Editorial

Response to perioperative statin therapy in cardiac surgery: a matter of race and timing?

Tyler P. Rasmussen[1], Prashant D. Bhave[2]

[1]Department of Internal Medicine, [2]Division of Cardiovascular Medicine, Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA, USA

Correspondence to: Tyler P. Rasmussen, MD, PhD. Department of Internal Medicine, University of Iowa Carver College of Medicine, 200 Hawkins Dr, E325 GH, Iowa City, IA 52242, USA. Email: tyler-rasmussen@uiowa.edu.

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We read with great interest the recent article by Zheng *et al*. describing the STICS clinical trial testing whether perioperative rosuvastatin administration lowers rates of postoperative atrial fibrillation (AF) and myocardial infarction after coronary artery bypass grafting (CABG) or CABG plus aortic valve surgery (1). These are important questions because we know that postoperative AF after cardiac surgery has significant implications on health care outcomes and costs (2). Notably, the STICS study revealed no difference in postoperative AF rates between placebo and rosuvastatin treated groups. This data supports very different conclusions than previous studies, which have tested a similar question and found a significant reduction in postoperative AF with perioperative statin therapy in both cardiac and non-cardiac surgery (3,4). We surmise that there are methodological, demographical, and pharmacological aspects of this new study that may help explain the unexpected results.

We'd first like to examine some details of study design that may have influenced the results. Specifically, individuals were included independent of statin naïvety, whereas the ARMYDA trial only included statin naïve patients (3). The supplementary material cites studies involving statin naïve patients as a rationale for their study design (1,5-7), which suggests the authors should have considered excluding patients on statin therapy. The inclusion of patients on statin therapy was intended to be counterbalanced by a statin holiday, which began at the time of enrollment in the study. However, the length of statin holiday was not regulated in the study; further the distribution of actual statin holiday durations was not provided in the manuscript. The inclusion of statin treated patients and the permitting of an unspecified holiday from statin therapy could have affected the results of this study.

Additionally, the timing of perioperative rosuvastatin initiation was not tightly controlled in this study. The authors allowed subjects to begin rosuvastatin therapy from 2 up to 8 days prior to surgery, whereas the ARMYDA trial began all subjects on atorvastatin at 7 days preoperatively. Another recent study by Pierri *et al*. which showed a dose dependent trend toward lower postoperative AF for perioperative atorvatatin with on-pump CABG, also used 7 days of statin therapy prior to surgery (8). Based on the results of these studies, we speculate that at least 1 week of pre-operative statin therapy may be needed to achieve benefit. To the authors credit, they performed a subgroup analysis of patients who began rosuvastatin ≤2 days preoperatively versus >2 days and found no difference between groups. However, it may be important to note that patients on statins and patients beginning rosuvastatin ≤2 days preoperatively trended towards placebo benefit for postoperative AF. We suggest that the results of the STICS trial would be more credible had the authors set a more strict, uniform, and prolonged time period for preoperative rosuvastatin therapy.

We were interested to see that roughly 20% of patients received either glucocorticoids or non-steroidal anti-inflammatory drugs (NSAIDs) because both classes of drugs have been shown to reduce postoperative AF (9,10). Administration of these drugs was comparable between groups, but could be a confounding variable.

In addition to study design, demographical

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characteristics of the study population could partially explain the low incidence of postoperative AF. Specifically, the mean ages for both rosuvastatin and placebo groups were less than 60, whereas the ARMYDA trial mean ages were above 65. The ATRIA study found that prevalence of AF increased from 0.1% among adults <55 years of age to 9% in octogenarians (11). The STICS trial studied a young cohort in which AF would be expected to be relatively infrequent compared to older populations undergoing cardiac surgery (12). Studying an older population would likely yield higher postoperative AF rates and broaden the therapeutic window for rosuvastatin.

Ethnicity plays an important role in determining the risk of postoperative AF (13). Another factor that may help explain contradictory findings in the STICS and ARMYDA trial is that the STICS trial was conducted in China, while the ARMYDA trial was undertaken in Western Europe. Genetic variants among Chinese subjects are being identified that may alter the pharmacokinetics of statin therapy (14,15). A multi-ethnic, multi-center trial is needed to determine what role ethnicity plays in determining response to perioperative statin therapy as it relates to AF.

It should be noted that the preoperative medical management of the study cohort was variant from guideline recommendations. In our experience, the vast majority of patients indicated for elective CABG meet criteria for statin therapy. The most recent ACC/AHA guidelines state that patients less than 75 years old with atherosclerotic cardiovascular disease should be on a high-intensity statin, unless patients are intolerant, in which case they should be on low- or moderate-intensity statin therapy (16). Within the overall cohort, 87% of study participants underwent CABG but only 34% of patients were on statin therapy prior to enrollment in the study, suggesting that optimal medical management was not achieved. Suboptimal medical management prior to study enrollment could affect the ability of subjects to respond to preoperative statin therapy, especially with a short duration of treatment as in the group treated for 2 days preoperatively.

Another surprising result is that the rosuvastatin group had higher incidence of acute kidney injury versus placebo in the STICS trial. Statins have been shown to prevent contrast induced kidney injury (17,18) and preserve glomerular filtration rate in chronic kidney disease (19); statins may even lower postoperative renal replacement therapy rates (20). In most studies, statins do not increase the risk of acute kidney injury over placebo (21,22). The finding of elevated acute kidney injury risk in the rosuvastatin group is unexpected. The STICS study stands as an outlier in this respect. The clinical significance of this difference in acute kidney injury is unclear and we struggle to posit a plausible mechanism for this finding. Perhaps this study population has a propensity to increased muscle injury, such as subclinical rhabdomylolysis, in the setting of cardiac surgery and statin use. Notably, however, a recent population based study showed no higher incidence of statin adverse events in Chinese populations (23). Even so, measurement of serum creatinine kinase may have served to elucidate the mechanism of acute kidney injury. Regardless, the high rate of acute kidney injury suggests the STICS trial study group responds uniquely to statin therapy when compared to other populations.

Ultimately, future studies should address the role of statin therapy in patients undergoing cardiac valve surgery to reduce postoperative AF because these patients may have a higher prevalence of statin naïve patients. A randomized controlled trial with this model could address statin versus placebo, as well as a head-to-head comparison of atorvastatin and rosuvastatin in terms of postoperative AF rates because trials with atorvastatin suggest a benefit of perioperative statin therapy (3,8). A trial of this nature could help address whether statin initiation at the time of preoperative planning is indicated and whether there is any real difference in outcomes between atorvastatin and rosuvastatin. To date, almost all studies testing whether statins confer perioperative benefit have been performed at single centers, inherently limiting the heterogeneity of the study group. We suggest that a multi-continent multi-center randomized control trial would help allay any concerns about whether patient demographics were responsible for this study result. Specifically, populations from east Asia and western Europe should be studied in aggregate given the conflicting findings of the STICS and ARMYDA trials.

The STICS trial investigators should be congratulated on completing this ambitious study. Ultimately, however, we do not think the results of this trial will change preoperative planning for patients at our center undergoing CABG or CABG plus valve surgery. The vast majority of our patients being considered for bypass surgery are on chronic statin therapy and we find limited evidence to support cessation of statin therapy perioperatively. We find the higher incidence of acute kidney injury in the STICS trial to be interesting and plan to closely monitor whether this phenomenon exists in our center's population of patients who undergo cardiac surgery while on rosuvastatin therapy.

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Footnote

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