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Non-steroidal anti-inflammatory drugs in the pharmacological management of osteoarthritis in the very old: prescribe or proscribe?

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***Abstract*:** Osteoarthritis (OA) is the most common form of arthritis worldwide, and ranges in the top 5–10 most disabling diseases. Contrary to common opinion, this disease is severe, often symptomatic, and may lead to loss of mobility and independence, as well as being responsible for increased frailty and excess mortality [standardized ratio: 1.55 (95% confidence interval, CI: 1.41–1.70)]. The incidence of OA increases dramatically with age in an increasingly ageing world. Therefore, practitioners involved in the management of OA often have to manage very old patients, aged 75–80 years and above, as part of their daily practice. Treatment options are limited. In addition to education and physical treatments, which are at the forefront of all treatment recommendations but require a low level of symptoms to be implemented, many pharmacological options are proposed. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used as a second-line treatment but with great caution. However, the precise incidence of cardiovascular, renal, and gastrointestinal adverse events in very elderly patients is unclear. All of these risks are increased in the elderly. The relative risks can be extrapolated from various studies. However, what is the absolute risk according to age categorization? The answer to this question is important because NSAIDs should be used in very elderly patients with OA only if full information has been provided and the decision to prescribe this treatment is shared between the patient and their doctor. This article reviews the risks and currently available recommendations, and proposes practical options and warnings to allow for a responsible and limited use of NSAIDs in the very old.

Plain language summary

NSAIDS in the very Old : Prescribe or Proscribe?

- Osteoarthritis (OA) in the very old is a serious disease leading to loss of independence, frailty, and excess mortality. Quantitative data from clinical trials and population-based observational studies on the risk of NSAID-related side effects allow the prescriber to provide more accurate information to each patient. If there is no contraindication, the decision to initiate NSAID therapy in a very old OA patient should be made in a shared manner, with the patient fully informed of the risks.

Keywords: NSAIDs, osteoarthritis, very old, benefit/risk, shared prescription

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Introduction

Treating multiple osteoarthritis (OA) pain in very old patients (⩾75–80 years) is a frequent challenge for general practitioners, rheumatologists, and orthopedists in daily clinical practice. The objective to relieve pain in such frail people must be weighed against iatrogenic risks.

Treatment options are limited. International recommendations on OA management rightly advocate a non-pharmacological approach.[1–6] However, these treatments are often slow-acting, insufficiently effective, and difficult to implement in very old patients suffering from severe pain.[7] Reducing pain, bringing patients to the Patient Acceptable Symptom State,[8] seems a mandatory prerequisite for any physical treatment.

Because of its good safety record, paracetamol is used widely but its effectiveness on OA pain is currently questioned. A recent meta-analysis suggested that paracetamol was almost useless.[9] Non-steroidal anti-inflammatory drugs (NSAIDs) are more likely to reduce pain.[10] With NSAIDs, the number needed to treat to achieve a reduction of at least 50% in pain intensity after 12 weeks of treatment is between 4.7 and 8.4, depending on the drug used (naproxen 1000 mg, celecoxib 200 mg or ibuprofen 2400 mg).[11] In knee OA, a recent systematic review and meta-analysis found statistically significant and clinically important effects of NSAIDs on pain as early as 2 weeks after initiation with a standardized mean difference (SMD) of −0.43 [95% confidence interval (CI) −0.48, −0.38]. This treatment effect remained statistically significant up to 26 weeks [SMD −0.21 (95% CI −0.39, −0.03)].[12]

Opioids, recommended as a second-line treatment, are effective but very badly tolerated. Although there is no specific accurate data on safety in the elderly, a poor safety profile has been outlined, in particular with an increased risk of falls and related fractures, of confusion, renal impairment, and all-cause mortality, compared with NSAIDs.[13] The global number needed to harm has been estimated as high as five.[14]

The use of systemic corticosteroids in the treatment of pain in osteoarthritic patients has been the subject of only a few publications with contradictory results.[15,16] Because of their potential side effects [water retention, diabetes destabilization, osteoporosis, adverse cardiovascular (CV) effects...], their prescription in elderly people with OA is not recommended; they could be used for very short-term or palliative administration in patients at the end of life.[5]

Despite their frequent and sometimes serious side effects, should we still use NSAIDs in very old people? Should we discourage our patients from continuing to use over-the-counter (OTC) NSAIDs? And can we establish and quantify the risks of NSAIDs in this segment of the population and accurately inform the patient?

