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COMMENTARIES

Non-steroidal anti-inflammatory drugs and atherothrombotic risk in older patients: where do we stand?

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Abstract

The evidence linking the use of non-steroidal anti-inflammatory drugs (NSAIDs) with increased atherothrombotic risk is controversial, particularly in older patients. This population is consistently underrepresented in epidemiological studies. Moreover, several confounding factors such as co-morbidities, polypharmacy, and institutionalisation might affect the interpretation of studies on the real association between NSAID use and cardiovascular risk. These issues are herewith discussed together with a proposed mechanism to explain the results of recent studies demonstrating a relatively low atherothrombotic risk associated with NSAIDs in older patients. Suggestions for future research directions are also provided.

Keywords: *non-steroidal anti-inflammatory drugs, atherothrombotic risk, inflammation, ageing, cardiovascular system*

Non-steroidal anti-inflammatory drugs (NSAIDs) are extensively prescribed in older patients for the treatment of musculoskeletal disorders, a common reason for consultation in primary care and specialist clinics [1]. In the United Kingdom the use of NSAIDs has been fairly stable over the last decade (15–20 million prescriptions yearly) [2]. In general, NSAIDs are classified according to their relative inhibitory selectivity for the two main isoforms of the cyclooxygenase (COX) enzyme, COX-1 and COX-2. Selectivity is assigned on the basis of *in vitro* data, usually the ratio of the IC_{50} values (the NSAID concentration at which activity is inhibited by 50%) for COX-2 and COX-1. A low COX-2/COX-1 ratio is interpreted as evidence of COX-2 selectivity. However, clinical interpretation of the ratio is problematic because it differs markedly according to the assay system used (e.g. a 150-fold variation for meloxicam) and fails to account for the multiple mechanisms of NSAIDs inhibition [3].

Despite the caveats on the classification of NSAIDs, current evidence suggests the use of COX-2 selective NSAIDs and non-selective NSAIDs (ns-NSAIDs) increases atherothrombotic risk, in particular myocardial infarction (MI) and stroke [4]. This might have enormous health and financial implications in the older population. The proposed mechanisms responsible for the detrimental cardiovascular effects of NSAIDs are secondary to their inhibitory effects on COX. In the cardiovascular system, the products of COX regulate complex interactions between platelets and the vessel wall [5]. There is evidence that ns-NSAIDs and selective COX-2 inhibitors either increase blood pressure and/or diminish the blood pressure-lowering effect of antihypertensive drugs [6, 7]. The selective inhibition of COX-2 might lead to a reduced synthesis of prostacyclin by the endothelium, leading to an imbalance between prostacyclin and platelet-derived thromboxane that could trigger the onset of a thrombotic event [8]. Moreover, NSAIDs exert detrimental effects on fluid balance. The decrease in prostaglandin I_2 and prostaglandin E_2, derived mainly from COX-2 in the renal cortex and juxtaglomerular cells, causes a decrease both in renal blood flow and in glomerular filtration rate [9]. There is also recent evidence *in vitro* that several ns-NSAIDs inhibit aldosterone metabolism, with possible untoward effects on fluid retention, blood pressure control and cardiovascular remodelling [10].

Concerns over the potential increase in atherothrombotic risk associated with NSAID use have been expressed by the American Heart Association and, more recently, by the

Medicines and Healthcare products Regulatory Agency in the United Kingdom [11, 12]. Following the withdrawal of rofecoxib in 2004, specific concerns apply to the selective COX-2 inhibitor celecoxib (estimated hazard ratio of cardiovascular events 1.6, 95% CI 1.1–2.3) and the ns-NSAIDs diclofenac (1.63, 95% CI 1.12–2.37) and ibuprofen (1.51, 95% CI 0.96–2.37) [12–14]. The risk estimates seem to be higher with longer duration of treatment and high doses. However, in 2006 the European Union Committee for Medicinal Products for Human Use adopted a more prudent approach recommending that all NSAIDS should be used at the lowest effective dose for the shortest possible time [15]. These position statements are largely based on meta-analyses of either randomised controlled trials, for which cardiovascular events were not pre-specified primary end-points, or observational studies in the general population [14, 16]. Do the results of these studies necessarily apply to the older population? It does not seem to be the case.

