The relationship between non-steroid anti-inflammatory drugs and cardiovascular risk -the myths, the misconceptions, the news, the realities-

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Abstract

While the number of clinical experiments investigating the effects of non-steroid anti-inflammatory drugs (NSAIDs) on the cardiovascular (CV) events has significantly increased over the last two decades, basic research related to the mechanism by which NSAIDs cause CV dysfunction is limited. High variability in the clinical trials conducted (different populations, dosages, exposure and types of NSAIDs) has led to results which are difficult to interpret and compare between studies. Are there some NSAIDs safer than other from the standpoint of CV risk? We have try to answer at some aspects of this question.

Key words: non-steroid anti-inflammatory drugs, cardiovascular risk

Pain is the most common reason for patients coming to their physician and the number is anticipated to rise with the increase in population ages and chronic conditions [1]. For osteoarthritis (OA) especially, NSAIDs remain the most effective option for pain relief [2,3]. A risk that appears in several randomized studies was an increase in adverse cardiovascular (CV) events in patients taking ciclooxygenase (COX)-2 inhibitors for months or years. In Europe, the European Medicines Agency (EMA) had indicated that an increased risk of MI and stroke may be a class effect of all COX-2 inhibitors. In 2005, the EMA advised that NSAIDs should not be used in patients with ischemic heart and/or cerebrovascular diseases and should have caution prescribing COX-2 inhibitors for patients with risk factors (peripheral arterial disease, diabetes) and should be use the lowest effective dose of COX-2 for the shortest possible duration [4]. The US Food and Drug Agency (FDA), in 2007, declined to make limiting statement

COX-2 inhibitors (celecoxib, rofecoxib, etoricoxib, etc.) carried a greater CV risk than the older **non-selective NSAIDs** (nsNSAID: indometacin, diclofenac, ibuprofen, piroxicam, naproxen) or newer **selective NSAIDS** (sNSAIDS: nimesulid, meloxicam, sulindac). [5].

Are there some NSAIDs safer than other from the standpoint of CV risk? All the NSAIDs have CV risk, but the evidence of the CV risk associated with NSAIDs is less clear cut than that for gastrointestinal (GI) complications. As with the risk for GI complications, any risk for CV adverse events is probably dose-dependent. The risk of CV events associated with COX-2 selective inhibitors agents use is similar to that associated with the use of most nsNSAIDs [6].

A recent meta-analysis including 31 trials (more than 116.000 patients taking

NSAIDs or placebo) found an increase in **myocardial infarction (MI), stroke and CV death** in patients taking NSAIDs. Rofecoxib was associated with the highest risk for MI (Risk Ratio for CV events 2,12) and was withdrew in 2004 because of CV effects. Ibuprofen was associated with the highest risk for stroke (3,36), followed by diclofenac (2,86). Etoricoxib was linked to the highest rate of CV death (4,07) followed by diclofenac (3,98). Naproxen (0,82), diclofenac (0,82) and etoricoxib (0,75) did not appear to significantly affect the risk for MI. All NSAIDs (1,58-4,07) except naproxen (0,98) demonstrated some increase in the risk for CV death [7].

Patients with COX-2 selectively suppressor might have an imbalance in prostaglandin (PG) I_2 and tromboxan (Tx) A_2 production, resulting in a **prothrombotic** state raising the potential for CV adverse events [8]. Aspirin exerts its prolonged anti-platelet effect because it irreversibly acetylates platelet COX. Others nsNSAIDs are reversible inhibitors of the COX, so their platelet inhibitor effect disappears as their plasma levels dissipates. Naproxen is one of the longer acting nsNSAIDs, thus may offer some antitrombotic protection. A recent meta-analysis (the CNT-Coxibs and Traditional NSAID Trialists-Collaboration) found that celecoxib, diclofenac or ibuprofen increased the rate of major CV events by about a third (not so significant for ibuprofen), but naproxen did not [9].

