen has been reported in several studies to be the NSAID with the lowest cardiovascular risk[1] but is associated with a higher risk of gastrointestinal bleeding than the COX2 inhibitors and the other non-selective NSAIDs; in patients with MI, gastrointestinal bleeding is associated with a poor prognosis[32,33]. However, NSAID-associated gastrointestinal risks can be mitigated by the use of gastroprotective drugs[34].

Previously, the use of NSAIDs was thought to be risk-neutral over short treatment periods and at low doses, which might (partly) explain why NSAIDs are still used in patients with heart disease. However, studies have subsequently suggested that no safe treatment window exists for patients with cardiovascular disease taking NSAIDs. Observational studies have explored the timing of risk onset. In 2011, our group reported an increased risk of death and recurrent MI according to duration of NSAID treatment in patients with previous MI[9]. Among Danish patients having a first MI between 1997 and 2006, increased cardiovascular risk was found after 7 days of rofecoxib treatment[9]. Of note, in the same study, the risks of death and recurrent MI associated with the commonly used, non-selective NSAID diclofenac increased immediately after the start of treatment and persisted thereafter[9]. The results suggested that diclofenac was associated with an even higher risk of death and recurrent MI than the selective COX2 inhibitor rofecoxib, which was withdrawn from the market in 2004. Systematic reviews of observational studies report an increased risk within 1 week of treatment with diclofenac, ibuprofen and (variously) naproxen[1,27,28]. The risk seemed to be dose dependent and was most pronounced at high doses of celecoxib, ibuprofen and naproxen, whereas both low and high doses of diclofenac were associated with a consistently increased risk of MI[1,27,28]. A 2012 study reported on the long-term cardiovascular risks linked with the use of NSAIDs among Danish patients after MI[35]. The risks of death and of a composite end point of coronary death or non-fatal recurrent MI were persistently increased, independent of the time since the first MI.

Randomized studies. Among early examinations of randomized data, a 2006 meta-analysis of randomized trials reported that selective COX2 inhibitors were associated with an increased risk of serious vascular ischaemic events (predominantly MI), as were high doses of diclofenac and ibuprofen but not of naproxen[36]. In 2011, a network meta-analysis included data from 31 randomized studies and reported that cardiovascular risks were elevated with selective COX2 inhibitors (etoricoxib, lumiracoxib and rofecoxib) as well as with diclofenac and ibuprofen but not with naproxen[31].

In 2013, a meta-analysis of individual-level patient data, including >350,000 participants from 757 different randomized trials, found that selective COX2 inhibitors (rate ratio (RR) 1.37, 95% CI 1.14–1.66) and diclofenac (RR 1.41, 95% CI 1.12–1.78) were associated with an increased risk of vascular events compared with placebo[32]. COX2 inhibitors were also associated with an increased rate of vascular death (RR 1.58, 95% CI 1.00–2.49). However, naproxen did not increase the risk of vascular events or vascular death. These risk estimates were in broad agreement with those from the observational studies.

The findings from this meta-analysis provided insights into the importance of baseline cardiovascular risk on the magnitude of the annual risk of exposure to NSAIDs. Accordingly, exposure of low-risk patients to NSAIDs confers a small absolute increase in risk, whereas treatment of higher-risk patients with a COX2 inhibitor or diclofenac is associated with more cardiovascular events, some of which might be fatal. For example, the absolute excess risk of major fatal or non-fatal vascular events for patients with a low baseline cardiovascular risk treated with a high-dose COX2 inhibitor, diclofenac or ibuprofen was 2 events per 1,000 patients. For patients with a high baseline cardiovascular risk, the excess risk of major fatal or non-fatal vascular events with a high-dose COX2 inhibitor, diclofenac or ibuprofen was 9, 10 and 12 events per 1,000 patients, respectively.

NSAID–aspirin interactions. Pharmacodynamic interactions occur between aspirin and both ibuprofen and naproxen but not between aspirin and either diclofenac or celecoxib. Ibuprofen and naproxen impair the access of aspirin to its COX1-binding site, thereby reducing the degree of platelet thromboxane inhibition that aspirin can otherwise achieve. High levels of thromboxane inhibition by aspirin seem to be necessary to block thromboxane-induced platelet aggregation reliably, but the clinical