This is crucial for true shared decision-making. Patients are more willing than their physicians to accept a risk of harm for successful NSAID therapy.[11] The purpose of this article is to examine the potential risks and benefits of NSAID therapy in very elderly patients with OA and to provide an update on data that may help share the decision to prescribe NSAIDs with the patient.

Methods

We first searched the Medscape and Cochrane databases using the search terms “older” or “very old” or “elderly” or “geriatric” and “osteoarthritis” and “NSAID” or “non-steroidal anti-inflammatory drugs.”

After selecting appropriate publications, we searched their bibliographies manually for relevant papers, then extended the search to meta-analyses, recommendations, and reviews of recent literature dealing with the treatment of OA and pain in geriatrics.

Who are we talking about?

This viewpoint focuses on patients aged over 75, even 80, years old in whom OA is extremely frequent. Its related functional disability combined with other co-morbidities, is responsible for a high burden in terms of pain, functional impairment, and loss of independence. In this age group, one person in five with hip or knee OA is inadequately relieved by analgesics and still experiences severe or extreme pain.[17]

Ageing, with multiple co-morbidities such as impaired renal, cardiovascular, and hepatic functions and changes in body composition, modifies drug pharmacokinetics and pharmacodynamics, increasing their iatrogenicity.

What are we talking about?

OA is a severe condition that is not sufficiently often taken into consideration. In a population-based cohort, with a 14-year median follow up, OA patients had a standardized mortality ratio of 1.55 (95% CI 1.41–1.70) compared with the general population.[18] In a population cohort aged 55+ years with at least moderately severe symptomatic hip and/or knee OA, the adjusted hazard-ratio (aHR) of all-cause mortality per unit increase of the Health Assessment Questionnaire (HAQ) walking score was 1.30 (95% CI 1.22–1.39, $p < 0.001$); the aHR when using a walking aid *versus* not using one was 1.51 (95% CI 1.34–1.70, $p < 0.0013$).[19] More recently, in a sample of 1709 participants in the Johnston County Osteoarthritis Project (mean age of participants 59.5 ± 9.5 years) with symptomatic knee OA and not reporting CV disease (CVD) at baseline, it was shown that functional worsening, assessed by the Health Assessment Questionnaire (HAQ), the time to complete five chair stands, and gait speed during an 8-foot walk was associated with a significantly increased risk of CVD on all three functional measures: HAQ odds ratio (OR) = 2.49 (95% CI 1.90–3.25), chair stands OR = 1.58 (95% CI 1.20–2.08), and 8-foot walk OR = 1.53 (95%CI 1.15–2.04).[20]

In a European survey of 2455 individuals aged 65–85 years, clinical OA at any site (hip, knee, hand) was associated with frailty.[21] Increasing walking capacity and reducing disability with effective treatments probably reduce OA-associated mortality risk. Most patients with OA are willing to accept some additional risk of stomach bleeding and/or heart attack/stroke to gain pain relief .[22] Statistical studies support a bimodal distribution of pain treatment response in chronic pain patients.[23] Only a few OA patients are good responders with a decrease in pain of more than 50%.[11] It is in this group of patients that the benefit/risk ratio of NSAID treatment could be the most valuable. However, although the prevalence of OA increases dramatically with age, we lack specific data in very old OA patients.

What are specific NSAID-related risks?

The side effects of NSAIDs are numerous and can be serious: hypersensitivity, dizziness and falls, headaches, rare hepatotoxicity, drug interactions, possible chondrotoxicity, etc. The major side effects of NSAIDs are gastrointestinal GI complications, renal disturbances, and CV events. These side effects are related to the inhibition of cyclo-oxygenase (COX) enzyme activity and prostaglandin synthesis. They can be severe, leading to death, especially in frail patients. They may occur early in the course of treatment, although in most studies the risks appear to increase with longer use or higher doses.

