Letters to the Editor

Statins with equivalent lipid-lowering capacity exhibit differential effects on atrial fibrillation after cardiac surgery

To the Editor:

We read with interest the study by Lertsburapa and colleagues1 highlighting the beneficial effects of preoperative statin therapy on atrial fibrillation (AF) after cardiac surgery. This nested cohort analysis constituted part of the Atrial Fibrillation Suppression Trials I, II, and III, which evaluated the effects of oral amiodarone, atrial septal pacing and preservation of aortic fat pad on AF after cardiac surgery. A total of 555 patients were studied. Postoperative AF occurred in 27.8% of the patients receiving statins versus. 36.6% not receiving statins, demonstrating a statistically significant reduction in postoperative AF in response to statin therapy.

In an attempt to correct for the confounding effects of such variables as age, preoperative AF, and valve surgery, Lertsburapa and colleagues1 performed a stepwise multivariate regression analysis, which confirmed the beneficial impact of statin treatment on postoperative AF. However, it is well-established that in nonrandomised comparative studies, multivariate analysis alone may not be sufficient to adjust for treatment-selection bias and other balancing methods will have to be employed.2

Lertsburapa and colleagues1 suggest a dose-dependent effect of statins on postoperative AF. Atorvastatin ≥40 mg or equivalent doses conferred the greatest effect when compared with no statins. Atorvastatin ≥20 mg but <40 mg, and <20 mg equivalents also conferred an incremental reduction in AF, albeit not statistically significant. Statin types were converted into atorvastatin equivalents based on their lipid-lowering properties as previously evaluated by efficacy comparison trials.3 The division of statin doses to high, intermediate and low is conventionally based on their lipid-lowering activity, such as modulation of inflammatory response and atrial structural remodeling.4 However, we suggest that since there is an indication of differential effect of equivalent statin doses, appropriate methodological measures need to be in place when assessing outcomes beyond their lipid-lowering capacity.

Our group has recently examined the effect of varying doses of statins on postoperative AF in 623 patients undergoing cardiac surgery.4 We concur with Lertsburapa and colleagues that statins significantly reduce AF and that this effect is dose-related. However, following propensity score analysis, we identified that the antifibrillatory effect of statins did not match their lipid-lowering capacity. More specifically, simvastatin 20 mg, which is an atorvastatin 10 mg equivalent based on lipid-lowering efficacy, demonstrated a statistically significant effect on postoperative AF when compared to no statins (OR 2.32, 95% CI 1.30-4.11), whereas atorvastatin 10 mg had no impact on AF (OR 1.05, 95% CI 0.55-1.99). In addition, the beneficial effect of simvastatin 40 mg (OR 3.89, 95% CI 2.03-7.45), which is an atorvastatin 20 mg equivalent, was significantly more pronounced than the effect conferred by atorvastatin 20 mg (OR 1.99, 95% CI 1.00-3.94) or atorvastatin 40 mg (OR 2.76, 95% CI 1.24-6.15) when compared to no statins.

In conclusion, there is enough evidence to support the antiarrhythmic role of statins through mechanisms independent of their lipid-lowering activity, such as modulation of inflammatory response and atrial structural remodeling.5 However, we suggest that since there is an indication of differential effect of equivalent statin doses, appropriate methodological measures need to be in place when assessing outcomes beyond their lipid-lowering capacity.

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References


Reply to the Editor:
My coauthors and I thank Drs Kourliouros, Roberts, and Jahangiri for their interest in our recent study.1 We do not disagree with their suggestion that different statins may exhibit varying degrees of pleiotropic effects (eg, anti-inflammatory effects), and thus believe that their hypothesis that statins may have differential abilities to prevent postcardiothoracic surgery (CTS) atrial fibrillation is not unreasonable. It is, however, important to note that the intent of our nested cohort study was to assess whether statins as a class are associated with reductions in post-CTS atrial fibrillation when used in patients who already have a high background use of β-blockers (84%) and appreciable use of prophylactic amiodarone (44%), rather than to evaluate individual statins or a dose-response relationship.1 Our primary analysis was worthwhile, because a large proportion of patients in ARMYDA-3—the only randomized controlled trial designed to assess the effect of a statin (atorvastatin at 40 mg/d) on post-CTS atrial fibrillation as a primary end point—did not receive β-blockers (arguably the criterion standard preventative strategy), and virtually none received prophylactic amiodarone.2 This treatment pattern likely explains the high incidence of post-CTS atrial fibrillation (57%) seen in the ARMYDA-3 control group.

Despite the criticism from Kourliouros, Roberts, and Jahangiri of our dose-response analysis, we believe that it provides valuable data to support the claim of a dose-response effect of statins on post-CTS atrial fibrillation. We would have liked to evaluate different statins and doses independently; however, the relatively small number of patients receiving a statin and the heterogeneous uses of different statins and doses by patients enrolled in the cohort would have resulted in an underpowered analysis.3 That being said, we applaud the work of Kourliouros, Roberts, and Jahangiri in conducting an additional analysis to further the research in this area.3 Ultimately, as Kourliouros, Roberts, and Jahangiri suggest, all nonrandomized studies likely suffer from some degree of bias or confounding, which is why a randomized, controlled trial will be needed to determine definitively whether different statins exhibit different abilities to prevent post-CTS atrial fibrillation and whether dose-response relationships do, in fact, exist.

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References

Box lesion or not—Still unsettled question
To the Editor:
I read with interest the article by Voeller and associates4 in the April 2008 issue of the Journal. This is a single center study looking at occurrences of atrial arrhythmias on follow-up in patients who had the Cox maze IV procedure with and without box lesions. Although the authors have acknowledged several limitations, I would like to point out another important limitation. Over 60% of the patients had concomitant procedures, and a significant proportion of them had valve operations, which is a significant confounder for occurrence of postoperative atrial arrhythmias. Analysis of the lone Cox maze IV group would probably offer better insight into the benefit of the box lesion. However, the numbers seem to be so small that there may not be adequate power for this analysis. I will look forward to any follow-up data in the future from the authors.

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Aortic valve replacement dilemma: mechanical or biological prosthesis?
To the Editor:
The selection of the appropriate prosthesis for aortic valve replacement (AVR) is still open to debate in the case of patients in the sixth and seventh decades of life. Recently Brown and colleagues,1 from Mayo Clinic, reported in the Journal on an interesting retrospective study about this topic. By means of patient matching according to clinical features, they observed in their population a survival advantage after aortic valve replacement with a mechanical prosthesis relative to a bioprosthesis. Brown and colleagues stated that the study was subject to selection bias and noted that despite case matching and statistical analysis, surgical bias cannot be eliminated. Also, in our opinion, it is virtually impossible to avoid at all biases and confounding factors in clinical studies. Nevertheless, the recording of aortic valve replacement as associated or not with coronary artery bypass grafting simply as a binary variable could be quite misleading in drawing conclusions from data analysis. In fact, age being equal, surgeons could elect to implant a bioprosthesis rather than a mechanical valve in patients affected by more severe coronary artery disease. Both the extent—isolated single-vessel disease versus triple-vessel disease—and the