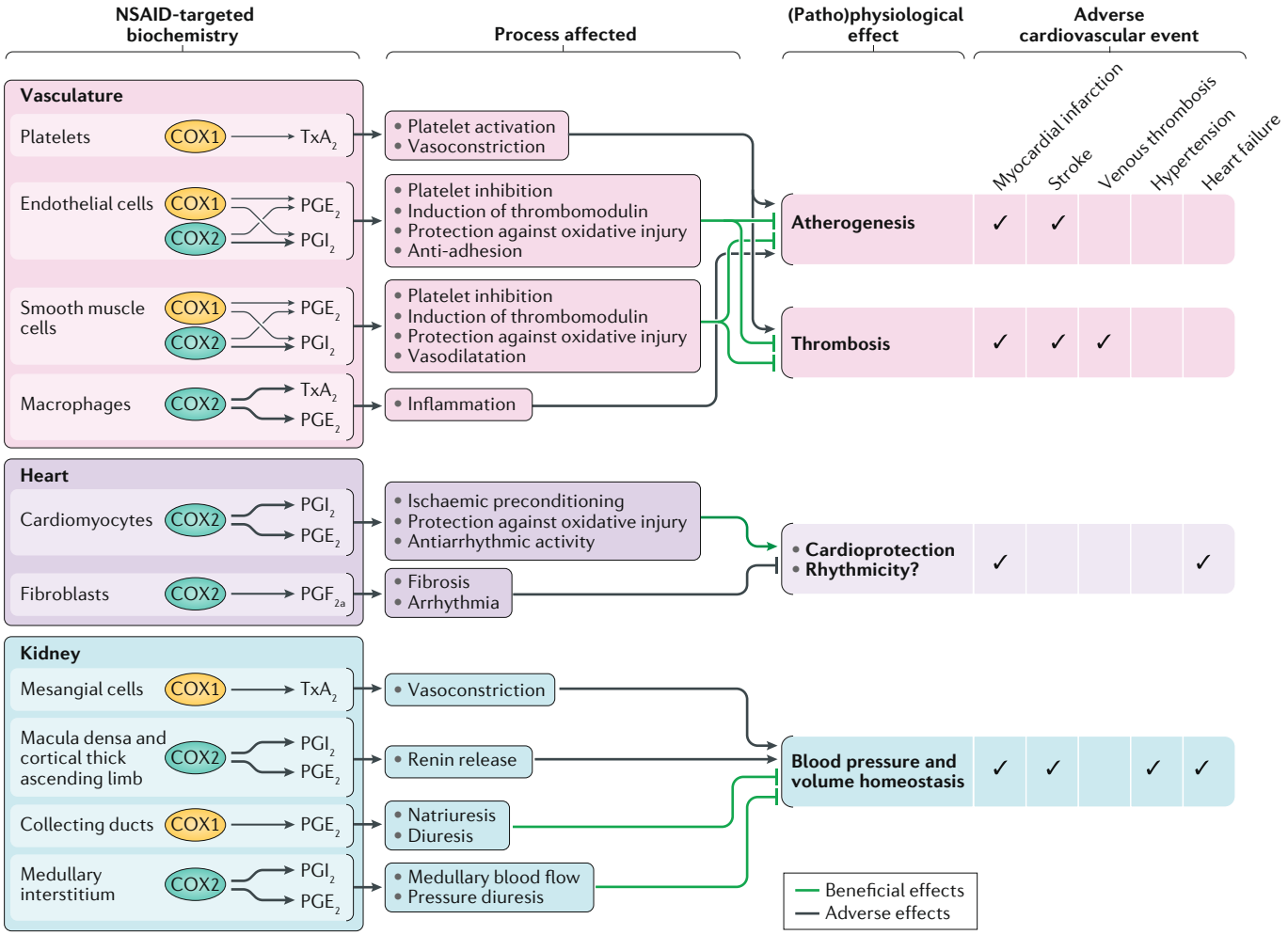

Fig. 2 | **Mechanisms underlying adverse cardiovascular events associated with NSAIDs.** The figure shows cyclooxygenase 1 (COX1) and COX2 products in the vasculature, heart and kidneys, the processes affected, the related beneficial and adverse physiological effects, and the influence on the cardiovascular system that can arise owing to nonsteroidal anti-inflammatory drug (NSAID) use. PG, prostaglandin; TxA_2, thromboxane A_2. Adapted with permission from REF.[21], Annual Reviews.

effect of the pharmacodynamic interaction with ibuprofen or naproxen, in terms of thrombotic risk, is uncertain[37,38]. This uncertainty is reflected in the European and US regulator-approved product information for both ibuprofen and naproxen.

NSAIDs and atrial fibrillation

NSAIDs have been associated with an increased risk of atrial fibrillation. The biological explanation is not fully understood but is speculated to involve adverse effects on fluid retention, serum electrolytes and blood pressure[23,39–42].

