

Respiratory tract infections, NSAIDs and acute myocardial infarction: is understanding interaction between risk factors the key to personalising prevention?

Editorial on: Acute Respiratory Infection and Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) on Risk of Acute Myocardial Infarction: A Nationwide Case-Crossover Study

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Respiratory tract infections, NSAIDs and acute myocardial infarction: is understanding interaction between risk factors the key to personalising prevention?

Acute respiratory infections are increasingly recognised as triggers of acute cardiovascular events¹. Observational studies using large electronic healthcare databases have shown an approximately two to five-fold transient increase in the risk of acute myocardial infarction, stroke and other thrombotic events such as deep venous thrombosis after acute respiratory infection (ARI)²⁻⁴. Although the coding of ARI in these studies is frequently based on clinical, rather than microbiological criteria, evidence that some specific infections trigger vascular events comes indirectly from vaccine trials. Meta-analysis of randomized controlled trials of influenza vaccine in patients with existing cardiovascular disease showed a reduced risk of major adverse cardiovascular outcomes at one year⁵. For pneumococcal vaccine, meta-analyses of observational studies suggest a small protective effect against cardiovascular events in people aged >65 years^{6,7}, but trial evidence is lacking. In people who develop ARI, there remain unanswered questions about how different ARI treatments might modulate vascular risk.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to reduce pain, fever and inflammation associated with acute infections as well as symptoms of chronic musculoskeletal and other inflammatory conditions. While the risk of gastrointestinal haemorrhage associated with these drugs has long been recognised, in recent years attention has focussed on adverse cardiovascular effects. Initially, concerns about increased risk of acute cardiovascular events arose when the new class selective COX II inhibitors, with lower risks of gastrointestinal bleeding, were introduced⁸⁻¹⁰. However, a growing body of evidence has now established that risks of vascular events are increased by traditional non-selective NSAIDs, notably diclofenac¹¹. The US Food and Drug Administration (FDA) recommended that the selective COX-2 inhibitors rofecoxib and valdecoxib be removed from the market in 2004 and 2005¹², and recently issued a black box warning that NSAIDs can cause heart

attacks¹³. In the UK, NICE recommends cautious prescription of NSAIDs based on assessing an individual's risk factors such as history of cardiovascular and gastrointestinal illness, using the lowest effective dose for the shortest duration necessary to control symptoms and opting for naproxen or low-dose ibuprofen for their more favourable thrombotic cardiovascular safety profile¹⁴. Nevertheless, some NSAIDs such as ibuprofen are widely available over the counter, and in the US, NSAIDs are reportedly taken at least once per week by 50% of people over the age of 65 years¹⁵.

In this issue of the *Journal of Infectious Diseases*, Wen and colleagues provide evidence for a dual effect of acute respiratory infection and NSAIDs on myocardial infarction risk in a case crossover study of 9,793 patients from Taiwan¹⁶. Using comprehensive claims data over a 7-year period from the National Health Research Insurance Database, which covers ~99% of the population, they showed that acute respiratory infections treated with NSAIDs had a stronger association with AMI than ARIs not treated with NSAIDs or NSAID treatment alone. A series of sensitivity analyses strengthened the validity of the results and reduced the risk of bias due to inappropriate control time window selection. This study represents an important step towards understanding the interaction between transient, non-traditional AMI risk factors.

The effects of NSAIDs are largely mediated through inhibition of cyclooxygenase (COX), which prevents the conversion of arachidonic acid into its biologically active derivatives¹⁷ and thus profoundly alters prostaglandin homeostasis¹⁵. Different NSAIDs have different activity profiles against the COX-1 and COX-2 isoforms. It is likely that the cardiovascular risk associated with non-selective and COX-2 inhibitors results from various mechanisms including altering the balance of thromboxane and prostacyclin leading to increased platelet aggregation and vasoconstriction, as well as fluid and sodium retention¹⁷. Acute respiratory infections induce a range of haemodynamic, pro-coagulant and pro-inflammatory effects that contribute to the risk of cardiac complications¹⁸. It is certainly plausible that interaction between these deleterious mechanisms may in part explain the

greater risk of AMI seen in ARIs treated with NSAIDs compared to untreated ARIs or NSAID use alone.

