Do non-steroidal anti-inflammatory drugs increase or decrease cardiovascular risk in patients with rheumatoid arthritis?

Sirs,

Large epidemiological studies have shown that non-steroidal anti-inflammatory drug (NSAID) use associates with increased cardiovascular disease (CVD) risk in the general population (1, 2). Several clinical trials have also shown a higher risk of CVD events in patients treated with selective cyclooxygenase-2 inhibitors (coxibs) compared to placebo (3). On the other hand, it is accepted that rheumatoid arthritis (RA) *per se* associates with increased CVD risk, to a degree comparable to that observed in diabetes mellitus, as suggested by similar levels of preclinical atheromatosis (4), and adverse cardiovascular outcomes (5). This is attributed to the combined effects of chronic systemic inflammation and the accumulation of traditional risk factors, such as hypertension (6) and dyslipidaemia (7), modified by treatment modalities. Therefore, rheumatologists are currently advised to prescribe NSAIDs with caution in RA patients (8). Surprisingly, however, past and recent epidemiological evidence suggests differently.

In 2008, Goodson *et al*. utilised data from the UK Norfolk Arthritis Register to investigate possible associations between NSAID use and cardiovascular mortality in patients with inflammatory polyarthritis (9). The study included 923 patients with new onset inflammatory polyarthritis who were followed-up for a median of 10.7 years. Of the 203 deaths recorded over this time period, 85 were attributed to CVD. Interestingly, multivariate analysis indicated that baseline and ever-use of NSAIDs during follow-up was associated with reduced risk for CVD mortality (adjusted odds ratio 0.54, 95% CI 0.34–0.86 and adjusted hazard ratio 0.38, 95% CI 0.23–0.66, respectively). Increased duration of NSAID exposure did not correlate with lower CVD mortality in this study. The authors suggested their findings reflected either the effect of multiple unmeasured confounding factors or a true cardioprotective effect of NSAIDs in patients with chronic inflammation, which could be mediated through pharmacological modification of the eicosanoid pathway; they also clearly acknowledged that inaccurate assignment of NSAID exposure was also possible, as was doctor-channelling of NSAIDs away from frail patients with CVD.

A second study from Spain (10), reporting on the usage pattern of NSAIDs in a group of 789 RA patients, observed a decline in the percentage of patients taking NSAIDs from 78% in year 2000 to 66% in year 2004 and a parallel increase in the consumption of anti-ulcer agents, regardless of the wider use of coxibs. Here again, the investigators found no association between NSAID intake and cardiovascular events in patients with RA, although it should be kept in mind that patients receiving these drugs were both younger and had less cardiovascular complications.

More recently, Lindhardsen *et al*. (11) conducted a large scale longitudinal cohort study using data from the Danish nationwide registry to identify the risk of major CVD associated with the use of NSAIDs in patients with RA. The study involved 17,320 RA patients matched for age and sex with 69,280 controls at a 4:1 ratio and followed up for a median of 4.9 years. The cardiovascular risk associated with overall NSAID use was small and significantly lower in RA patients compared to controls [HR 1.22 (95% CI 1.09–1.37) *vs*. 1.51 (1.36–1.66), $p<0.01$]. This held true for the individual NSAIDs investigated, with the exception of rofecoxib and diclofenac, both of which were found to confer increased cardiovascular risk to RA patients. An increased rofecoxib-associated cardiovascular (myocardial infarction) risk in RA patients was also shown in a Cochrane database metaanalysis of two randomised controlled trials that compared rofecoxib to placebo and naproxen, respectively (12).

The safety of NSAIDs is of primary concern for the rheumatologist, given that RA remains a chronic condition often necessitating long-term analgesia. Patients with RA are prone to comorbidities, including their high risk for CVD, and receive several other drugs, including synthetic or biologic DMARDs, that may interfere with the use of NSAIDs. A recently published Cochrane systematic review addressed the safety of using NSAIDs concurrently with methotrexate in patients with inflammatory arthritis and concluded that the combination seems to be safe, provided appropriate monitoring is performed (13). As far as treatment of RA patients with cardiovascular comorbidities is concerned, no specific evidence exists in the literature. Current guidelines recommend NSAIDs should be used with caution in this patient population, while stressing the need for additional attention in RA patients with cardiovascular risk factors or established CVD (14). It would be premature to suggest that this latter recommendation be reappraised in view of the recent findings that fail to associate NSAIDs with a higher CVD risk in patients with RA. Clearly, more questions than answers seem to have emerged regarding the benefits and risks of NSAIDs in the treatment of RA, emphasising the necessity for further research in this field.