Several observational studies have reported an increased risk of atrial fibrillation with NSAIDs[43–47]. These data were combined in a meta-analysis involving >400,000 cases of atrial fibrillation[48]. Compared with non-users, overall NSAID use was associated with a modest 12% increased risk of atrial fibrillation (RR 1.12, 95% CI 1.06–1.18); both case–control and case–cohort studies showed consistent results[43–47]. When stratified by duration of NSAID use, new users had the highest risk (RR 1.53, 95% CI 1.37–1.70)[48]. This observation might be explained by post-initiation occurrence of heart failure or renal impairment in susceptible patients, but no definitive explanation so far exists. Among individual NSAIDs, diclofenac was associated with the highest risk of atrial fibrillation[46,48]. Subgroups of patients with pre-existing heart failure (RR 1.82, 95% CI 1.42–2.32) or chronic kidney disease (RR 1.58, 95% CI 1.34–1.85) were at high risk of developing atrial fibrillation after initiating NSAID therapy[48]. A meta-analysis in 2006 that included 114 randomized studies reported that rofecoxib was associated with an increased risk of cardiac arrhythmia (RR 2.90, 95% CI 1.07–7.88)[43]. However, the meta-analysis was limited by the inclusion of only 286 incident arrhythmias, so no analysis of subtypes was possible.

NSAIDs and heart failure

For patients with heart failure, the use of NSAIDs is discouraged in clinical guidelines owing to the increased risk of fluid retention and worsening of heart failure. Nevertheless, a Danish study showed that >34% of patients

with incident heart failure were prescribed NSAIDs after discharge from hospital[7]. A population-based study from Canada reported an increased risk of hospital admission for heart failure associated with non-selective NSAIDs and rofecoxib but not with celecoxib (compared with non-use)[49]. A nested case–control study based on real-world data from >10 million patients from four European countries found that NSAIDs in general raise the risk of hospitalization for heart failure and death in patients with established heart failure, but the risk varied according to dose and the particular NSAID used (compared with past use)[50]. A major cause for concern was that commonly used NSAIDs, such as diclofenac, ibuprofen and naproxen, were all associated with an increased risk of hospitalization for heart failure and that high doses of diclofenac or ibuprofen more than doubled the risk.

An observational study including patients admitted to hospital for heart failure in Denmark found that the use of NSAIDs was associated with an increased risk of death and readmission for heart failure (compared with non-use)[7]. A clear dose-dependent increase in risk existed and the risk of death was particularly elevated with high doses of diclofenac (>100 mg daily; HR 5.54, 95% CI 5.08–6.03) and rofecoxib (>25 mg daily; HR 3.54, 95% CI 3.12–4.02), whereas the risk of death was slightly lower with high doses of ibuprofen (>1,200 mg daily; HR 2.83, 95% CI 2.64–3.02) and celecoxib (>200 mg daily; HR 2.72, 95% CI 2.45–3.02). High doses of NSAIDs were also associated with an increased risk of readmission for heart failure: rofecoxib (HR 1.86, 95% CI 1.46–2.35), diclofenac (HR 1.42, 95% CI 1.17–1.73), celecoxib (HR 1.26, 95% CI 1.04–1.53) and ibuprofen (HR 1.18, 95% CI 1.04–1.33). Naproxen has been considered the safest non-selective NSAID with regard to cardiovascular risk, but data from this observational study indicated that the use of high doses of naproxen (>500 mg daily) is also associated with an increased risk of death (HR 1.97, 95% CI 1.64–2.36) and readmission for heart failure (HR 1.18, 95% CI 1.00–1.40). A case–control study from Canada including 2,256 elderly patients with heart failure reported higher risks of death and recurrent heart failure associated with the use of rofecoxib or non-selective NSAIDs compared with the use of celecoxib[51]. Another case–control study reported an increased risk of heart failure with the use of rofecoxib or indomethacin compared with the use of celecoxib[52].

In a meta-analysis of data from randomized studies, a twofold increase in the risk of heart failure was associated with all NSAIDs (compared with non-use)[32]. Of note, the risk was similar for selective COX2 inhibitors and non-selective NSAIDs. Therefore, the use of NSAIDs is a concern in populations with a high baseline cardiovascular risk such as patients with heart failure. Although differences in risk might exist between individual NSAIDs, limiting the use of all NSAIDs — both selective COX2 inhibitors and non-selective NSAIDs — in patients with heart failure seems prudent.

