Prevention of atrial fibrillation: another good reason to recommend statins to women?

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The global burden of atrial fibrillation (AF) is large and growing. AF already affects roughly 6.7 million people in the USA and Europe, accounting for one-third of admissions to hospital for cardiac arrhythmia, and these figures are expected to increase progressively in coming years. While the principal pathogenetic features of AF include automatic ectopic foci in the thoracic veins and multiple wavelet generation within the left atrium, recent studies suggest that inflammation is also associated with development of AF. This concept has led to a growing interest in the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, as potential therapeutic agents for AF due to their potential anti-inflammatory effects. Other potential antifibrillatory effects of statin treatment have been proposed, including antioxidant effects, improvement in endothelial function, reduction of neuro-hormonal activation and beneficial effects on atrial cellular and electrophysiological remodelling. However, the clinical efficacy of statin treatment for prevention of AF has not been well established, and data examining the impact of statin treatment on AF in women have been especially limited.

In this issue of Heart, Pellegrini et al used the cohort of the Heart and Estrogen/Progestin Replacement Study (HERS) to investigate the effect of statin treatment on prevalence and incidence of AF in 2673 postmenopausal women with stable coronary artery disease (see article on page 704). Cross-sectional analysis of the cohort at enrolment showed a 65% lower odds of having AF in women who were receiving statin treatment, even after adjustment for potential confounding variables. Longitudinal analysis over the mean follow-up of 4.1 years showed that women taking a statin at baseline were 55% less likely to develop AF than those who were not. Combining the data, 69 of 1697 women (4.1%) who were not taking statins at baseline had AF at baseline or during the follow-up period, while only 19 of 976 women (2.0%) who were taking statins at baseline had AF at any point in the study.

Before translating these results into clinical practice, clinicians should consider several important limitations to this study. First, the study design is not a randomised controlled trial and is, therefore, inherently subject to selection bias and potentially unknown confounding factors that may lead to a misleading conclusion. For example, although observational studies suggested that angiotensin II receptor blockers may prevent AF, a recent randomised controlled trial showed that valsartan did not reduce AF recurrence. Indeed, the principal findings of the HERS trial itself refuted data from observational studies, suggesting that hormone replacement therapy reduces cardiac events in women.

Another limitation is the relatively small number of end points. In their study, both the prevalence (1% at enrolment) and the incidence of AF (0.5% a year) were lower than in previous reports in this age group, and the absolute number of women who developed new AF was only 59. As the authors noted, the low prevalence and incidence of AF may be partially explained by limited surveillance for AF and the computer-based diagnosis of AF, each of which is an additional limitation to the study.

Statin status was defined by drug use at enrolment, and no data are available as to how many cohort subjects crossed over between the statin and non-statin groups during the follow-up period. No data on statin dose or low-density lipoprotein levels are provided. Furthermore, the temporal relationship between statin use and presence of AF at baseline is undefined. Therefore it is uncertain whether the association between statin use and lower rates of AF is truly causative.

Finally, it should be noted that all patients in HERS had coronary artery disease, and that the results may not apply to AF occurring in other clinical circumstances.

Despite these limitations, the fine study of Pellegrini et al adds to a growing body of clinical reports which suggest that statins reduce the burden of AF. The evidence appears most persuasive for a protective effect of statins after cardiac surgery, where inflammation is likely to have an important aetiological role.

Other studies have shown the efficacy of statin treatment in reducing AF recurrence after electrical cardioversion, after pacemaker implantation and in patients with paroxysmal AF. A meta-analysis of six controlled studies of statin treatment to prevent AF in 3557 patients in a variety of clinical settings concluded that statins decreased the risk of AF with an odds ratio of 0.59 (95% confidence interval 0.18 to 0.85, p = 0.02). The data are not uniformly favourable, however, and the largest single trial, reported only in abstract form, showed no short-term reduction in AF incidence in patients with acute coronary syndrome treated with a high-dose statin.

A clear strength of the present study by Pellegrini et al is its focus on women, a group often under-represented in studies of cardiovascular disease. The findings not only have potential clinical implications for prevention of AF in women, but also serve as supportive evidence to recommend statin treatment to appropriate women with dyslipidaemia and coronary artery disease. It should be noted that in the HERS, only 37% of women (all of whom had established coronary disease) were taking statins. Were the study to be conducted today, all participants would be eligible for statin treatment by current guidelines.

The AHA Guidelines for the Prevention of Cardiovascular Disease in Women recommend use of a statin in women with coronary heart disease or risk equivalents. However, statins may be underused in women in current clinical practice. For example, Daly et al analysed 1580 patients with stable coronary artery disease in the Euro Heart Survey who were eligible for statin treatment and found that significantly fewer women than men were appropriately treated (45% vs 51%, p < 0.001). Furthermore, the disparity persisted at 1-year follow-up. Simpson et al performed a 6-year cross-sectional study of 14 435 patients in Scotland with stable coronary disease...
from 1997 to 2002 and found a marked increase in the appropriate use of statins over time in all patients.14 However, the gap between men and women in statin use actually widened over the study period (from 4.3% in 1997 to 9.6% in 2002).

The cause of this gender disparity in statin use has not been identified, but differences in perceived risk by both doctors and patients may play an important role.17 Although some analyses question the utility of using statins for primary prevention of major cardiovascular events in women, the available evidence shows similar benefit of statin treatment for men and women for both primary and secondary indications.18 19 The benefit appears to extend to apparently healthy women at least 60 years of age without hyperlipidaemia but with raised high-sensitivity C-reactive protein levels.20 One potential gender-specific adverse event that might influence statin use in women is the excess risk of breast cancer reported in one study,21 but this finding was not confirmed in other statin trials, and no biological basis has been established. In the recently reported JUPITER trial, cancer mortality was actually lower in the group randomised to statins.22 In the recently reported trials, and no biological basis has been established. In the recently reported trials, and no biological basis has been established.

How should clinicians use the findings from the study of Pellegrini et al to guide decisions on statin use in women? The results of this study strengthen our ability to recommend a statin in women within the current indications and guidelines, and may help to reduce underuse of statins in women. However, the findings are not sufficient to justify recommending a statin solely for the prevention or treatment of AF in women for whom statins are otherwise not indicated. Although statins are relatively benign drugs with a low incidence of adverse reactions, use of these drugs specifically for AF prevention will require further evidence. In patients who already have AF, clinicians need to be aware of potential drug interactions between certain statins, warfarin and some antiarrhythmic drugs, including amiodarone.

More randomised controlled trials are needed to assess the efficacy and safety of statin treatment for both prevention and treatment of AF in women and in men. Useful data could come from retrospective analysis of existing randomised trials of statin treatment, where baseline and follow-up electrocardiography were performed. Whether statin treatment will prove to be a remedy to ease the global burden of AF remains to be seen. In the interim, the work of Pellegrini et al should provide another nudge toward appropriate use of statin treatment in women and an impetus toward further research in this important field.

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