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Cardiovascular and cerebrovascular risk with nonsteroidal anti-inflammatory drugs and cyclooxygenase 2 inhibitors: latest evidence and clinical implications

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***Abstract*:** Observational studies and meta-analyses have shown that the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), especially when prescribed at high doses for long periods of time, can potentially increase the risk of cardiovascular diseases. The increased thrombotic risk related to the use of NSAIDs is mainly due to their cyclooxygenase 2 selectivity. The dosage use, the formulation selected and the duration of the therapy are other factors that can significantly impact on the cardiovascular risk. In order to minimize the risk, prescription of the right drug based on the patient's features and the different safety profiles of several NSAIDs that are available on the market is key for their appropriate administration. Despite the baseline cardiovascular and gastrointestinal risk of each patient, monitoring of patients is suggested for increases in blood pressure, development of edema, deterioration of renal function, or gastrointestinal bleeding during long-term treatment with NSAIDs.

Keywords: nonsteroidal anti-inflammatory drugs, cyclooxygenase 2 inhibitors, cardiovascular risk, cerebrovascular risk, paracetamol

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Background

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) can be associated with a wide spectrum of adverse events (AEs) affecting the cardiovascular (CV), cerebrovascular and gastrointestinal (GI) systems, the kidney, the liver and the skin.[1,2] For several years clinicians have focused their attention on reducing the incidence and clinical consequences of GI bleeding, considered the most frequent NSAID-related AE.[3,4] More recently, the European Medicines Agency (EMA) has also started considering the prothrombotic potential effect of NSAIDs.[5–9]

NSAIDs act by blocking the two main isoforms of cyclooxygenase (COX-1 and COX-2), which are the enzymes that catalyze the formation of prostanoids from arachidonic acid (AA).[10] In 2004 rofecoxib was withdrawn from the market due to a higher risk of CV AEs even caused by consumption of standard doses. In fact, COX-2 inhibition can damage the endothelium, leading to a prothrombotic state which increases the CV risk.[11] Recent observational studies and a meta-analysis have shown that even the administration of some nonselective NSAIDs such as aceclofenac, diclofenac and high doses of ibuprofen can increase the risk of CV events, especially when prescribed for long periods of time.[9,12,13] These drugs have therefore received the same warnings as selective coxibs. Although the absolute CV NSAID-related risk may be relatively low, the widespread diffusion of these molecules make their impact on CV disease a considerable issue in clinical practice worldwide.

Unfortunately, NSAID-related AEs are mainly due to their mechanism of action, therefore the absence of risk associated with their use is a utopian target in daily practice.[14]

This review aims at providing a summary of current literature relevant to the safety profile of available NSAIDs, mainly focusing on NSAID-related CV and cerebrovascular risk. The purpose is to support the clinician in NSAID prescription to minimize the risk, selecting the right drug according to each

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patient's features and the different safety profiles of several NSAIDs that are available on the market.

Methods

We conducted a qualitative review of the literature updated to 2016, searching for the terms 'non-steroidal anti-inflammatory drugs', 'cardiovascular risk and anti-inflammatory drugs', 'COX-2 inhibitors', 'COX-2 and cardiovascular risk', 'paracetamol and COX-2', 'NSAIDs and EMA', 'NSAIDs and recommendations'. Prioritization was given to information arising from data collected in randomized controlled trials and meta-analyses.

Mechanism of CV increased risk related to NSAID administration

It has been postulated that the increased CV risk associated with the use of NSAIDs may be related to the degree of COX-1 and COX-2 potency, which determines the inhibition of the antithrombotic hormone prostacyclin (PGI2) and the proaggregatory and vasoconstrictive agent thromboxane A2 (TXA2).[14,15] PGI2 is usually involved in the homeostasis of the endothelial cells, produces vasodilation and antagonizes platelet aggregation.[14,15] The increased platelet reactivity due to the action of NSAIDs on the PGI2 might be counteracted by a concomitant inhibition of platelet COX-1 activity and the relative conversion of the proaggregatory and vasoconstrictive agent thromboxane A2 (TXA2) from the AA. However, except for low doses of aspirin (75–150 mg), nonselective NSAIDs and selective NSAIDs do not seem to affect platelet COX-1 activity at the degree necessary (>95%) to inhibit the proaggregatory effect of TXA2.[16] Since enzyme inhibitors are described according to their efficacy in blocking the target enzyme, the parameter IC80 has been introduced, defined as the concentration of inhibitor which results in 80% reduction in COX activity. The 80% of inhibition of COX-2 enzyme represents the inhibition needed to produce the therapeutic effects of NSAIDs. The lower the value of IC80, the higher the potency. For NSAIDs, the results of inhibitor assays are commonly expressed as a ratio of IC80 for the enzymes COX-2/COX-1. A smaller value of IC80 ratio therefore implies a greater selectivity for the COX-2 enzyme. The most commonly used NSAIDs can be ranked according to their IC80 ratio as etoricoxib < meloxicam < nimesulide < celecoxib < diclofenac < piroxicam < ibuprofen < naproxen < ketoprofen < ketorolac,[16] etoricoxib therefore being the most potent for COX-2 inhibition and ketorolac the least potent. Surprisingly nonselective NSAIDs such as meloxicam and nimesulide present an IC80 ratio lower than the selective celecoxib, suggesting a higher COX-2 potency.[17]

