## Obesity and the Risk of New-Onset Atrial Fibrillation

**To the Editor:** The study by Dr Wang and colleagues[1] provided evidence for an association between obesity and development of atrial fibrillation (AF). The authors proposed several underlying mechanisms but did not mention the potential role of inflammation in this setting. Accumulating evidence suggests that inflammation may have a significant impact on atrial remodeling, which favors perpetuation of AF.[2] Even though it is not yet clear whether inflammation represents a cause or a consequence of AF, it has been recently demonstrated that elevated inflammatory indexes such as C-reactive protein indicate an increased risk for future development of AF.[2,3] On the other hand, obesity has been clearly correlated with inflammation,[4] whereas weight loss significantly reduces the levels of inflammatory indexes.[5] It is therefore reasonable to assume that obesity-associated inflammation might contribute to the atrial remodeling. Whether this mechanism has a clinical impact on AF remains to be elucidated.

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**4.** Saito M, Ishimitsu T, Minami J, Ono H, Ohrui M, Matsuoka H. Relations of plasma high-sensitivity C-reactive protein to traditional cardiovascular risk factors. *Atherosclerosis*. 2003;167:73-79.
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**To the Editor:** In the study by Dr Wang and colleagues,[1] the Figure lists the underlying data for the Kaplan-Meier survival curves for the study. Presumably the total number of persons at risk in year zero should equal the total number of persons who survived to year 16 plus those who developed AF and those died in the follow-up period. This calculation works for the men. However, for the women, 2898 started the study while 2899 finished, died without developing AF, or developed AF (2093 + 572 + 234). Although this is not likely to affect the overall results, I am curious about this apparent discrepancy.

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**1.** Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. *JAMA*. 2004;292:2471-2477.

**To the Editor:** Dr Wang and colleagues[1] conclude that obesity is an important risk factor for AF and that this excess risk appears to be mediated by left atrial enlargement. We are concerned about 3 potential limitations of this study.

First, AF was diagnosed by electrocardiograms obtained either from hospital or physician charts or from routine Framingham clinical examinations. However, obese participants were approximately 2 to 3 times more likely to be receiving antihypertensive medications and approximately 2 to 5 times more likely to have diabetes than were normal-weight participants. As a result, obese participants are likely to have had more hospital and physician visits—and hence more chances of having their AF diagnosed. This is especially relevant to new-onset AF, in which spontaneous conversion to sinus rhythm occurs in almost two thirds of patients[2,3] and in which up to 90% of episodes are not even recognized by the patients.[4] The authors could avoid this problem by measuring AF solely from routine Framingham clinical examinations. Any misclassification would then be nondifferential, leading to a bias toward the null and a conservative estimate of association.

Second, the authors did not adjust for confounding by presence of pulmonary disease or hyperthyroidism. Finally, the data presented do not clearly delineate a temporal pattern, in the absence of which left atrial enlargement could be either a cause or a consequence of AF.

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**Letters Section Editor:** Robert M. Golub, MD, Senior Editor.

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**In Reply:** We agree with Drs Korantzopoulos and Kolettis that inflammation is another potentially important mechanism linking obesity and AF. Cross-sectional studies[1,2] have shown an association between C-reactive protein levels and AF, and a longitudinal study demonstrated that C-reactive protein levels predicted the development of AF over a mean follow-up of 7 years in the Cardiovascular Health Study cohort.[3] Obese individuals may have elevated C-reactive protein levels.[4] Thus, it is plausible that systemic inflammation contributes to the increased risk of AF observed in obese individuals. Because C-reactive protein levels were not routinely measured at our baseline examinations, we were unable to investigate this interesting hypothesis.

Regarding Dr Parish's question, the person-level data showed that 1 woman had AF a week before year 16. For the numbers at risk listed below the Kaplan-Meier figure, we collapsed the data by month; hence, that person is included in the year 16 column. At exactly year 16, only 2092 women were alive and free of AF. The unit of time in the Cox proportional hazards analyses was days, which allowed this participant to be included in the analyses because her AF occurred prior to year 16.

Drs Bajaj and Hillson raise the possibility that the association between obesity and incident AF was overestimated because obese individuals had more frequent hospital and physician visits (ie, ascertainment bias). To address this concern, we repeated the multivariable regression analyses restricted to AF diagnosed on electrocardiograms at the routine Framingham Heart Study examinations (67 events in men and 59 events in women). As in the article, analyses were adjusted for clinical risk factors and interim myocardial infarction or heart failure. The association between body mass index (BMI) and incident AF remained significant, with no attenuation in the adjusted hazard ratios in men (1.07 per 1-unit increment in BMI; 95% confidence interval [CI], 1.01-1.14; $P=.02$) or women (1.09; 95% CI, 1.04-1.15; $P<.001$). Obese individuals had a 2-fold risk of incident AF compared with individuals with normal BMI (adjusted hazard ratios: men, 2.02; 95% CI, 1.08-3.78; $P=.03$; women, 2.06; 95% CI, 1.04-4.05; $P=.04$).

We were unable to adjust for pulmonary disease or hyperthyroidism because these diagnoses were not ascertained in a standardized manner at the baseline examinations. A prior study from the Framingham cohort did not find an association between the results of pulmonary function testing and the risk of AF in ambulatory individuals.[5] Because hyperthyroidism is not associated with weight gain, we do not believe that failure to adjust for hyperthyroidism caused a bias away from the null.

We assume that left atrial enlargement preceded AF because none of the participants had a history of AF at the baseline examination. Nonetheless, we acknowledge the possibility that some participants may have had asymptomatic episodes of paroxysmal AF that were not identified by a physician or picked up on the routine Framingham Heart Study electrocardiograms.

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## Arthritis Medications and Cardiovascular Events

**To the Editor:** The Editorial by Dr Topol on the cardiovascular effects of coxibs[1] provides new evidence of the ongoing state of confusion involving patients, physicians, and health authorities. The available scientific data, far from clarifying the matter, add to the confusion. An example is the premature cessation of the Alzheimer Disease Anti-inflammatory Prevention Trial (ADAPT) due to an excess of cardiovascular events in the patients treated with naproxen, a nonselective nonsteroidal anti-inflammatory drug (NSAID) previously associated with a reduction in the risk of myocardial infarction.[2]

Hasty judgment should be avoided before jumping to the conclusion that the cardiovascular events must be a class effect. In the past, drugs have been withdrawn from the market due to adverse reactions not shared by other compounds of the same pharmacological class. For example, 2 histamine 2 receptor antagonists, oxmetidine[3] and niperoti-