Randomized cardiovascular outcome trials

Until the past 5 years, there was a lack of data from randomized clinical trials that directly focused on the cardiovascular safety of NSAIDs. Previous randomized studies have primarily focused on the gastrointestinal safety of COX2 inhibitors compared with non-selective NSAIDs[53,54] or on the prevention of colorectal adenoma with COX2 inhibitors compared with placebo[55–60]. In these studies, cardiovascular safety was not the primary objective and cardiovascular outcomes were secondary end points. Therefore, the results of the PRECISION trial[61], published in 2016, were keenly awaited. The PRECISION trial included patients with osteoarthritis or rheumatoid arthritis who were at increased cardiovascular risk and who were assigned to treatment with celecoxib, ibuprofen or naproxen. The primary composite end point consisted of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. More than 24,000 patients were included over a period of 8 years and followed up for a mean of 20 months. The primary outcome occurred in 2.3%, 2.7% and 2.5% of patients assigned to celecoxib, ibuprofen and naproxen, respectively (no significant between-group differences). However, the reliability of the study was diminished because 69% of patients discontinued the study drug and 27% discontinued follow-up. In addition, the doses of celecoxib (mean 209 ± 32 mg) prescribed were lower than those used in previous studies that reported an increase in cardiovascular risk[53,56,62]; the low doses were likely to be suboptimal for adequate pain relief. The doses of naproxen (mean dose 852 ± 103 mg) and ibuprofen (2,045 ± 246 mg) were similar to or higher than those used in previous randomized studies. Furthermore, the low event rate observed does not reflect the high-risk population that was targeted for the study.

The role of aspirin in mitigating the cardiovascular risk of NSAIDs is unresolved. In the PRECISION study, patients were stratified at enrolment according to their history of aspirin use, but actual aspirin use or dosages used concomitantly with NSAID use were not recorded[63]. The PRECISION study found no significant interaction between aspirin use and NSAID use, but owing to methodological problems, the study did not clarify whether aspirin protects against NSAID-associated cardiovascular risk[38]. Although the PRECISION study provides insights into the cardiovascular safety of non-selective NSAIDs and COX2 inhibitors, the study has major caveats that limit the generalizability and interpretation of its findings.

The SCOT trial[64] included patients aged >60 years who had osteoarthritis or rheumatoid arthritis, were free from established cardiovascular disease and were chronically taking non-selective NSAIDs. Patients were randomly assigned to switch to celecoxib or to continue non-selective NSAID treatment. The primary outcome was the composite of cardiovascular death, non-fatal MI or stroke, or hospitalization for acute coronary syndrome. The median duration of follow-up was 3 years and 7,297 patients were included in the study. The primary end point occurred in 0.95% and 0.86% of patients assigned to celecoxib and non-selective NSAIDs, respectively. Although the SCOT trial found that celecoxib was non-inferior to non-selective NSAIDs in terms of cardiovascular events, the trial had a much lower event rate than was expected and also had high withdrawal rates from the study drug (50.9% in the celecoxib group and

30.2% in the non-selective NSAID group). For both the PRECISION and the SCOT trials, whether the dosages of celecoxib used were pharmacoequivalent to those of the non-selective NSAIDs used is questionable[65]. A lower exposure to celecoxib would favour this drug because of a lower risk of adverse events. Therefore, the shortcomings of the PRECISION and the SCOT trials make the data on the safety of celecoxib inconclusive.

NSAIDs, antithrombotics and bleeding

Several studies have reported on the risks of bleeding in patients with acute coronary syndromes treated with antithrombotic drugs[33,66]. The concomitant use of NSAIDs and antithrombotic drugs, and especially the use of celecoxib and diclofenac, as well as the use of widely available, over-the-counter NSAIDs such as ibuprofen, has been reported to increase the risk of bleeding in patients after MI[10]. No safe therapeutic window for concomitant NSAID and antithrombotic drug use exists, given that even short-term treatment (0–3 days) is associated with an increased risk of bleeding compared with no NSAID use[10].

In randomized studies, non-vitamin K antagonist oral anticoagulants (NOACs) were associated with lower overall rates of bleeding than warfarin; however, this reduction was mainly attributable to a decrease in intracerebral bleeding, and no clear advantage in terms of gastrointestinal bleeding was reported[67–69]. In post-hoc analyses of the RE-LY study[70] and the EINSTEIN study[71], the use of NSAIDs among patients taking NOACs was associated with an increased risk of major bleeding, including gastrointestinal bleeding, compared with non-use of NSAIDs. An observational study showed that NOACs were associated with less gastrointestinal bleeding than vitamin K antagonists, but concomitant NSAID use negated this advantage[72]. Nevertheless, worldwide, NOACs are increasingly the preferred option for anticoagulation in patients with newly diagnosed atrial fibrillation[73].

In patients with venous thromboembolism taking rivaroxaban or the combination of enoxaparin and a vitamin K antagonist, concomitant NSAID use was associated with a 1.8-fold increased risk of clinically relevant bleeding and a 2.4-fold increased risk of major bleeding[71].