Based on previous assumptions, it seems that the higher the level of COX-2 inhibition and the lower the level of COX-1 inhibition, the greater the thrombotic risk related to NSAIDs. As suggested in previous literature, the extent of inhibition of COX-2-dependent prostacyclin may represent an independent key determinant of the increased risk of myocardial infarction (MI) among NSAIDs with nonfunctional suppression of platelet COX-1. Therefore, the assessment of whole blood COX-2 may represent a surrogate end point to predict the CV risk of these drugs.[18] Nevertheless, the increased thrombotic risk related to NSAIDs is mainly but not only related to the COX-2 potency of each molecule[6] and such results need to be confirmed in clinical settings, since questions still remain about the exact mechanisms underpinning NSAID-associated CV events.

In fact, as shown by Warner and colleagues,[16] nimesulide is a preferential COX-2 inhibitor but in contrast to coxibs, it seems to exhibit no significant CV toxicity. Moreover, Lapi and colleagues[19] recently showed that nimesulide does not show a statistically significant increase in the number of cerebrovascular events.

The extent of patient exposure in terms of dose and duration might represent another important determinant of CV risk. Since a linear relationship exists between the degree of inhibition of COX-2 and the degree of inhibition of PGI2 *in vivo*, reduction of the dose could translate into a reduction of the CV risk.[20] In clinical practice, NSAIDs are still frequently administered at supratherapeutic doses. In fact, it has been shown that even a dose of diclofenac as small as 25 mg, administered orally, is effective in the treatment of postoperative acute pain.[21] Furthermore, in a study published by McCormack and Scott in 2008,[22] the reduction of the intravenous dose of diclofenac from 75 mg to 37.5 mg was not related to more severe pain referred by the patient. A similar result was achieved in same clinical context by a recent study by Dietrich and colleagues[23] in which the subcutaneous administration of 25 and 50 mg of diclofenac proved to be equally effective as a higher dose of 75 mg. Therefore excessive doses of NSAIDs may also account for CV toxicity. Finally, an important determinant of the differences among NSAIDs in terms of therapeutic and toxic effects might be represented by

Table 1. FDA strengthens warning that non-aspirin NSAIDs can cause heart attacks or strokes (see also http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm).

FDA strengthens warning that non-aspirin NSAIDs can cause heart attacks or strokes
The risk can occur as early as the first weeks of using an NSAID
The risk may increase with longer use of the NSAID
The risk appears greater at higher doses
Newer information is not sufficient for the FDA to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID
NSAIDs can increase the risk in patients with or without heart disease or risk factors for heart disease
Patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors
There is an increased risk of heart failure with NSAID use

FDA, US Food and Drug Administration; NSAID, nonsteroidal anti-inflammatory drug.

the pharmacokinetic features such as half life and type of formulation, which can influence the extent and duration of patient exposure.[20]

The necessity to use the lower effective dose for a shorter period of time was recently noted by the US Food and Drug Administration about the thrombotic risk related to NSAIDs (Table 1).[24]

Beyond the ischemic cardiopathy: the cerebrovascular risk

The studies related to the prothrombotic effect of coxibs or nonselective NSAIDs are mainly focused on ischemic cardiopathy, while the evidence concerning the risk of ischemic stroke/transient ischemic attack and hemorrhagic stroke is still debated.[25–28] The paucity of stroke events in the overall population, when compared with CV events, plays a central role in the lack of clarity about possible relationship between cerebrovascular risk and NSAID administration. Much of the data are therefore derived from observational studies and meta-analyses rather than randomized controlled trials.

