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Respiratory Tract Infections, Nonsteroidal Anti-inflammatory Drugs and Acute Myocardial Infarction: Is Understanding Interaction Between Risk Factors the Key to Personalizing Prevention?

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(See the major article by Wen et al on pages 503-9.)

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Acute respiratory infections (ARIs) are increasingly recognized as triggers of acute cardiovascular events [1]. Observational studies using large electronic healthcare databases have shown an approximately 2–5-fold transient increase in the risk of acute myocardial infarction (AMI), stroke, and other thrombotic events such as deep venous thrombosis after ARI [2–4]. Although the definition 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. One 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 1 year [5]. For pneumococcal vaccine, meta-analyses of observational studies suggest a small protective effect against cardiovascular events in people aged >65 years [6, 7], but

controlled trial evidence is lacking. In people who develop ARI, unanswered questions about how different ARI treatments might modulate vascular risk remain.

Nonsteroidal 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. Although the risk of gastrointestinal hemorrhage associated with these drugs has long been recognized, 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 cyclooxygenase 2 (COX-2) inhibitors, with lower risks of gastrointestinal bleeding, were introduced [8–10]. However, a growing body of evidence has now established that risks of vascular events are increased by traditional nonselective NSAIDs, notably diclofenac [11]. The US Food and Drug Administration recommended that the selective COX-2 inhibitors rofecoxib and valdecoxib be removed from the market in 2004 and 2005 [12] and recently issued a black-box warning that NSAIDs can cause heart attacks [13]. In the United Kingdom, the National Institute for Health and Care Excellence 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 favorable thrombotic cardiovascular safety profile [14]. Nevertheless, some NSAIDs such as ibuprofen are widely available over the counter, and in the United States, NSAIDs are reportedly taken at least once per week by 50% of people aged >65 years [15].

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 9793 patients from Taiwan [16]. Using comprehensive claims data over a 7-year period from the National Health Research Insurance Database, which covers approximately 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 toward understanding the interaction between transient, nontraditional AMI risk factors.

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The effects of NSAIDs are largely mediated through inhibition of COX, which prevents the conversion of arachidonic acid into its biologically active derivatives [17] and, thus, profoundly alters prostaglandin homeostasis [15]. Different NSAIDs have different activity profiles against the COX-1 and COX-2 isoforms. It is likely that the cardiovascular risk associated with nonselective 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 retention [17]. Acute respiratory infections induce a range of hemodynamic, procoagulant, and proinflammatory effects that contribute to the risk of cardiac complications [18]. It is certainly plausible that interaction between these deleterious mechanisms may, in part, explain the greater risk of AMI seen in individuals with ARIs treated with NSAIDs compared with those with untreated ARIs or those with 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 study by Wen and colleagues 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 indication [20]. This is the situation in which the clinical indication for prescribing drugs such as NSAIDs (eg, 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 compared to other ARIs and no ARI, the limited data on illness severity available in health insurance claims databases makes 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 bias [21] 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 use of multiple nonparenteral NSAIDs during an ARI. No data were available on the effects of naproxen or ibuprofen, the two NSAIDs currently considered to have the most favorable thrombotic cardiovascular safety profiles [14]. Although minor differences in effect size were seen among different nonparenteral NSAIDs, the overlapping confidence intervals and relatively small sample sizes in each stratum make these results difficult to interpret. Although 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 nonselective 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 contributions that different respiratory organisms make to vascular risk. In the study by Wen and colleagues, ARI episodes were based on

codes for outpatient visits with clinically diagnosed infection, rather than laboratory-confirmed organisms, but the authors note that a good correlation (0.71) has previously 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 illness [22], but this is not an exact science. Basing studies on laboratory indices of infection will help to inform the use of targeted vaccinations to reduce vascular risk. Whereas influenza and pneumococcal vaccines are currently recommended for some groups at high risk of cardiovascular complications, including those aged >65 years and people with existing heart disease [23], better understanding the organisms involved will improve mechanistic understanding and 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 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 study by Wen and colleagues, but these should be considered as a treatment option, especially for severely ill patients admitted to hospital with an ARI likely due to influenza [13]. In the future, better characterization of the interactions between infections, NSAIDs, and other genetic, sociodemographic, and clinical cardiovascular disease risk factors 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.

Notes

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