CV adverse effects. The adverse effects of NSAIDs on the CV system appear to be based primarily on two distinct mechanisms:

- First, water and salt retention, dependent primarily on the inhibition of renal medullary COX-2, leading to increased renin production and the possible development of reno-vascular hypertension and heart failure. The activity of COX-2-derived prostanoids in renal medullary occurs mainly under conditions of sodium depletion or overloading. This effect, which is not very large in healthy people, can have important repercussions when there are, as is common in elderly patients, pre-existing pathological conditions such as high blood pressure, liver or kidney failure, etc.
- Secondly, an effect on the vascular endothelium and platelets leading to a thrombotic risk. This action was first attributed to an imbalance in the production of thromboxane A2 (TXA2), which is pro-aggregating and vasoconstrictive and primarily under the control of COX-1, and the COX-2 related production of prostacyclin (PGI2), which is anti-aggregating, vasodilating, and inhibits the vascular response to TXA2. This hypothesis would explain the better CV safety of naproxen, which strongly inhibits COX-1 with an aspirin-like effect that counterbalances the negative effect of COX-2 inhibition. According to this hypothesis, the most COX-2 selective NSAIDs should present the greatest thrombotic risk, which has not been verified for celecoxib. It has now been established that COX-2 selectivity alone is not the cause of the CV risks of non-steroidal anti-inflammatory drugs,[24] and each NSAID may have a unique safety profile. Some authors have postulated that CV risks are much more related to the potency of COX-2 inhibition than to the selectivity of the drug; the most effective drugs would also be the most hazardous to the CV system.[25] This issue remains controversial.[26]

The nature and frequency of CV side effects of NSAIDs remain debated, with significant differences and sometimes conflicting results between randomized, double-blind clinical trials conducted in selected populations, excluding patients at higher risk of side effects, and epidemiological and case-control studies that are more subject to statistical biases, in particular protopathic biases.[25,27]

Hypertension. Inhibition of COX-2 blocks its natriuretic effect *via* the renin-angiotensin pathway. NSAIDs also inhibit the vasodilating effect of prostaglandin and stimulate the production of various vasoconstrictor factors such as endothelin-1. In the general population,[28] as in the elderly population,[29] NSAID therapy increases systolic blood pressure by approximately 5 mmHg on average and has little or no effect on diastolic blood pressure. This increase would be different with different NSAIDs and greater with higher doses of NSAIDs.[30] It is particularly marked with the prior use of antihypertensive drugs, even if the blood pressure was previously effectively treated,[28] mainly diuretics, especially loop diuretics, angiotensin-converting enzyme inhibitors.[31] This situation is very common in the elderly; in France, in 2014, 58% of subjects over the age of 75 were receiving antihypertensive treatment, 39% bitherapy, 14% triple therapy, and 7% four or more different treatments.[32]

Heart failure. The risk of heart failure (HF) is related directly to elevated blood pressure, with increased systemic vascular resistance and water-sodium retention caused by inhibition of renal prostaglandins.

A large and extensive meta-analysis conducted by an international group (CNT meta-analysis) analyzed data from randomized clinical trials of at least 4-weeks duration comparing NSAID with a placebo or another NSAID.[33] Individual data, when available from the sponsors, was used. Data from 639 clinical studies were aggregated in an analysis of 68,342 person-years for placebo-comparisons and 165,456 person-years for comparisons between NSAIDs. Individualized data were available for 192,881 patients, mean-age 61.2 ± 11.3 years, 63% treated for OA. The coxib group included celecoxib, rofecoxib, lumiracoxib, etoricoxib, and GW403681; this group was compared with diclofenac 150 mg daily (rarely 100 mg), ibuprofen 2400 mg per day, and naproxen 1000 mg (rarely 440 mg). The relative risk (RR) of hospital admission for HF in patients using high doses of NSAIDs compared with placebo was around two, regardless of the NSAID used (naproxen, diclofenac, ibuprofen, coxib).

A meta-analysis of observational studies demonstrated a significantly higher risk of HF in NSAID users [pooled risk ratio (RR) = 1.17 (95% CI: 1.01–1.36)]. This increased risk was observed for traditional NSAIDs [RR = 1.35 (95% CI: 1.15–1.57)], but there was no statistically significant risk of HF with coxibs (RR = 1.03, 95% CI: 0.92–1.16). For the authors, this non-significant result could be related to insufficient sample size.[34]

The SOS project is a nested case-control study using five population-based healthcare databases from four European countries [the Netherlands, Italy, Germany, and the United Kingdom (UK)].[35] In this cohort of several million individuals with an average age of 77 years [standard deviation (SD): 11], the incident rate of HF was 37.5 per 10,000 person-years, comparable with that reported in population-based studies. Current NSAID users (within the previous 14 days) had an increased risk of hospitalization for HF (adjusted OR 1.19; 95% CI 1.17–1.22) compared with past use of any NSAID. This risk is increased by diclofenac, ibuprofen, indomethacin, ketorolac, naproxen, nimesulide, piroxicam, etoricoxib, and rofecoxib, but not by standard doses of celecoxib. This study indicates that this increasing risk of HF is dose-dependent for most NSAIDs.