In a study by Lapi and colleagues,[19] a cohort of 29,722 patients with a diagnosis of osteoarthritis (OA) treated with NSAIDs were evaluated to determine whether the use of NSAIDs is associated with an increased risk of cerebrovascular events. In a study period of 10 years, the authors identified 1566 cases of cerebrovascular events without any correlation between current use of NSAIDs compared with past use. Among individual NSAIDs, diclofenac and ketoprofen were significantly associated with an increased rate of cerebrovascular events. The most frequent event was hemorrhagic stroke following the use of ketoprofen.[19]

Another study assessed the risk of nonfatal ischemic stroke related to NSAIDs in 2888 patients, considering also the effects of dose, exposure and independent CV risk: the authors did not observe any increased risk with NSAIDs as a group. Nevertheless, an increased risk was found with diclofenac and aceclofenac, in particular when used at high doses, over long-term periods (>365 days) and in patients with a high background CV risk. The concomitant use of aspirin did not show a significant effect modification.[25]

High dosages of naproxen exert a near complete COX-1 inhibition, which suggests a possible protective effect for MI compared with rofecoxib.[29] However, two studies found that the use of naproxen was associated with a higher stroke risk.[30,31] Naproxen effect on blood pressure could explain the higher risk of cerebrovascular events, since hypertension represents a well known risk factor for stroke; however, naproxen shows the lowest risk for CV events.[32] Further studies will be required to reach conclusive evidence about naproxen.

Few systematic reviews have analyzed the possible correlation between NSAIDs and cerebrovascular events. In 2006, a large meta-analysis including 85,000 patients from 40 trials comparing COX-2 inhibitors with either placebo or nonselective NSAIDs demonstrated no increase in stroke risk.[33] In 2011 a meta-analysis by Trelle and colleagues[34] included 31 studies, of which 26 provided data of cerebrovascular events (only 337 events). Rofecoxib and celecoxib showed the smallest risk estimates for stroke, while ibuprofen and diclofenac showed the highest risk. Another meta-analysis in 2013 compared coxibs with placebo, diclofenac, ibuprofen or naproxen. The authors found no association between any NSAID and stroke events, although they again highlighted the small incidence of events.[35] Another

meta-analysis attributed to rofecoxib and diclofenac the highest risk of ischemic stroke.[36] The evidence for a clear relationship between NSAIDs and stroke events remains uncertain, thus no definitive recommendations can be drawn. Caution suggests considering alternative analgesics in specific high-risk patient populations, such as older people, and to limit the duration of therapy whenever possible.

NSAIDs and their effect on blood pressure

As reported by Lapi and colleagues,[19] a possible explanation for the increased risk of cerebrovascular events related to the use of NSAIDs could be their effect on blood pressure. Even the mechanism by which NSAIDs increase blood pressure is still not clear. The blockage of the COX enzyme and the relative inhibition of prostaglandin (PG) synthesis,[37] which induces vasoconstriction, as well as volume expansion, due to impaired sodium excretion, all seem to play an important role.[37] NSAIDs can also potentially decrease the effectiveness of the commonly used antihypertensive drugs.

Hypertension is commonly reported by patients older than 65 years with a diagnosis of osteoarthritis.[28] In this population even a small decrease in the diastolic blood pressure by 5–6 mm Hg due to an effective hypertensive therapy can lead to a 67% decrease in the risk of cerebral stroke and a 15% decrease in the risk of ischemic heart disease. The frequent coadministration of antihypertensive agents and NSAIDs in this population has led Kalafutova and colleagues[28] to review their potential interaction. The impact of NSAIDs on the effectiveness of antihypertensive therapy is mainly related to the role of PGs in the mechanism of action of each class of antihypertensives.[37,38] Diuretics work on blood pressure, decreasing extracellular water volume and the total peripheral resistance. NSAIDs decrease their effect leading to an increased retention of water and salts.[39] Moreover NSAIDs can interfere with some of the mechanisms potentially involved in the reduction of blood pressure mediated by β blockers, including the reduction of cardiac output, inhibition of the renin–angiotensin–aldosterone system, the reduction in plasma volume, as well of vasomotor tone and peripheral vascular resistance.[40] Bradykinin enhances the antihypertensive effect of angiotensin-converting enzyme (ACE) inhibitors, stimulating the release of PGs, which play a key role in vasodilation. NSAIDs block vasodilation by inhibiting PGs, thereby significantly lowering the antihypertensive effect of ACE inhibitors.[41] With the same mechanism and with the same degree, NSAIDs affect the functioning of angiotensin II blockers.[41,42] However, NSAIDs do not significantly interact with calcium channel blockers. In fact, their antihypertensive effect is not dependent on the action of PGs.[37]