Recent studies have shown that the atherothrombotic risk imparted by NSAIDs is somewhat lower with advancing age. For example, Garcia Rodriguez *et al.* observed that the NSAID-associated relative risk of MI was 1.61 (95% CI 1.27–2.04) in patients aged 50–59 years, 1.34 (95% CI 1.18–1.53) in those aged 60–74 years and 1.22 (95% CI 1.03–1.45) in those aged 75–84 years [17]. Similarly, Fosbol *et al.* observed much higher hazard ratios for the composite end-point of death and MI in the 30–50 year group vs the entire population studied [18]. These findings could be attributable to the phenomenon of 'depletion of susceptibles'. However, there might be other explanations.

We have recently studied the impact of NSAID use on MI and stroke in a cohort of ~320,000 Australian veterans (mean age 80 years). Perhaps surprisingly, neither selective COX-2 inhibitors nor ns-NSAIDs exerted any significant effect on these outcomes [19, 20]. For example, the odds ratio of MI associated with NSAID use at least once over the last 2 years was 1.00 (95% CI 0.96–1.04) for NSAIDs as a whole, 1.02 (95% CI 0.97–1.07) for ns-NSAIDs and 1.02 (95% CI 0.97–1.06) for selective COX-2 inhibitors [20]. Similar results were obtained with the individual ns-NSAIDs diclofenac and ibuprofen [20]. It might be worth noting that variables sometimes neglected, e.g. institutionalisation and renal failure, were considered as confounding factors [19, 20].

With advancing age come an increased number of co-morbidities, which increase *per se* atherothrombotic risk. For example, moderate–severe chronic kidney disease has recently emerged as a strong and independent predictor of cardiovascular morbidity and mortality in the older population [21]. Whilst institutionalised patients might have sub-optimal control of cardiovascular risk factors due to reduced contact with health care professionals, moderate–severe chronic kidney disease appears to be more prevalent in institutionalised vs non-institutionalised patients [22]. In our study, NSAID use was strongly associated both with renal failure ($P = 0.004$) and with institutionalisation ($P < 0.001$) [19]. Not considering such variables might affect the interpretation of studies on the real association between NSAID use and cardiovascular outcomes in the older population.

Why would older patients have a relatively lower NSAID-associated atherothrombotic risk compared to younger cohorts? There is overwhelming evidence that inflammation promotes the onset and progression of atherothrombosis [23]. It is also known that ageing is associated with a pro-inflammatory state, which might explain at least partly the increased incidence of atherothrombotic events in the older population [24]. We propose that NSAIDs might also exert protective cardiovascular effects by virtue of their anti-inflammatory activity. These effects, resulting in enhanced plaque

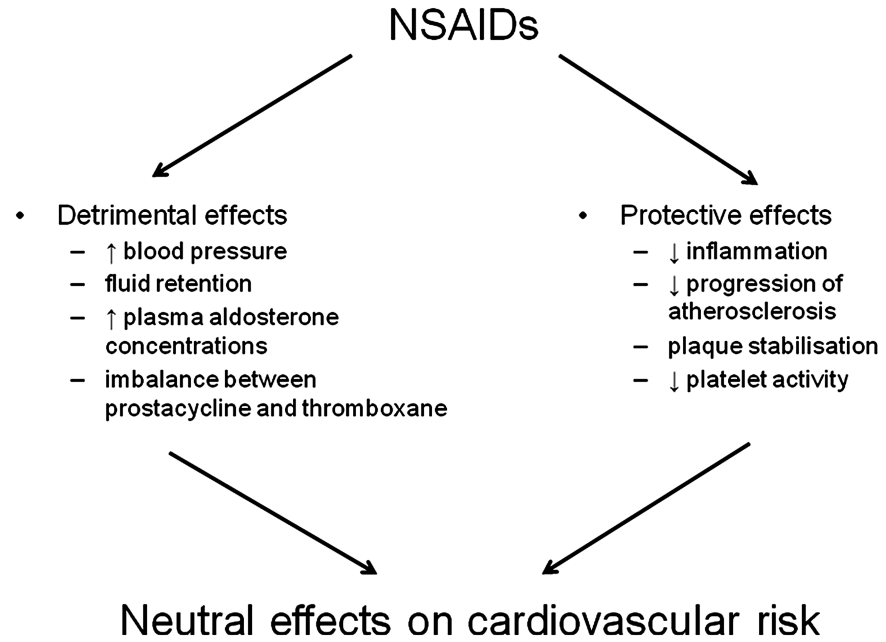

Figure 1. Proposed cardiovascular effects of non-steroidal anti-inflammatory drugs (NSAIDs) in the older population.

stabilisation as well as reduced platelet activity, might counterbalance the detrimental effects of these drugs on blood pressure and fluid retention previously discussed [25, 26]. This might result in an overall neutral effect on atherothrombotic risk (Figure 1) [23]. Clearly, more fundamental and clinical studies are warranted to corroborate this hypothesis.