HF is common in the very elderly. Its clinical symptoms may be very mild in patients with a sedentary lifestyle with reduced physical activity due to osteoarticular pathologies. Treatment with NSAIDs may result in decompensation of pre-existing HF, leading to hospitalization. This exacerbation may be worsened by the interaction of NSAIDs with treatments (diuretics, angiotensin converting enzyme inhibitors, etc.) that reduce their effectiveness.

Atrial fibrillation (AF) is facilitated by age, high blood pressure, history of myocardial infarction (MI), or HF (which it aggravates), and can lead to thromboembolic complications such as strokes. Several studies have suggested that the use of NSAIDs increases the risk of AF. A population-based prospective cohort study of elderly people [mean age 68.5 years (SD 8.7)] in the Rotterdam Study found that the current use of NSAIDs was

associated with increased risk compared with never use (HR 1.76, 95% CI 1.07–2.88). Recent use (within 30 days after discontinuation of NSAIDs) was associated with an increased risk of AF compared with never use (HR 1.84, 95% CI 1.34–2.51).[36]

Stroke. In their meta-analysis of individual participant data from randomized trials for the CNT collaboration, there is no evidence that any NSAID significantly increases the risk of stroke.[33] A meta-analysis of observational studies published in 2015 concluded that, overall, patients on NSAID therapy did not have a significant risk of stroke.[37] However, there was a significant increase in risk among diclofenac or meloxicam users (RR 1.27; 95% CI, 1.02–1.59 and RR 1.27; 95% CI, 1.08–1.50, respectively). A recent population-based case-control study, not included in this meta-analysis, also concluded that there was no increased risk of stroke with traditional NSAIDs as a group (OR = 1.03; 95%CI, 0.90–1.19).[38] A significant increased risk was found with diclofenac and aceclofenac. This risk was greater at high doses, in the case of prolonged exposure and in patients with CV risks. The European case–control study in the SOS Project concluded that the use of coxibs (OR = 1.08, 95% CI 1.02–1.15) and use of traditional NSAIDs (OR = 1.16, 1.12–1.19) were associated with an increased risk of ischemic stroke.[39] Significantly increased risks (in decreasing order) were found for ketorolac, diclofenac, indomethacin, rofecoxib, ibuprofen, nimesulide, diclofenac with misoprostol, and piroxicam. Naproxen, meloxicam, celecoxib, and ketoprofen showed no elevated risk. Ischemic stroke risk associated with NSAIDs seemed higher in younger individuals, males, and those with a prior history of ischemic stroke. Surprisingly, the increase in risk would be most pronounced during the first 7 days of treatment, and, to a lesser extent, for treatments longer than 90 days.

MI and coronary risks. In the meta-analysis of the CNT collaboration, the risk of infarction or death from coronary heart disease was increased over placebo when a coxib was used (RR = 1.76 95%CI, 1.31–2.37), diclofenac [adjusted risk ratio (aRR) = 1.70 95% CI, 1.19–2.41] or ibuprofen (aRR = 2.22 95% CI, 1.10–4.48), but not naproxen (aRR = 0.84 95% CI, 0.52–1.35).[32]

A Bayesian meta-analysis of individual patient data using Canadian and European healthcare databases found an increased risk of MI within the first 7 days of treatment, with no further increase in risk with longer treatment (except perhaps for diclofenac). There was a relationship between increasing NSAID daily dose and risk of acute MI. The ORs for the five NSAIDs studied were 1.24 (0.91–1.82) for celecoxib, 1.48 (1.00–2.26) for ibuprofen, 1.50 (1.06–2.04) for diclofenac, 1.53 (1.07–2.33) for naproxen, and 1.58 (1.07–2.17) for rofecoxib.[40] Concomitant use of cardioprotective aspirin does not appear to reduce the risk of acute MI with NSAIDs.[41] A subsequent analysis using data from the Quebec administrative health cohort confirmed that all five NSAIDs, including naproxen, are associated with increased risk of MI. This increased risk exists for celecoxib after continuous use for more than 30 days, whereas, for the other four NSAIDs, it occurs within 7 days of use.[42]

