

Association between use of non-steroidal anti-inflammatory drugs and risk of myocardial infarction in patients with spondyloarthritis and osteoarthritis

Non-steroidal anti-inflammatory drugs (NSAIDs) have anti-inflammatory, antipyretic and analgesic effects and are widely used clinically for the treatment of osteoarthritis (OA), rheumatoid arthritis (RA) and many other inflammatory diseases.¹ At present, NSAIDs are the first-line therapy for psoriatic arthritis and axial spondyloarthritis (SpA),²⁻⁴ but the use of NSAIDs may be related to the risk of myocardial infarction (MI).^{5,6} Recently, we read with great interest the paper entitled 'Risk of myocardial infarction with use of selected non-steroidal anti-inflammatory drugs in patients with spondyloarthritis and osteoarthritis' published online in 19 April 2018 in *Annals of the Rheumatic Diseases*. Dubreuil *et al* concluded that compared with remote use of any NSAIDs, the use of diclofenac in SpA was related to twofold to threefold risk of MI, but the use of naproxen did not increase the risk of MI in OA or SpA.⁷ Certainly, the findings of Dubreuil *et al* will be significant for clinicians, while there are still several questions that we would like to communicate with the authors.

First, the diagnostic criteria of MI are not clearly described in the study. According to the third universal definition of MI,⁸ we can diagnose the patient as MI if one of the conditions is met. (1) To detect a rise and/or fall of cardiac biomarker values (preferably cardiac troponin (cTn)) and at least one value above the 99th percentile upper reference limit (URL). (2) Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new left bundle-branch block, but death occurred before cardiac biomarkers were obtained or increased. (3) Percutaneous coronary intervention correlated MI: a rise of cTn values (>5×99th percentile URL) in patients with normal baseline values (≤99th percentile URL). (4) Stent thrombosis related to MI when detected by coronary angiography. Therefore, providing a uniform and accurate diagnostic criteria for MI will help us to know the selection criteria for patients.

Second, the definition of OA is not described in this article. At present, there is no consensus about the classification criteria of OA. American College of Rheumatology (ACR) classification criteria⁹ and the Kellgren and Lawrence (K-L) system¹⁰ are the most frequently used criteria. The ACR classification criteria are based on clinical manifestation (pain or stiffness in joint), laboratory and radiographic aspects of OA, while the K-L system identifies and grades OA depend on radiographs. However, there are subgroups of patients who have only radiographic but not symptomatic OA and vice versa owing to the heterogeneity of OA,¹¹ so it might be better to clarify the definition of OA in this report.

Third, the age span of patients in the study is too large (18–89 years old). The incidence of MI is different in different age groups. According to previous study, the risk of MI among older patients was greater and the size of this population was increasing.¹² Moreover, patients aged 65 years and older with MI are a heterogeneous group by age.¹³ The author does not seem to consider that the prevalence of MI in patients of different ages before taking medicine is not the same.

Fourth, the information about the use of NSAIDs was not shown in detail in this paper. NSAIDs play an important role in the remission treatment of OA so that a large number of

Table 1 International osteoarthritis diagnosis and treatment guidelines

Guidelines	Recommended usage
AAOS	Patients with knee OA and high risk of gastrointestinal tract: topical NSAIDs and non-selective oral NSAIDs combined with gastrointestinal protection agents.
AGS	Patients with local non-neuronal persistent pain: topical NSAIDs.
EULAR	Patients with hand osteoarthritis: topical medication is better than systemic treatment. Patients with knee osteoarthritis: topical NSAIDs are effective and safe.
NICE	Patients with knee or hand OA: to add topical NSAIDs based on core therapy to relieve pain. Topical NSAIDs should be used prior to oral NSAIDs, cyclo-oxygenase-2 inhibitors or opioids.
OARSI	Patients with knee OA: topical NSAIDs are effective adjuvant therapy and alternative treatment for oral analgesic/anti-inflammatory treatment.

AAOS, American Academy of Orthopaedic Surgeons; AGS, American Geriatrics Society; EULAR, The European League Against Rheumatism; NICE, The National Institute for Health and Care Excellence; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International.

guidelines have provided relevant therapeutic opinions on the treatment of OA by NSAIDs and recommended topical NSAIDs as first-line drugs for OA (table 1).¹⁴⁻¹⁶ The authors have pointed out that some patients may take NSAIDs inconsistently, only on an as-needed basis for pain. We considered whether the participants can be divided into different subgroups according to their drug use frequency or dosage in order to avoid this limitation. Therefore, the detailed usage of NSAIDs may be of great importance.

Last but not least, many drugs are used for the treatment of OA at present including glucosamine drugs (such as chondroitin sulfate (CS)), corticosteroid drugs (such as glucocorticoids (GCs)) and so on. CS can significantly reduce serum total cholesterol, low-density lipoprotein and triglyceride levels, which may be associated with the risk of MI.¹⁷ Besides, GCs also may influence the risk of MI,¹⁸ which can be mediated by its deleterious effects on hypertension, hyperlipaemia, glucose tolerance, accelerated atherosclerosis and coagulation disturbances.¹⁹⁻²¹ How does the author rule out the effect of other osteoarthritis medications which the patients may take on MI?

We utterly respect the great contributions of the authors. Meanwhile, we would be very interested in the authors' response regarding the above issues.

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Contributors All authors were involved in the study conception, manuscript drafting and revising and final approval of the submitted version.

Funding This work was supported by the Fundamental Research Funds for the Central Universities of Central South University (Grant No. 2018zts930), the Central South University Sports Medicine Scholarship and the National Natural Science Foundation of China (Grant Nos. 81000821 and 81672176).

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

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To cite Zhou J, Xiao Y, Li C, *et al.* *Ann Rheum Dis* 2019;**78**:e78.

Received 11 May 2018

Accepted 12 May 2018

Published Online First 25 May 2018



► <http://dx.doi.org/10.1136/annrheumdis-2018-213771>

Ann Rheum Dis 2019;**78**:e78. doi:10.1136/annrheumdis-2018-213752

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