In contrast to the evidence for an NSAID hypertensive effect, in a study among patients with hypertension and coronary disease, it was found that chronic NSAID use for nearly 3 years was actually associated with slightly lower blood pressure levels compared with nonuse.[43] Thus any hypertension-mediated effect may be specific to the duration of NSAID use and warrants further clinical investigation.

Nonselective NSAIDs and regulators

The review related to the safety profile of NSAIDs and coxib, conducted by the Committee for Medicinal Products for Human Use (CHMP) and started in 2005, concluded that, if properly prescribed, the benefits of nonselective NSAIDs outweigh their risks, even though a small increased incidence of thrombotic events associated with their use could not be excluded.[6] In particular, the CV risk seems increased if NSAIDs are administered at high doses for long-term treatment. In 2006, the EMA also concluded that a small increased risk of thrombotic events could not be excluded with nonselective NSAIDs, including diclofenac, particularly when they are used at high doses for long-term treatment.

In 2011, based on new data published by Fosbøl and colleagues and Garcia Rodriguez and colleague,[7,18,20] the UK drug regulatory agency required a new review of the committee for medicinal products for human use (CHMP) related to the safety profile of the most commonly used nonselective NSAIDs worldwide: diclofenac, ibuprofen and naproxen. With the same finality, EMA asked the European Commission to develop a research project called 'safety of non-steroidal anti-inflammatory drugs' (SOS).[44] The final aim of SOS is to develop decision models starting from the results of a nested case control study conducted in a cohort of 8.5 million new NSAID users that allow for regulatory and treatment decisions based on balancing the relative GI and CV safety of coxibs and nonselective NSAIDs.[44]

Based on the epidemiological data and the SOS findings, CHMP concluded its revision in 2012 with the opinion that current treatment advice adequately reflects the knowledge regarding the safety and efficacy of naproxen and ibuprofen, but they decided to modify advice related to diclofenac.[12] The January 2015 edition *of Drug Safety Update* reported that oral diclofenac was no longer available without prescription. This edition also highlighted updated prescribing advice for aceclofenac, which is now contraindicated in people with certain CV disease, in line with diclofenac and COX-2 inhibitors.

Diclofenac is among the most prescribed NSAIDs due to its favorable GI safety profile and efficacy for pain relief, but showed a dose-related CV effect, which increases for the higher doses and becomes comparable to the coxibs.[3,18,20] The role of the dose in the incidence CV AEs related to the use of NSAIDs was confirmed by the Pharmacovigilance Risk Assessment Committee (PRAC) of EMA, which has recently completed a review showing a small increase in the risk of CV problems, such as heart attacks and strokes, in patients taking high doses of ibuprofen (at or above 2400 mg per day).[11] The review clarifies that the risk with high-dose ibuprofen is similar to the risk seen with COX-2 inhibitors and diclofenac.[11] In 2015, a multidisciplinary group of experts published a meta-analysis of individual participant data from randomized trials, focusing on upper *versus* lower GI risk of COX-2 selective and nonselective anti-inflammatory drugs and on the interaction at both the GI and CV level of either class of drugs with low-dose aspirin in patients affected by OA. The panel stated the following: efficacy of both selective and nonselective NSAIDs is comparable in treating OA pain, although specific patient response should always guide the therapy; NSAID use is associated with increased risk, reduced for celecoxib, of AEs throughout the entire GI tract, associated with substantial mortality and is not preventable with protonic pump inhibitors (PPIs) in the lower GI tract; the association of cardioaspirin and celecoxib is related to lower GI risk than the association of other NSAIDs and cardioaspirin; the risk of CV events associated with celecoxib use is similar to that associated with the use of most nonselective NSAIDs, making coxibs the drugs of choice for patients taking low-dose aspirin for CV or cerebrovascular prevention.[35] The relative safety of celecoxib has also been confirmed in a recent randomized prospective study in terms of noninferiority of celecoxib compared with ibuprofen or naproxen in 24,081 patients with regard to the outcome of CV death (including hemorrhagic death), nonfatal MI or nonfatal stroke. However, the risk of GI events was significantly lower with celecoxib than with naproxen or ibuprofen, while the risk of renal events was significantly lower with celecoxib than with ibuprofen and comparable to naproxen.[45] Therefore, caution is recommended in prescription of NSAIDs in patients at high CV risk, weighing the risk to benefit ratio for each patient and limiting use to the shortest possible period and the lowest effective dose.