The risk of acute MI was also studied in the SOS project. The study cohort included 8,535,952 new NSAID users, of whom 101,227 patients experienced an acute MI (AMI) after inclusion. Association with AMI was evaluated for 28 individual NSAIDs. The risk of MI with current use of any NSAID compared with past use of any NSAID is increased with OR = 1.08 (95% CI 1.06–1.11). Estimates of the RR of AMI differ slightly between 28 individual NSAIDs. The RR was statistically significant for 12 of the 28 NSAIDs studied. It was highest for ketorolac, followed, in descending order of point estimate, by indomethacin, etoricoxib, rofecoxib, diclofenac, the fixed combination of diclofenac with misoprostol, piroxicam, and ibuprofen. It was correlated with COX-2 potency, but not only with coxibs. Higher doses showed higher risk estimates than lower doses; for duration, no clear patterns were seen.[43]

GI adverse events. GI adverse events range from heartburn, dyspepsia, and bloating to major GI averse events, such as bleeding, ulceration, and perforation of the stomach or the intestine that can occur without any signal symptom and can be fatal.

Approximately half of patients who regularly take NSAIDs have gastric erosions, and 10–30% have gastric ulcers on endoscopy, but clinically significant problems are uncommon.[44] There is no correlation between NSAID gastropathy and upper abdominal symptoms frequently experienced by patients taking NSAIDs. The risk of GI complications increases with age and with history of peptic

ulcer disease or gastrointestinal hemorrhage, high doses of NSAIDs, and concomitant use of corticosteroids.[44]

The 2007 OARSI International COX-2 Study Group Workshop reported that several meta-analyses showed a RR of serious adverse GI effects in people who were current users of NS NSAIDs to be three-to-four times that of non-users in the general population.[45]

A nested case control study conducted between January 2000 and 2005 found an adjusted RR of upper GI complications associated with current use of 3.7 (95% CI: 3.1–4.3) for traditional NSAIDs (tNSAIDs) and 2.6 (95% CI: 1.9–3.6) for coxibs. Daily dose was a predictor of increased risk for both tNSAIDs and coxibs. Users of tNSAIDs with a prolonged plasma half-life or slow-release formulations had an augmented risk of upper GI tract complications.[46]

A systematic review of observational studies on NSAIDs and upper GI bleeding/perforation published between 2000 and 2008 calculated a pooled RR estimates of upper GI bleeding/perforation of 4.50 [95% CI 3.82–5.31] for traditional NSAIDs and 1.88 (95% CI 0.96–3.71) for coxibs. The RR of upper GI tract hemorrhage/perforation varies among NSAIDs at doses commonly used in the general population. The RR was 2.69 (95% CI 2.17–3.33) for ibuprofen, 2.12 (95% CI 1.59–2.84) for rofecoxib, 1.44 (95% CI 0.65–3.2) for aceclofenac, 1.42 (95% CI 0.85–2.37) for celecoxib, 3.98 (95% CI 3.36–4.72) for diclofenac, 4.15 (95% CI 2.59–6.64) for meloxicam, 5.40 (95% CI 4.16–7.00) for indomethacin, 5.57 (95% CI 3.94–7.87) for ketoprofen, 5.63 (95% CI 3.83–8.28) for naproxen, 9.94 (95% CI 5.99–16.50) for piroxicam, and 14.54 (95% CI 5.87–36.04) for ketorolac. There was no significant correlation between this risk and the degree of COX-1 inhibition. Drugs with a profound and coincident inhibition (>80%) of both COX isozymes or with a long half-life or slow-release formulation were associated with a higher risk.[47]

A meta-analysis of nine randomized clinical trials comparing celecoxib with nonselective NSAIDs revealed that celecoxib had fewer GI side effects. However, this improved safety cannot be extrapolated to the entire coxib class,[48] and concomitant administration of celecoxib with low-dose cardioprotective aspirin often appeared to negate the GI-sparing advantages of celecoxib over NSAIDs. Also, in elderly patients (⩾65 years, mean age: 71.9 years duration of treatment: ⩾2 weeks) digestive toxicity appears to be lower with celecoxib and diclofenac than with naproxen and ibuprofen.[49]

For the CNT meta-analysis, all NSAIDs increased upper GI complications (COX-2 inhibitors RR = 1.81 95% CI 1.17–2.81; diclofenac RR = 1.89 95% CI 1.16–3.09; ibuprofen RR = 3.97 95% CI 2.22–7.10; and naproxen RR = 4.22 95% CI 2.71–6.56).[33]