Strengths and limitations of the data

Evidence on the excess cardiovascular risk of both non-selective NSAIDs and selective COX2 inhibitors has accumulated and is supported by the proposed physiological mechanisms for cardiovascular risk and by the pharmacological properties of NSAIDs[15,74]. Much of the detailed evidence on individual NSAID risks, dose–risk relationships and exposure–time risk comes from observational studies that are limited by unmeasured confounding and which cannot firmly establish causality. Meta-analyses of observational data, including of individual patient-level data, have helped to provide some overall perspective, although they cannot eliminate all the shortcomings of the original data[1,27,28,32]. Secondary findings in randomized studies of arthritis pain management and prophylactic treatment of gastrointestinal adenomas have supported the observational findings[53–57].

The gold standard in the hierarchy of evidence comes from well-designed, randomized clinical trials with robust end points. The few randomized clinical trials that had a primary focus on cardiovascular safety of NSAIDs were hampered by slow recruitment, high rates of treatment discontinuation, high numbers of patients lost to follow-up, low event rates and a lack of pharmacoequivalent dosages of the drugs being compared[61,64]. Therefore, despite including >30,000 patients, these studies have not provided the much-needed evidence on the comparative safety of individual NSAIDs in patients at risk of cardiovascular events. Consequently, the ability of regulators and medical societies to provide evidence-based advice on the use of NSAIDs is greatly limited.

Patterns of use of analgesics

The widespread use of NSAIDs among individuals at increased cardiovascular risk despite the drawbacks of these drugs might suggest high levels of analgesic effectiveness. However, more realistically, the use of NSAIDs is likely to reflect the limited therapeutic options available for common painful conditions, especially musculoskeletal ailments, such as osteoarthritis and back pain, and particularly among older people with or at risk of comorbidities. In broad terms, the main alternatives to NSAIDs are opioids and paracetamol (acetaminophen). In some specific pain indications, drugs from other therapeutic groups, such as anti-epileptics and antidepressants, might be helpful.

Freely available, international data on analgesic use are limited, and published studies of analgesic use are typically confined to a therapeutic group or to a particular pain indication[75–78]. Although not widely investigated, individual physician practices seem to differ considerably, including when prescribing to people at risk of NSAID-associated complications[79]. National consumption volumes of NSAIDs and of the alternatives also differ, as demonstrated by defined daily doses consumed per 1,000 inhabitants per day in data from the OECD Health Statistics 2019 (FIG. 3). The analgesics are categorized according to the Anatomical Therapeutic Chemical classification system to level 3 for NSAIDs (M01A group) and to level 2 for the most common alternatives (N02 group, which includes opioids, paracetamol, analgesic-dose aspirin and anti-migraine drugs). Owing to between-country differences in data-collection methods, country consumption volumes should not be compared, but within-country patterns can be examined. After 2005, when the cardiovascular risks of NSAIDs began to be widely acknowledged, the consumption of NSAIDs (ATC code M01A) decreased in many countries whereas the consumption of the alternative options (ATC code N02) generally increased (FIG. 3). The patterns cannot be analysed in detail because information on individual drugs or on user profiles is not available, but the data suggest that the information on the potential harms of NSAIDs had some effect on the choice of analgesics after 2005.

The preferred choice of NSAIDs differs between countries, as demonstrated in a study examining