Paracetamol (acetaminophen) and CV/ cerebrovascular risk

Despite some previous data suggesting a possible association of paracetamol with CV risk[46] due to its effect on blood pressure,[47] a retrospective analysis by Fulton and colleagues[48] confirmed the safety of acetaminophen after collecting data from the UK Clinical Research Practice Datalink. No relationship could be found between verified acetaminophen prescription data and risk of MI or stroke in patients with hypertension over a 10-year period. Among the 10,878 acetaminophen-exposed individuals aged at least 65 years, there was no relationship between risk of MI, stroke or any CV event and acetaminophen exposure compared with the 13,618 individuals not exposed. The results when men and women were analyzed separately were similar and even high-frequency users (defined as receiving a prescription for >75% of months) were not at increased risk. The safety of paracetamol was also confirmed in another cohort study of 36,754 patients diagnosed with OA and with a first-time prescription of NSAIDs between 2002 and 2012.[49] CV and cerebrovascular events were identified in 2182 cases: no association was found between the use of acetaminophen containing medication and the occurrence of acute CV or cerebrovascular events. These findings support the choice of acetaminophen therapy for OA-related pain, especially in those patients presenting with cerebrovascular and CV morbidities or related risk factors.[49]

The efficacy of paracetamol and selective NSAIDs has been compared, postulating celecoxib to be superior to acetaminophen in acute postoperative pain relief.[50] Also a 2004 meta-analysis by Lee and colleagues[51] found that NSAIDs are superior to acetaminophen for reducing certain types of OA

Table 2. General rules to improve the safety profile of NSAIDs in clinical practice.

Use the lowest effective dose for a shorter period of time
If prescribed as an analgesic drug, stop administration after 7 days if no benefit is reported
If prescribed as an anti-inflammatory drug, stop administration after 3 weeks if no benefit is reported
If it is possible avoid concomitant therapy with corticosteroids, anticoagulants, low-dose aspirin or antiplatelet agents

NSAID, nonsteroidal anti-inflammatory drug.

pain. Data were confirmed in a 2006 Cochrane review comparing the safety and efficacy of acetaminophen with placebo and NSAIDs: NSAIDs were superior to acetaminophen using Western Ontario and McMaster Universities (WOMAC) OA scores for pain and functional outcomes. The review also found that acetaminophen was superior to placebo on several pain measures while no significant WOMAC score differences were demonstrated between treatments.[52–54]

NSAIDs in clinical practice

The clinical decision-making process, leading to the prescription of NSAIDs, involves the selection of a significant number of molecules, types of preparations and dosages. The choice of NSAID to be used in clinical practice depends on the characteristics of each patient. In particular, a review of the medical history including advanced age, history of GI ulcer, hypertension, ischemic heart disease, kidney diseases and concomitant treatment with corticosteroids, aspirin, anticoagulants and antihypertensive drugs is essential (Table 2). In 2015, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis stressed the importance of assessing each patient's risk/benefit ratio before starting therapy with NSAIDs.[55,56]

In the last few years, the literature has shown that NSAIDs are nonhomogeneous as a drug class and there are vast differences between individual molecules, not only in terms of AEs but also in their efficacy. Recently, da Costa and colleagues[57] published a network meta-analysis assessing the effectiveness of different preparations and doses of NSAIDs used to treat OA-related pain. The authors considered trials published between 1980 and 2015, with at least 100 patients per group, comparing any of the following interventions: NSAIDs, paracetamol, or placebo, for the treatment of OA pain. The study included 74 randomized trials with a total of 58,556 patients. The treatment effect was evaluated in terms of improving function and pain relief.[57] Higher dosages of diclofenac (150 mg/day) seemed to be the most effective combination molecule dose. In fact, the approved maximum daily dose of diclofenac showed an effect size of 1.5 times the minimum clinically important difference for chronic pain, corresponding to a difference of 14 mm on a visual analogue scale.[57] The meta-analysis also demonstrated that the 100% probability to report a minimum clinically improvement in terms of pain management and improved function is associated with the use of diclofenac 150 mg/day, etoricoxib 60 mg/day or rofecoxib 25 mg/day, which are the NSAIDs with the highest CV risk. Compared with the other NSAIDs, celecoxib, diclofenac and naproxen showed a linear correlation between analgesic effect and dose.[57] Unfortunately, a similar correlation between dose and CV risk was shown by McGettigan and Henry[51] in their meta-analysis, which included 2.7 million patients exposed to NSAIDs.