Because many CV patients are under aspirin antiaggregant prevention, does NSAID interfere with this action? COX-2 inhibitors do not interfere with the antiplatelet effect of low-dose aspirin and should represent the NSAIDs drug of choice for patients aspirin for CV and cerebrovascular prevention [6]. NsNSAIDs, being COX-1 inhibitors impaired TxA2 synthesis and platelet aggregation. With the exception of diclofenac and meloxicam, most of all nsNSAIDs can interfere with the antiaggregant effect of aspirin [10,11]. No association was made between the use of acetaminophen and the occurrence of CV events. This information supports the choice of acetaminophen (paracetamol) therapy for OA-related pain, especially in those patients presenting with cerebrovascular and CV morbidities [12]. The treatment-guidance algorithm allows naproxen or low-dose celecoxib as the preferred agents in patients with high CV risk, adding a pomp proton inhibitor (PPI), if patients added also a high GI risk [1,6,13].

A special situation occurs in post-MI patients. Management guidelines advise that all patients with MI should be prescribed dual antithrombotic therapy (DAPT) (aspirin and clopidogrel for up to 12 months and a 1 agent after) and others patients has additional indication for OAC [14,15]. **NSAIDs may not only increase bleeding risks but also may increase the risk of CV events**. Among patients receiving antithrombotic therapy after MI, the use of NSAIDs (especially diclofenac, aceclofenac, ketoprofen) is associated with increased risk of bleeding and excess thrombotic events, even after short-term treatment (less than 1 week) (16-18). The risk associated with use of NSAIDs among patients after a first MI persists for at least 5 years after the acute event [16]. Naproxen is the NSAID with the lowest relative CV risk, but naproxen and ibuprofen are associated with a high risk of GI bleeding, which is associated with poor prognosis in MI patients.. The use of NSAIDs after a first MI is associated with increased risk for CV death and nonfatal MI [16-18].

The Danish register researchers analyzed the association between the concomitant use of NSAIDs and antithrombotic medication (aspirin, clopidogrel, and/or OAC therapy) and adverse CV outcomes/bleeding risks in more than 60.000 patients admitted with a

first-time MI (2002-2011). Overall, 34% of the MI patients had a prescription for a least one NSAIDs. Among them, 30% experienced a CV event (CV death, recurrent MI or stroke). The overall risk of bleeding was more than twofold higher among post-MI patients who concomitantly takes an NSAID compared with those who were not. The bleeding risks depended on the antithrombotic regimen but were all significantly increased among those taking DAPT or OAC and NSAID. [19,20].

Recent evidence shows that **concomitant use of NSAIDs in anticoagulated atrial fibrillation (AF) patients carries a real risk of serious bleeding, as well as thromboembolism**. Bleeding risk in patients with AF can be associated with a number of clinical features [21]. AF patient population is often elderly and has multiple comorbidities. Adding aspirin to OAC substantially increases bleeding risk, especially the intracranial hemorrhage [21,22]. NSAIDs have generally increased GI bleeding risk, the data for bleeding risks with these drugs in anticoagulated AF patients were limited, so it was generally presumed that adding NSAIDs to anticoagulation should, such as aspirin, confer excess risk [22]. Regular NSAID use was often an exclusion criteria for randomized trials of anticoagulants for stroke prevention in AF [23-25].

Some interesting studies stipulate that **use of NSAIDs is associated with an increase in risk of AF**. The association was found for new users, with a 53% increase in risk. Among new users of NSAIDs and COX-2 inhibitors, risk for AF is increased with older age, chronic kidney disease and rheumatoid arthritis (RA). NSAIDs differentially modulate PV (pulmonary veins) and atrial electrophysiological characteristics. Celecoxib increased PV triggered activity through enhancement of the sodium-calcium exchanger (NCX) current, which contributed to its arrhythmogenesis These findings suggest that AF needs to be added to the CV risks to be considered when prescribing NSAIDs [26,27].

