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EDITORIALS

NSAIDs and atrial fibrillation

The risk is unproved, but NSAIDs should be used with caution in high risk patients anyway

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More than two million Americans and more than four million people in the European Union have paroxysmal or persistent atrial fibrillation.[1] Its prevalence increases dramatically with advancing age, rising from 0.1% in adults younger than 55 years to 9.0% in those aged 80 or more.[2] Atrial fibrillation is associated with an increased long term risk of stroke, heart failure, and death. The healthcare costs related to this condition are substantial, largely as a result of hospital admissions, consultations, diagnostic and therapeutic procedures, and drug treatments. Many patients with atrial fibrillation need lifelong treatment with oral anticoagulants for stroke prevention, which requires careful dosing and laboratory monitoring; safety concerns about the risk of bleeding persist for these patients even under the most ideal systems of care. For these reasons, any opportunity to reduce the risk of atrial fibrillation, particularly in older adults, would be welcome. In the linked case-control study (doi:10.1136/bmj.d3450), Schmidt and colleagues describe an association between the use of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclo-oxygenase-2 (COX 2) inhibitors and atrial fibrillation or flutter.[3]

In 2008, an expert panel convened by the National Heart, Lung, and Blood Institute highlighted that although treatments for atrial fibrillation have been studied extensively, prevention has received relatively little attention.[4] Modifiable risk factors include hypertension, diabetes, obesity, and smoking.[5] Predisposing clinical conditions include heart failure, myocardial infarction, valvular heart disease, thyroid disease, and sleep disordered breathing. These risk factors and predisposing conditions probably interact with various non-modifiable risk factors including age, sex, race, and genetic factors.

The identification of drug related precipitants of atrial fibrillation adds an interesting new dimension to its prevention.[6] Using administrative data for a Danish population from 1999 to 2008, Schmidt and colleagues examined the risk of atrial fibrillation or flutter associated with the use of non-selective NSAIDs or selective COX 2 inhibitors.[3] After adjustment for age, sex, and selected risk factors for atrial fibrillation, they found a significant increase in the risk of atrial fibrillation or flutter with current drug use compared with no use (non-selective NSAIDs: adjusted odds ratio 1.17, 95% confidence interval 1.10 to 1.24; COX 2 inhibitors: 1.27, 1.20 to 1.34). Risks were greatest for new users compared with non-users (non-selective NSAIDs: 1.46, 1.33 to 1.62; COX 2 inhibitors: 1.71, 1.56 to 1.88), but much less strong for long term users compared with non-users (non-selective NSAIDs: 1.05, 0.98 to 1.13; COX 2 inhibitors: 1.10, 1.03 to 1.18).

An association between use of NSAIDs and atrial fibrillation has important clinical and public health implications because of the high prevalence of use of these agents, particularly among older adults, and the increasing prevalence of atrial fibrillation with advancing age. The validity of the study's findings must be carefully considered, however, because case-control studies are susceptible to unmeasured confounders, potentially limiting the inferences that can be drawn from the results.[7] Adjusting for covariates modestly reduced the strength of the associations between the use of non-selective NSAIDs and COX 2 inhibitors and atrial fibrillation or flutter. However, Schmidt and colleagues lacked data on several important clinical measures, such as body mass index. Obesity is strongly associated with osteoarthritis,[8 9] one of the most common indications for treatment with NSAIDs. This unmeasured confounding variable could have affected the study's findings, because obesity is an established risk factor for atrial fibrillation. Schmidt and colleagues' efforts to estimate the effects of a hypothetical confounder only partially allay these concerns about unmeasured confounding.

The current study is not the first case-control study to report an association between the use of NSAIDs and atrial fibrillation. A study that used data from the United Kingdom General Practice Research Database found that current use of NSAIDs was associated with an increased risk of atrial fibrillation, yet the results of that study differed from the current findings in that risk was greatest for long term users rather than for new users.[10] In both studies, the dose-response relation was not consistent, which makes the association even more tenuous.[7]

The association between NSAIDs and atrial fibrillation does not imply a cause and effect relation. One proposed explanation for the association is: "the existence of an underlying inflammatory condition, increasing the risk of AF [atrial

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fibrillation] on the one hand and prompting the use of NSAIDs on the other."[10] Perhaps a more likely scenario is that these agents trigger or exacerbate clinical conditions, such as heart failure and hypertension, that lie along the causal pathway of atrial fibrillation.

What should clinicians do in practice in the light of current evidence? With uncertainty regarding a plausible biological mechanism, the susceptibility of case-control studies to unmeasured confounders, and inconsistent results in the two studies performed to date, a cautious approach seems warranted in applying the study's results to the care of patients. However, NSAIDS (non-selective NSAIDs and COX 2 inhibitors) should continue to be used very cautiously in older patients with a history of hypertension or heart failure, who are already at high risk for adverse effects of these drugs, regardless of whether an association between NSAIDs and atrial fibrillation actually exists.

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