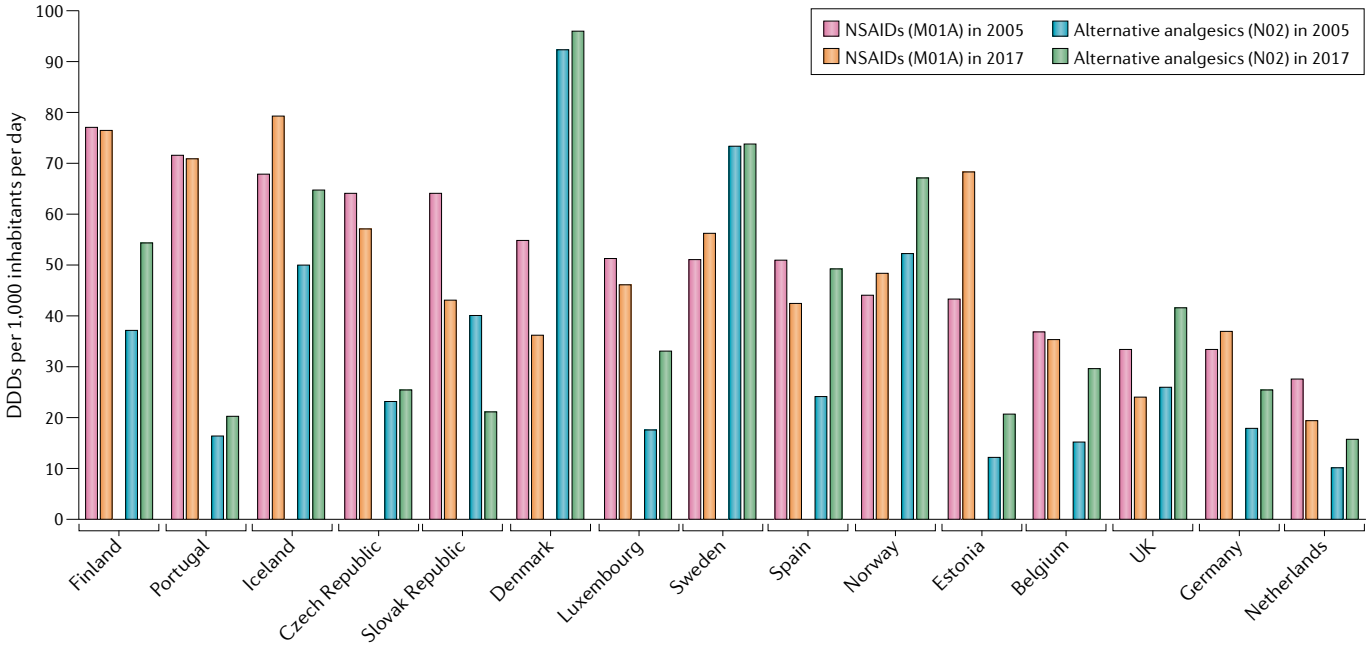

Fig. 3 | **OECD data on analgesic consumption by country for 2005 and 2017.** The data are reported as defined daily doses (DDDs) per 1,000 inhabitants per day and are categorized according to the international Anatomical Therapeutic Chemical (ATC) classification system at Level 3 (pharmacological subgroup) for nonsteroidal anti-inflammatory drugs (NSAIDs) (ATC M01A: anti-inflammatory and anti-rheumatic products, nonsteroid) and at Level 2 (therapeutic subgroup) for the alternative analgesics (ATC N02 group: opioids, salicylates, paracetamol and anti-migraine drugs). The Organisation for Economic Co-operation and Development (OECD) does not include information on individual NSAIDs (M01A group) and does not provide ATC Level 3 data for the N02 analgesics, which have to be considered as a group. The countries are presented in decreasing order of NSAID use in 2005. The data highlight the changes in within-country analgesic use between 2005 and 2017. Between-country comparisons are unreliable owing to differences in how each country collects data. All countries provide data on reimbursed prescriptions as well as hospital and non-reimbursed prescriptions; over-the-counter (non-prescription) NSAID sales are included for the Czech Republic, Denmark, Estonia, Finland, Iceland, Norway and Sweden. Data on over-the-counter use cannot be distinguished from overall NSAID use or overall N02 category use.

commercial sales data in 2011 from 15 low-income, middle-income and high-income countries[80]. Some countries had high sales of NSAIDs that were barely used in others; for example, mefenamic acid in Pakistan and the Philippines, piroxicam in Indonesia and Thailand, and naproxen in Canada and England. Overall, the highest sales, on the basis of measures of defined daily doses, were of diclofenac, ibuprofen, naproxen, mefenamic acid and celecoxib[80].

Analgesic consumption is not driven entirely by prescribers' choices because patients can self-prescribe NSAIDs that are available for purchase without prescription. The most commonly available NSAIDs include ibuprofen (widely sold in pharmacies and supermarkets), diclofenac and mefenamic acid (both available in some countries as pharmacy-only over-the-counter medicines) and naproxen (sold over the counter in pharmacies in some countries and also in supermarkets in others such as the USA). Most NSAIDs are also widely available for online purchase. Similarly, among alternative analgesic options, paracetamol, low-dose codeine and analgesic-dose aspirin are widely available over the counter, whereas high-dose codeine and other opioids are prescription-only medicines. By allowing the sale of NSAIDs without the necessary professional advice on appropriate use and possible adverse effects, health-care authorities signal to the general public that these drugs are safe to use. This safety is also perceived by consumers with comorbidities and elevated cardiovascular risks who might be using other drug treatments and who are put at risk of serious drug–drug interactions, treatment failure or worsening of the condition.

Guidance on NSAID use

No single, up-to-date, evidence-based, multidisciplinary guidance is available from specialist professional groups jointly on NSAID use in patients at risk of adverse effects, including those with cardiovascular risks. However, advice from individual professional groups is largely aligned. For example, guidance on the management of musculoskeletal conditions, such as osteoarthritis and back pain, seems to be reasonably consistent across Australia, Europe and the USA[81–84]. Generally, for osteoarthritis, non-pharmacological treatments are suggested first, followed by medicines, starting with topical NSAIDs and then systemic NSAIDs at the lowest effective dose for the shortest period possible. Oral paracetamol is recommended in some patients despite evidence that this drug is of little use when used alone and is not without safety concerns[85]. Opioids are recommended with caution if not excluded completely[81]. The American College of Rheumatology guidance

"conditionally recommends" that opioids should not be used[83], and Australian guidance "strongly recommends against" opioid use[84]. NSAIDs provide the greater symptomatic benefit notwithstanding the cardiovascular risks[81]. The European League Against Rheumatism has issued recommendations on cardiovascular risk management in patients with inflammatory joint disorders and addresses the issue of NSAID use (Recommendation 9), noting that, among the commonly used NSAIDs, diclofenac seems to have the highest cardiovascular risk and naproxen the lowest[82].