There is no statistically significant difference in major GI side effects between nonselective NSAIDs and coxibs prescribed with proton pump inhibitors (PPIs).[50] PPIs used to protect the upper GI tract do not have a protective effect on the lower GI tract and may worsen NSAID-induced enteropathy.[51,52] This is of importance because it is estimated that more than two out of three patients taking long-term selective and nonselective COX-2 inhibitors develop enteropathy with intestinal inflammation, increased intestinal permeability, protein leakage, erosions, diverticula and risk of intestinal perforation, risk of occlusion, and diaphragm-like stricture.[53] For some authors, these complications of the lower GI tract may be as frequent and severe as those of the upper tract.[54]

A national Spanish study, published in 2005, found a mortality rate of 5.6% in hospitalized patients due to serious events related to the upper or lower GI tract.[55]

Renal adverse events. Renal adverse events are important to consider in the very old. NSAIDs can induce hyperkaliemia, and sodium and fluid retention, especially in subjects with pre-existing diabetes mellitus, cardiac, renal, or hepatic impairment. This may result in peripheral edema, increased blood pressure and lower efficacy of antihypertensive treatments, congestive heart failure, and acute kidney injury (AKI). AKI triggered by NSAIDs is increased by concomitant use of a diuretic and/or a renin-angiotensin inhibitor, and also in the dehydrated elderly with impaired renal function.[56] In a recent meta-analysis, the OR of AKI due to current NSAIDs exposure in older people (>50 years) was 2.01 (95% CI 1.52–2.68) but lower: 1.73 (95% CI 1.32–2.29) with COX-2 inhibitors, although this difference was not statistically significant.[57] The risk of chronic renal failure associated with the use of NSAIDs was assessed by a systematic review and

meta-analysis of observational general practice or population studies featuring patients aged 45 years and over. Regular-dose NSAID use did not significantly affect the risk of accelerated chronic kidney disease (CKD) progression; pooled OR = 0.96 (95% CI: 0.86–1.07), but high-dose NSAID use significantly increased the risk of accelerated CKD progression; pooled OR = 1.26 (95% CI: 1.06–1.50).[58]

Risk of all-cause mortality in the elderly

Published studies do not provide a definite conclusion on the risk of mortality from any cause related to NSAID use. Thus, two studies, conducted using data from Australian veterans' administrative databases, reached different conclusions. For one, there is a reduction in all-cause mortality if an NSAID, whether selective or nonselective, has been used in the previous 2 years. The risk of death appears to be inversely related to the number of prescriptions provided.[59] For the other, there was a significantly higher mortality risk. The risk ratios and 95% CI relative to the control group (adjusted for age, sex, and CV risk) were: celecoxib 1.39 (1.25, 1.55), diclofenac 1.44 (1.28, 1.62), meloxicam 1.49 (1.25, 1.78), rofecoxib 1.58 (1.39, 1.79), nonselective NSAIDs 1.76 (1.59, 1.94).[60] The authors of the latter study indicate that these different results may be related, in part, to a more restrictive definition of NSAID exposure in their study than in the previous one.

In the meta-analysis of the CNT collaboration, using data from clinical trials conducted in a population with an average age of 61 years, the risk of death from any cause was significantly higher only in patients allocated to coxib, without excess risk for naproxen or ibuprofen, or even diclofenac, despite a clear increase in the risk of death from vascular causes for the latter.[33]

NSAIDs should certainly be discouraged in patients with severe renal impairment or heart failure. These are common conditions in the very old and should be routinely investigated before prescribing. NSAIDs should also be avoided in patients with a history of perforation, bleeding or GI ulcer, active peptic ulcer, hemorrhage, severe hepatocellular failure, coronary artery bypass graft, or history of aspirin or NSAIDs-related allergy or asthma.

Beyond these statements, what are current international recommendations from academic societies regarding the use of NSAIDs for OA management in the elderly?

What do international OA recommendations for the very old say?

International recommendations for OA treatment make little or even no mention of age.[61]

The European League Against Rheumatism (EULAR) recommendations for knee OA support paracetamol as the first line, and, if successful, the preferred long-term oral analgesic.[1] NSAIDs should be considered in patients unresponsive to paracetamol. In the case of increased GI risk, nonselective NSAIDs and gastroprotective agents or coxibs should be used.

The American College of Rheumatology (ACR) recommends "considering topical NSAIDs prior to use of oral NSAIDs".[2] However, ACR strongly recommends oral NSAIDs in knee, hip, and hand OA, without any mention of age.