There are other issues to be considered when interpreting the results of studies on NSAID use and atherothrombotic risk such as the observational and retrospective nature of some and the lack of pre-defined cardiovascular end-points of others. As observational studies generally rely on the information collected from prescription databases, it is not possible to confirm whether a prescribed NSAID is actually taken by the patient. Moreover, the over-the-counter availability of some NSAIDs is not captured by such databases.

So, where do we stand with the issue of cardiovascular safety of NSAIDs? It is our opinion that at present there is no strong evidence for a clinically relevant increase in atherothrombotic risk associated with NSAID use in older patients, particularly in people >80 years. This is not to say that such drugs cannot cause untoward effects, particularly when administered at high dose and in conjunction with other offending agents in patients with advanced cardiac and/or renal failure [27].

Further evidence is urgently needed to better characterise the atherothrombotic risk profile of NSAIDs, and their subclasses, in the older population. New, adequately powered, prospective studies should assess primary cardiovascular end-points, taking into account the multitude of confounding factors potentially able to affect the association between NSAID use and atherothrombotic risk. Whilst funding such studies is problematic as many NSAIDs are off patent a Scottish study currently under way might help to address some of these issues. The SCOT (Standard care vs Celecoxib Outcome Trial) study is a 3-year safety study designed to compare the cardiovascular and gastrointestinal safety of celecoxib vs traditional ns-NSAIDs in 16,000 patients aged ≥60 years with arthritis and without established cardiovascular disease [28]. The primary composite end-point is non-fatal MI, non-fatal stroke or cardiovascular death retrieved by record-linkage analysis of hospitalisations and deaths. Although there is no placebo arm, the results of the SCOT study should shed some lights on the impact of NSAID use on atherothrombotic risk specifically in older patients. It may not be enough, but it is a step in the right direction.

Conflicts of interest

None declared.

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Simplifying stroke risk stratification in atrial fibrillation patients: implications of the CHA_2DS_2–VASc risk stratification scores

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Atrial fibrillation (AF) is a major risk factor for stroke and thromboembolism but this risk is not homogeneous among patients with AF, being dependent upon associated risk factors such as advancing age, hypertension, congestive heart failure, prior stroke, diabetes mellitus and structural heart disease [1]. Current guidelines [2–4] recommend warfarin for those at high risk, aspirin for low risk and 'either aspirin or warfarin' for those at intermediate risk. Based on stroke risk factors, many risk stratification schemas have been developed in order to categorise a patient's risk of stroke and aid decisions regarding the most appropriate thromboprophylaxis.

Many of the stroke risk stratification schemes employ stroke risk factors that have been derived from non-warfarin arms of clinical trial cohorts. The Stroke Risk in AF Working Group compared 12 stroke risk stratification schemas [5], five of which were based on expert consensus and seven on event-rate analyses. The number of risk factors included in each schema varies between 4 and 8, with all schema including previous stroke/transient ischemic attack (TIA), and almost all included patient age, hypertension and diabetes mellitus [5]. Perhaps the most widely used of the published stroke risk stratification schemes is the $CHADS_2$ score (Congestive heart failure, Hypertension, Age >75, Diabetes mellitus and prior Stroke or transient ischaemic attack) [6], derived from the Atrial Fibrillation Investigators and SPAF risk schema and initially validated in a hospitalised AF cohort [1, 6, 7]. However, the problem with current stroke risk stratification schemas is that, when applied to the same cohort of patients, the absolute stroke rates by risk group and the percentage of patients categorised as low, intermediate or high risk would vary considerably depending upon which stroke risk scheme is employed [5, 8–10].

The majority of stroke risk schema have derived risk factors from non-anticoagulated patients in clinical trials, and as such, these risk factors may not be equally applicable to non-trial cohorts or anticoagulated patients. Indeed, a comparison of five stroke risk schema [1, 6, 7, 11, 12] in non-anticoagu-