From a multidisciplinary perspective, a summary of advice from gastroenterology, rheumatology and geriatric professional groups on the appropriate use of NSAIDs, published in 2013, noted that the first-choice analgesic recommended by all groups tended to be paracetamol (despite its lack of benefit), followed by NSAIDs at the lowest possible dose for the shortest time, co-prescribed with gastroprotection if chronic use was needed, and that NSAID use should be avoided in patients with cardiovascular disease[86].

Cardiology professional groups have issued few guidance statements on NSAID use among patients with or at risk of cardiovascular disease. Neither the British Heart Foundation nor the ESC (the European oversight organization for 57 national cardiac societies) have formal guidelines although, in 2016, an ESC working group on cardiovascular pharmacology published a position paper on NSAIDs[87]. Over a decade ago, the ACC Foundation, the American College of Gastroenterology and the AHA issued an expert consensus statement on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use[88]. The AHA published a scientific advisory in 2005 on cardiovascular risk[89] but no update has been published. The Australian Heart Foundation briefly advises that NSAIDs should be avoided, and paracetamol (alone or combined with codeine) used instead[90].

The major specialty professional groups, including cardiovascular, rheumatology, pain and gastrointestinal societies, need to align their views and provide an up-to-date, evidence-based consensus statement on NSAID use in the context of both patient and drug risks. Given the complexities and value judgements on the benefits and risks inherent in pain management, an algorithm to aid decision-making would be of assistance for patients and prescribers alike. An holistic approach to NSAID use for patients with cardiovascular risks and who need pain relief is suggested in BOX 1.

Box 1 | Clinical guide to NSAID use in patients with cardiovascular risks

- Patients and clinicians should share decision-making through an understanding of the personal benefit–risk balance for the patient involved and by adopting an holistic perspective on overall function and wellness in addition to the acute need for pain control
- Agree on whether the underlying cause of the pain can be addressed definitively and, if so, the time frame and actions needed to achieve this outcome
- Address the pain situation
  - Define the desired or needed therapeutic benefits
  - Consider the non-pharmacological and pharmacological options available to help to achieve these benefits
  - Set out the benefits and risks in each case
  - When considering nonsteroidal anti-inflammatory drugs (NSAIDs), identify the patient's cardiovascular, gastrointestinal, renal and other physiological risks that are potentially vulnerable to NSAID-associated adverse effects
  - Review existing medications and the potential effect of adding NSAID therapy
- Prioritize non-pharmacological approaches and instigate them first, if at all possible
  - Set a date to review their effectiveness
  - Keep a patient pain/effect diary
- Depending on the site and intensity of the pain, a topical NSAID might be helpful[81]
- If use of a systemic NSAID is chosen
  - Use should be viewed as a temporary adjunct to non-pharmacological measures
  - Adhere to regulator-approved product information advice (in general: lowest dose, shortest time)
  - Set a review date within a few days, a therapeutic benefit target and a stop rule
  - Keep a patient pain/effect diary
- Of the four widely investigated NSAIDs (celecoxib, diclofenac, ibuprofen and naproxen)
  - Select ibuprofen or naproxen as first alternatives (with gastroprotection) — both have an effective analgesic dose range within the lower end of cardiovascular thrombotic risk estimates, and gastrointestinal risks can be offset to some extent with gastroprotection[34]
  - Celecoxib doses up to 200 mg per day have similar cardiovascular risk estimates but seem to have poorer analgesic effects; at doses >200 mg per day, the cardiovascular thrombotic risk escalates
  - Avoid diclofenac
  - All four NSAIDs increase the risk of heart failure
- Adjunctive paracetamol might help to minimize NSAID needs
- Within 1 week, review the benefits of NSAID use and the patient's diary record and check for adverse effects, aiming to down-titrate or cease the NSAID use while adjusting or up-titrating non-pharmacological measures
- Make a plan for ongoing support, prioritizing non-pharmacological measures to optimize the patient's wellness, function and fitness, and to minimize the need for pharmacological measures
- For patients for whom this approach is unsuccessful, consider referral to a multidisciplinary pain team for assistance