The OsteoArthritis Research Society International (OARSI) updated recommendations do not recommend oral NSAIDs in knee OA in the context of frailty (but they do not mention age). NSAIDs with more favorable safety profiles may be used in frail patients in hip and polyarticular OA, at the lowest possible dose for the shortest possible duration.[3]

In the updated European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for the management of knee OA,[4] in the case of insufficient efficacy of a first step treatment (including SYSADOA: symptomatic slow acting drugs for osteoarthritis that are supposed to reduce the need for analgesics), ESCEO takes age into account and recommends, for considerations of safety, favoring topical over oral NSAIDs, particularly in patients aged 75 years old and over.

The American Geriatric Society (AGS) does not specifically target OA but focuses on persistent pain management in older patients with a strong recommendation[5]: traditional or selective NSAID use for chronic pain, should be rare, considered in highly selected individuals, and only if the foreseeable risks appear to be outweighed by therapeutic benefits. Peptic ulcer, chronic renal failure, or HF are absolute contraindications. In patients with hypertension, *Helicobacter pylori* infection, a history of peptic ulcer, concomitant use of steroids or inhibiting serotonin-reuptake antidepressants, NSAIDs should be avoided. Indomethacin should never be used in elderly patients.

Table 1. Number of CV and symptomatic upper GI adverse events by age group, for coxib and placebo. Additional unpublished data provided by the coxib and traditional NSAIDs collaboration with permission.

Baseline age (years)	Major vascular events			Symptomatic upper GI events		
	Allocated coxib	Allocated placebo	RR (99% CI)	Allocated coxib	Allocated placebo	RR (99% CI)
<60	50/10327	24/6866	1.44 (0.75–2.77)	44/10332	8/6873	2.74 (1.22–6.12)
60–69	84/7862	38/5632	1.51 (0.91–2.51)	54/7879	14/5647	2.11 (1.04–4.28)
70–79	103/6565	65/6522	1.42 (0.93–2.16)	42/6598	27/6542	1.35 (0.68–2.68)
⩾80	45/1198	27/1191	1.49 (0.77–2.88)	20/1194	8/1200	2.31 (0.80–6.70)

CI, confidence interval; CV, cardiovascular; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; RR, relative risk.

In 2012, the AGS updated the list of drugs whose potential risks outweigh the benefits in the elderly.[6] NSAIDs are stigmatized for their high GI risk in patients over 75 years or if they are taken concomitantly with corticosteroids, anticoagulants, or antiplatelet agents.

The Society specifies that this list is not intended to be used in a punitive manner. In any case, clinical judgement is irreplaceable and mandatory to allow for individualized adapted and shared therapeutic decisions between the therapist and the patient.

All these recommendations do not preclude using NSAIDs in very old OA patients without contraindications and severe co-morbidities. Although therapeutic indications appear to be limited, prescribing NSAIDs is possible for patients suffering from pain in whom first-line treatments have failed to significantly reduce pain and when predictable risks appear to be overweighed by therapeutic benefits.

Their prescription requires caution, careful monitoring, and, above all, the consent of the patient after complete information on the risk–benefit ratio. However, this assumes knowing the accurate quantified estimates of the GI, CV, and renal relative and absolute risks.

Do we have data on NSAIDs RRs in the elderly?

A review of observational studies conducted at the request of United States (US) health officials concluded that the RR of serious CV or GI side effect was independent of age.[62] Age undoubtedly increases the absolute risk but NSAIDs use-RR remains unchanged whatever the age.

The authors of the CNT meta-analysis came to the same conclusion: the RR of serious secondary events when using NSAIDs is not related to age.[32] We asked them to provide these rates according to age categorization: <60, 60–69, 70–79, ⩾80 years.[63] In their answer,[64] they confirmed they observed no evidence of a greater RR of serious CV event for COX-2 inhibitors ($p=0.88$), naproxen ($p=0.62$), or other NSAIDs ($p=0.18$), and no evidence of a greater RR of serious symptomatic upper GI side effect $p=0.28$, $p=0.37$, and $p=0.30$, respectively, in any of these age groups (Table 1). The conclusions of this meta-analysis of trials in selected patients are consistent with those of observational studies: NSAIDs increase CV and GI risks by a multiplying factor that can be estimated, and varies upon the risk and the NSAID, but is not dependent on age or other baseline patient characteristics.

Do we know what NSAIDs absolute risks are in the very old?

For care providers, the basic incidence of serious CV and GI diseases in the very old not using NSAIDs is difficult to ascertain. National or private insurance systems have databases. As far as we know, they have not yet reported accurate data on this major issue.