The case crossover design has the major advantage of eliminating the effect of fixed between-person confounders as each individual serves as their own control over time.¹⁹ Specifically, in the present study the effect of exposure to ARI and NSAIDs on AMI was compared within a 'case' period and a 'control' period for each patient. The authors also adjusted for time-varying confounding due to discordant concomitant medication use in their multivariable analysis. One potential limitation of the chosen design, however, which was noted by the authors in the discussion, is the risk of confounding by indication²⁰. This is the situation in which the clinical indication for prescribing drugs such as NSAIDs (e.g. severity of ARI, fever and pain), also affects the risk of experiencing the outcome (here, AMI). Although a sensitivity analysis to investigate the effect of NSAID use during different types of ARI showed that AMI risk was higher with NSAID use for influenza-related ARIs, other ARIs and no ARI, the limited data on illness severity available in health insurance claims databases made this impossible to evaluate further. The largest effect size was seen for parenteral NSAID use in the context of ARI, which again might suggest a more severe underlying illness. Both improving data availability on infection severity and considering the use of methods such as propensity scores to reduce bias²¹ will be important for future research in this area.

An important unanswered question that will inform clinical practice relates to the differential effects of specific NSAIDs used for symptomatic ARI relief on cardiovascular risk. In a supplementary analysis, Wen and colleagues stratified by type of NSAID to investigate separately the effects of diclofenac, mefenamic acid, the selective COX-2 inhibitors used in Taiwan (celecoxib, rofecoxib and etorcoxib) and using multiple non-parenteral NSAIDs during an ARI. No data were available on the effects of naproxen or ibuprofen – the two NSAIDs currently considered to have the most favourable thrombotic cardiovascular safety profiles¹⁴. Although minor differences in effect size were seen

between different non-parenteral NSAIDs, the overlapping confidence intervals and relatively small sample size in each stratum make these results difficult to interpret. While it is mechanistically plausible that, in the context of ARI as in other settings, selective COX-2 inhibitors may induce greater cardiac risk than some non-selective agents, this is not yet evident from available data.

In moving from considering ARI symptomatic treatments to designing targeted prevention strategies, it will be necessary to understand the relative contribution that different respiratory organisms make to vascular risk. In the present study, ARI episodes were based on codes for out-patient visits with clinically-diagnosed infection rather than laboratory-confirmed organisms, but authors note that previously a good correlation (0.71) has been shown between the codes used and the presence of respiratory pathogens. Other approaches that have been used to infer the causative organism from medical records data include using timing of an infection relative to specific organism circulation in the community, the influenza vaccination status of the patient and codes used to classify an illness²², but this is not an exact science. Basing studies using laboratory indices of infection will help to inform the use of targeted vaccinations to reduce vascular risk. While influenza and pneumococcal vaccines are currently recommended for some groups at high risk of cardiovascular complications including the over 65s and people with existing heart disease²³, better understanding the organisms involved will improve mechanistic understanding, help to inform clinical trials and design of preventive and therapeutic interventions.

The report by Wen and colleagues contributes to the evidence for dual effects of AMI triggers and highlights the need for cautious use of NSAIDs in the context of ARI; clinicians should consider interactions with both medical conditions and existing medications when prescribing NSAIDs for symptomatic ARI relief. Where NSAID use is deemed necessary, those judged safer from a CVD perspective, notably ibuprofen or naproxen, should be used. The role of antiviral agents such as neuraminidase inhibitors was not assessed in the present study, but these should be considered as a

treatment option, especially for severely ill patients admitted to hospital with an ARI likely to be due to influenza¹³. In future, better characterisation of the interaction between infections, NSAIDs and other genetic, socio-demographic and clinical CVD risk factors and therefore the populations at risk will help to inform stratified ARI management. Furthermore, studies of interventions such as influenza and pneumococcal vaccinations to reduce the risk of ARIs triggering cardiac events may provide findings that influence routine care in the near future.

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