Regulatory advice on NSAID use

Medicine regulatory authorities require that product information for individual NSAIDs includes information on their adverse effects, including their cardiovascular risks. In the USA in 2015, the FDA strengthened the warning label required on all prescription NSAIDs regarding the risk of MI or stroke[5]. Additionally, regulators have provided advice on NSAID use in patients with cardiovascular risks. The EMA issued advice on the risks associated with high-dose ibuprofen in 2015 (REF.[91]), on diclofenac in 2012 (REF.[92]), on non-selective NSAIDs in 2006 (REF.[93]) and on selective COX2 inhibitors in 2005 (REF.[94]). Within Europe, national regulatory agencies have issued similar advice. In Australia in 2014, the Therapeutic Goods Administration published a detailed review of the cardiovascular safety of NSAIDs and included recommendations on use and on labelling for prescription and over-the-counter products[95,96]. The National Institute for Health and Care Excellence in the UK has previously provided 'key therapeutic topic' advice — not formal guidance — on NSAID prescribing, including for people with cardiovascular risks but retired the advice from its 2018 update[97].

The pharmaceutical development pipeline

The toxicities of NSAIDs, the limited efficacy of paracetamol, and the increasing recognition of the health, social and economic drawbacks of opioids highlight the need for effective analgesics with low risk of harm in order to relieve the myriad 'everyday' pains that afflict individuals[98,99]. Unfortunately, the pharmaceutical development pipeline is not promising. Considerable focus has been placed by the FDA and by drug developers on 'abuse-deterrent' opioid formulations, but their effectiveness in this respect is unproven and they might simply divert user choice[100–103]. None has gained widespread acceptance and several formulations approved by the FDA have never been marketed. Products include combinations of an opioid with a deterrent agent, such as naltrexone, or with gel-forming excipients. If the tablet is crushed to allow parenteral use, the deterrent is released or a sticky gel is formed that cannot be injected[104].

Non-opioid products newly licensed by the FDA or that are in development include an injectable liposomal anaesthetic (bupivacaine) for post-surgical analgesia and a reformulation of a previously approved but discontinued fixed-dose combination of aspirin, orphenadrine and caffeine[105]. Bupivacaine has been accepted for review by the EMA.

Non-opioid analgesics under investigation and regulatory review include a μ-opioid agonist (NKTR-181)[106], nerve growth factor-blocking antibodies (such as fasinumab[107] and tanezumab[108]) and an injectable synthetic *trans*-capsaicin product (CNTX-4975)[109]. An FDA review of NKTR-181 has reportedly raised concerns about safety[110], although a company-funded study concluded it was safe and effective. Safety concerns have also slowed the regulatory assessment of tanezumab[111].

Conclusions

NSAIDs are among the most commonly used medications worldwide. Despite their well-documented cardiovascular risks, the lack of promising new, effective and safer alternatives has contributed to their continued widespread use because they provide effective analgesia in many pain situations. Compared with the main alternatives, NSAIDs are more effective than paracetamol and are not addictive, which is a huge advantage given the health, social and economic destruction associated with high levels of chronic opioid use[81,112]. In terms of their major downsides, the gastrointestinal toxicity of NSAIDs can be mitigated to some extent[34]. However, great care is needed to manage the cardiovascular risks of NSAIDs for individual patients effectively and, similarly, the bleeding risks arising from co-prescription of NSAIDs with other agents that increase bleeding. The balance must clearly be in favour of patient benefit, as judged carefully by both the patient and the prescriber concerned, and this adjudication should include regular reappraisal of the indication and the need for continued treatment (BOX 1).

Given the few alternatives to NSAIDs, pain management in high-risk patients with cardiovascular disease needs to be considered as an expert field and involve multiple health-care disciplines to tailor treatment to individual patient needs and to minimize the risk of adverse effects but also to provide adequate pain control. This process can involve pain experts, physiotherapists, rheumatologists, geriatricians, clinical pharmacologists and cardiologists to obtain a consensus to guide optimal treatment and goals for some individual patients. Physiotherapy, exercise and weight management could be feasible options for many patients to achieve better pain control, while minimizing pharmacological analgesic needs, and with additional benefits in the form of improved management of cardiovascular risk (BOX 1).

In ageing populations, the management of pain is an increasing challenge for health-care systems globally. Taking good care of patients with chronic pain, especially high-risk, elderly patients, puts pressure on welfare systems. Nevertheless, adequate pain control optimizes individual independence in daily life and minimizes the need for home care or residential assisted care. Sustaining a high quality of life without chronic pain should be a top priority for our society as well as a basic right for individuals. Therefore, health-care authorities and policymakers need to collaborate with patients, clinicians, scientists and the pharmaceutical industry to develop new and alternative solutions for pain management as an urgent priority.

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