To conclude, in contrast to what has been described in the general population, there is evidence to suggest that NSAIDs/Coxibs do not increase the cardiovascular risk in patients with RA, with the exception of rofecoxib. In comparison to previous years, use of NSAIDs has significantly declined in the RA population (10). This could be explained not only by the better disease control achieved in recent years with newer strategies and medications, but also by the reluctance to prescribe NSAIDs to RA patients, due to their higher CVD risk (5). Is it time to review this approach? No doubt, this counterintuitive effect of NSAIDs on CVD risk of patients with chronic inflammation has not been adequately addressed yet and there is no satisfactory explanation or potential underlying pathophysiological mechanisms. The use of other medications, particularly methotrexate and TNF-α inhibitors in RA has been linked with better CVD outcomes; this is thought to relate to endothelial dysfunction, oxidative stress, and leukocyte activation and vascular migration (15). It is possible that through anti-inflammatory effects on an overactive eicosanoid pathway, improved physical function and activity and other mechanisms (*e.g*. antiplatelet effects), NSAIDs may contribute to a modest reduction of the increased CVD risk in patients with high grade inflammation, such as those with RA, although they confer a higher CVD risk in the general population. This needs to be assessed in studies designed specifically for the purpose.

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References

1. HIPPISLEY-COX J, COUPLAND C: Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BMJ* 2005; 330: 1366.
2. CHAN AT, MANSON JE, ALBERT CM *et al*.: Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. *Circulation* 2006; 113: 1578-87.
3. BRESALIER RS, SANDLER RS, QUAN H *et al*.: Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005; 352: 1092-102.
4. STAMATELOPOULOS KS, KITAS GD, PAPAMICHAEL CM *et al*.: Atherosclerosis in rheumatoid arthritis versus diabetes: a comparative study. *Arterioscler Thromb Vasc Biol* 2009; 29: 1702-8.
5. PETERS MJL, VAN HALM VP, VOSKUYL AE *et al*.: Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease? A prospective study. *Arthritis Rheum* 2009; 61: 1571-9.
6. PROTOGEROU AD, PANAGIOTAKOS DB, ZAMPELI E *et al*.: Arterial hypertension assessed "out-of-office" in a contemporary cohort of rheumatoid arthritis patients free of cardiovascular disease is characterized by high prevalence, low awareness, poor control and increased vascular damage-associated "white coat" phenomenon. *Arthritis Res Ther* 2013; 15: R142.
7. ROBERTSON J, PETERS MJ, MCINNES IB, SATTAR N: Changes in lipid levels with inflammation and therapy in RA: a maturing paradigm. *Nat Rev Rheumatol* 2013; 9: 513-23.
8. PETERS MJ, SYMMONS DP, MCCAREY D *et al*.: EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010; 69: 325-31.
9. GOODSON NJ, BROOKHART AM, SYMMONS DP, SILMAN AJ, SOLOMON DH: Non-steroidal anti-inflammatory drug use does not appear to be associated with increased cardiovascular mortality in patients with inflammatory polyarthritis: results from a primary care based inception cohort of patients. *Ann Rheum Dis* 2009; 68: 367-72.
10. FERRAZ-AMARO I, MACHIN S, CARMONA L, GONZALEZ-ALVARO I, DIAZ-GONZALEZ F: Pattern of use and safety of non-steroidal anti-inflammatory drugs in rheumatoid arthritis patients. A prospective analysis from clinical practice. *Reumatol Clin* 2009; 5: 252-8.
11. LINDHARDSEN J, GISLASON GH, JACOBSEN S *et al*.: Non-steroidal anti-inflammatory drugs and risk of cardiovascular disease in patients with rheumatoid arthritis: a nationwide cohort study. *Ann Rheum Dis* 2013 Jun 8 [Epub ahead of print].
12. GARNER SE, FIDAN D, FRANKISH RR *et al*.: Rofecoxib for osteoarthritis. *Cochrane Database Syst Rev* 2005; 25: CD003685
13. COLEBATCH AN, MARKS JL, VAN DER HEIJDE DM, EDWARDS CJ: Safety of non-steroidal anti-inflammatory drugs and/or paracetamol in people receiving methotrexate for inflammatory arthritis: a Cochrane systematic review. *J Rheumatol Suppl*. 2012; 90: 62-73.
14. MARKS JL, VAN DER HEIJDE DM, COLEBATCH AN, BUCHBINDER R, EDWARDS CJ: Pain pharmacotherapy in patients with inflammatory arthritis and concurrent cardiovascular or renal disease: a Cochrane systematic review. *J Rheumatol Suppl*. 2012; 90: 81-4.
15. VAN BREUKELEN VAN-DER STOEP DF, KLOP B, VAN ZEBEN D, HAZES JMW, CABEZAS MC: Cardiovascular risk in rheumatoid arthritis: How to lower the risk? *Atherosclerosis* 2013; 231: 163-72.