The difference in terms of CV and GI risks among the NSAIDs and the availability of different formulations and dosages allow therapies to be customized according to the characteristics of every single patient (Table 3).[7,8,23,55] When there is not a higher risk for CV events, the administration of NSAIDs with a favorable GI profile is suggested: etoricoxib, celecoxib, diclofenac, ibuprofen and nimesulide are all suitable molecules while ketorolac and ketoprofen are less indicated in this setting. Furthermore, in patients with GI risk factors, the association of a PPI with the NSAID therapy is suggested. If the patient presents a considerable CV risk, COX-2 selective inhibitors, as well as high doses of diclofenac and ibuprofen, are contraindicated. If the patient already takes low doses of acetil salicilic acid for secondary CV prophylaxis, naproxen is considered the best choice for coadministration for short periods of time; it should be administered 2 h after the aspirin in order not to interfere with its mechanism of action.[58, 59] Moreover, in patients with a history of hypertension, the combined use of NSAIDs with

Table 3. Prevention of NSAID-related GI and CV risk.[13]

Patient without CV risk **No GI risk factors:** coxib, diclofenac, ibuprofen or nimesulide (avoid ketorolac and ketoprofen) **One or more GI risk factors:** coxib or diclofenac – ibuprofen – nimesulide + PPI **History of ulcer bleeding:** coxib – diclofenac + (PPI)
Patient with CV risk + no GI risk factors **CV < 3%:** Avoid coxib, aceclofenac, diclofenac >100 mg/die and ibuprofen ⩾2400 mg/die *If concomitant administration of low-dose aspirin:* Avoid ibuprofen; Administration of aspirin 2 h before naproxen + PPI **CV > 3%:** Administration of aspirin 2 h before naproxen + PPI
Patient with CV risk + one or more GI risk factors **CV < 3%:** Avoid coxib and aceclofenac, (diclofenac < 100 mg/die – ibuprofen <2400 mg/die – nimesulide) + PPI *If concomitant administration of low-dose aspirin*: Avoid ibuprofen; Administration of aspirin 2 h before naproxen + PPI **CV > 3%:** Administration of aspirin 2 h before naproxen + PPI
Patient with CV risk + history of ulcer bleeding If it is possible avoid NSAIDs and coxib If strictly necessary and CV < 3%: (celecoxib – diclofenac <100 mg/die – ibuprofen <2400 mg/die – nimesulide) + PPI
CV, cardiovascular; GI, gastrointestinal; PPI, proton pump inhibitor; NSAID, nonsteroidal anti-inflammatory drug.

antihypertensive therapy leads to worsened blood pressure control. Both hypertension occurrence and NSAID use increase with age and older populations are likely to be more predisposed to blood pressure elevation owing to NSAID use. Potentially, this increase can be very serious because even a relatively slight elevation in blood pressure (less than 5 mmHg) can contribute to increased occurrence of ischemic events or heart failure.[28]In summary, the real challenge in clinical practice seems to be finding the right balance between risk of AEs (CV and GI) and efficacy (pain relief and improved mobility).[57,60]

Conclusion

In the face of recent and growing concerns associated with the efficacy and safety profile of the most commonly used medications in the chronic treatment of pain, the importance of to depriving patients of their legitimate need for pain relief must be underlined.[44,61,62] Prescribing the right drug for the right patient is even more important for long-term therapies in order to reduce patient exposure to the risk of side effects and to enable early diagnosis of eventual AEs.

Despite the baseline CV and GI risk of each patient, it is suggested that patients are monitored for increases in blood pressure, development of edema, deterioration of renal function or development of GI bleeding during long-term NSAID therapy.

In conclusion, all NSAIDs are to varying degrees associated with GI, CV and renal AEs. The take-home message of current guidelines is therefore to use NSAIDs at the lowest effective dose and for the shortest period of time.

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