Drug interactions between NSAIDs and antihypertensive agents can lead to problems with blood pressure (BP) control in patients using both classes of medication at the same time. The mechanism by which NSAIDs influence BP is not completely clear, but seems to be blockage of COX and subsequent inhibition of PG synthesis [28]. BP can increase by up to approximately 5.0 mm Hg. NSAIDs are well known to diminish BP control in hypertensive patients as well as transform the prehypertensive state to hypertension (HT). Small increases in BP are known to increase CV risk. Different classes of antihypertensive drugs are not influenced in the same way. The level of interaction between NSAIDs and antihypertensive drugs depends on how big a role PG play in the mechanism of action of the antihypertensives [28-30]. By influencing PG synthesis, NSAIDs can limit their ability to regulate BP. (30). Certain drug classes, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics and their primary vasodepressor or BP-lowering effect are significantly attenuated by the co-administration of a NSAIDs or a coxib. The best drug class management appears to be the calcium channel blockers. Add or increase the dose of the diuretic in use to the regimen or consider lowering the dose of the NSAID or shift the time of day of dosing of the NSAID [29,30]. Prescribing NSAIDs should not forget that their use with antihypertensive therapy leads to worsened BP control. Both HT occurrence and NSAID use increase with age and older population are likely to be more predisposed to BP elevation using NSAID. Potentially, this increase can be serious because even a

relatively slight elevation in BP can contribute to an increase in the occurrence of MI or the risk of heart failure (HF) [28].

HF patients represent a unique subset of pain sufferers (67%). Pain symptoms may be directly attributed to HF complications (constipation, visceral ischemia, musculoskeletal fatigue, ascites, oedema) or may occur as a separate comorbid condition.[31,32]. Based on available evidence and current guidelines, clinicians must be careful that **most NSAIDs increase the incidence of HF**. The incidence may increase if the patient has heart disease (preexisting coronary artery disease-CAD) or CV risk factors. The mechanism of HF exacerbation included the inhibition of renal synthesized PG promoted sodium-fluid retention and minimized diuretic response [32].

A subsequent review of the PHARMO Institute for Drug Outcomes Research database detected a twofold increase in risk of HF hospitalizations in patients treated with diuretics who also took NSAIDs, the risk of HF admission occurs frequently within 30 days of NSAID initiation (56.8 %). These findings were consistent for all NSAIDs studied, demonstrating a class effect [33]. In 2013, the CNT Collaboration founded no difference in risk of HF admissions posed by coxibs compared with NSAIDs so they concluded that all NSAIDs, including coxibs, increase the risk of HF admissions. Consistent with older studies, high-dose NSAIDs were problematic and were associated with 99 % of the primary outcomes that occurred (9). These findings provided scientific confirmation that NSAIDs increase the risk of HF [9,32]. Most recent, the findings from the Standard Care versus Celecoxib Outcome Trial (SCOT) provide reassurance that celecoxib associated with concerns about elevated risk for MI in patients with CV disease (CVD), is as safe for chronic therapy as nsNSAIDs. The findings of SCOT investigators argue against concerns that even the older mainstay nsNSAIDs, predominantly diclofenac and ibuprofen reveal an untoward CV hazard [33].

The relationship between NSAIDs and CV events could be reversed? Is it possible that in some patients to obtain a CV protective effect by using NSAIDs. A recent study pospone that in the first 6 months, ankylosing spondylitis (OA) patients treated with NSAIDs had a no risk of cardiovascular disease (CVD) among those who were non-frequent users. The CV risk tended to decline with long-term use. In frequent NSAID users, there was no significant risk of CVD and, interestingly, there was a trend showing that the longer the use was, the lower the risk was. Even more, long-term frequent use of COX-2 seems to have a strong protective effect [34].

We have potential NSAIDs options for managing patients with chronic pain, But we have to be skillful in using correctly those options for each patient population according to individual CV risk profile [35].

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