An estimate of the absolute incidences can be drawn from the results of placebo groups from meta-analyses, but since patients with high CV or GI risk are excluded from trials their results cannot be extended to the real population.

Several scores to predict CV risk have been developed. The Heart Score of the European Society of Cardiology and the Framingham Coronary

Heart Disease Risk Score are not applicable beyond a certain age. The CV Risk Calculator of the American College of Cardiology and the American Heart Association is applicable to African-American and non-Hispanic white individuals between 40 and 79 years.[65] For older people, it only estimates a 10-year risk for atherosclerotic CV disease.

The QRISK, developed by Hippisley-Cox and based on the English/Welsh population, seems the only valid score in patients aged 30–84 years old. It allows for estimating the CV risk in the coming year.[66]

For GI pathologies, a British population-based controlled analysis, also developed by Hippisley-Cox, provides incidence of peptic ulcer or GI hemorrhage by sex and age in the general population.[67]

The combination of the age-related basic risk with the RR related to NSAID use provides an estimate of the incidence of adverse events and deaths due to NSAIDs (Tables 2 and 3). We are fully aware that this risk calculation remains imprecise, particularly due to the lack of epidemiological data on the incidence of CV and GI events in the general population. However, this data provides an order of magnitude that can be useful to the patient in making an informed decision about whether or not to take an NSAID and whether or not to consider this risk acceptable for symptom relief.

Conclusion

We believe there is room for NSAIDs in the treatment of OA in the very old. The disease is painful, disabling, and severe enough to justify, in some cases, the risks.

Table 2. Incidence of major vascular and severe upper GI events, expressed per 100 patient–years, in the placebo group of the CNT meta-analysis,[32] and according to HC epidemiological studies,[65,66] for a male subject in the UK, with no history but with treated hypertension.

	Age (years)	Placebo group	HC
Major vascular	70–79	1.0	2.0–3.3
Events	⩾80	2.3	3.0–4.0
Severe upper GI	70–79	0.4	0.2–0.4
Events	⩾80	0.7	0.4–0.8

GI, gastrointestinal; HC, Hippisley-Cox; UK, United Kingdom.

A small percentage of very old OA patients will respond to NSAIDs and experience a clinically significant improvement. They are the ones who will buy NSAIDs OTC or ask for a prescription from their healthcare provider. These patients should be fully aware of the risks and warnings regarding NSAID treatment. Recent data suggests the possibility of providing patients with quantitative information on CV and GI risks related to age, co-morbidities, or other risk factors and related to NSAID use. This may allow for making a shared decision, taking into account the patient's preferences and personal beliefs.

New evidence suggests that the frequency and severity of side effects may vary across drugs used. The prescriber, therefore, has to choose the treatment best suited to each patient's profile.

The prescription of NSAIDs in very old OA patients should respect their contra-indications and always be as short as possible, at the lowest effective dose, and under strict clinical and biological monitoring.

Table 3. Based on data from CNT meta-analysis and HC epidemiological studies[32,65,66]: RR of AEs during NSAIDs therapy and incidence per 100 patient–years of AEs observed, NSAIDs-related AEs, and NSAID-related death.

	Age (years)	Placebo group[18]	NSAID RR	Incidence AEs	Incidence NSAID-related AEs	NSAID-related death
Major vascular	70–79	1.0	0–1.4	1–1.4	0–0.4	0–0.1
Events	⩾80	2.3	0–1.4	2.3–3.2	0–0.9	0–0.3
Severe upper GI	70–79	0.4	2–4	0.8–1.6	0.4–1.2	0.008–0.024
Events	⩾80	0.7	2–4	1.4–2.8	0.7–2.1	0.014–0.042

AEs, adverse events; GI, gastrointestinal; HC, Hippisley-Cox; NSAIDs, nonsteroidal anti-inflammatory drugs; RR, relative risk.

Research agenda

Some questions still need to be addressed, amongst which:

- The need to access epidemiologic data on the frequency of the risk of GI, major CV events and AKI in the general population, according to age categorization, from public institutions, national health services, and private insurance databases.
- The need, while the published results remain contradictory, to better specify for each NSAID (and not only for the entire class of traditional NSAIDs or Coxibs) the relative frequency of the different risks.

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Conflict of interest statement

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Ethical issues

Our review did not require ethics committee approval because it was based on available, previously published information and analysis of datasets obtained from other researchers whose data were appropriately anonymized and whose informed consent had been obtained at the time of initial data collection.

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