Atrial fibrillation (AF) is a common arrhythmia after coronary artery bypass grafting (CABG). It is estimated to occur in about one-third of the patients post-CABG (1-3). In a prospective observational study of 1,878 consecutive patients undergoing CABG, post-CABG AF was associated with a four-fold increased risk of disabling stroke and a three-fold increased risk of cardiovascular mortality (1). The intense systemic inflammatory response associated with CABG has been implicated as an important mechanism of post-CABG AF (4,5). Statins or hydroxymethylglutaryl-CoA reductase inhibitors exert a pleiotropic or anti-inflammatory effect (6), which is thought to be associated with a reduction in the risk of post-CABG AF (7,8). Meta-analyses of randomized trials suggested that statin therapy reduces the risk of post-CABG AF (9,10). However, these randomized trials were limited by the small sample size, and the primary outcome of some of these studies was inflammatory markers, rather than post-CABG AF. These shortcomings have led to the recently published Statin Therapy In Cardiac Surgery (STICS) trial (11).

The STICS trial included 1,992 patients in normal sinus rhythm (not taking anti-arrhythmic agents at baseline, other than beta-blockers) scheduled to undergo elective CABG (87% of the patients), aortic valve surgery, or both. Subjects were randomized to rosuvastatin (n=960) versus placebo (n=962). Patients were recruited at a tertiary center in China. The study medication was initiated up to 8 days preoperatively (58% started the medication only 2 days or less), and continued for 5 days after surgery. The co-primary outcomes were postoperative AF, detected by continuous Holter monitoring for 5 days postoperatively, and perioperative myocardial injury (assessed by area-under-the-curve for Troponin I release). The risk of postoperative AF was similar in both groups: 203 patients (21%) in the rosuvastatin group versus 197 patients (20%) in the placebo group. In addition, rosuvastatin had no significant effect on Troponin I release (11).

The STICS trial was a well-designed study and recruited a large number of patients, however; the findings of the STICS trial were inconsistent with the previous studies. What could explain this difference? First, the pleiotropic effect has been shown to vary among the individual statins; favoring the more lipophilic statins such as atorvastatin and simvastatin (12). By performing a meta-analysis of randomized trials including the STICS trials, we showed that atorvastatin was associated with 49% reduction in the risk of postoperative AF, but this effect was not observed with rosuvastatin (P for interaction =0.046) (Figure 1). A second consideration is the duration needed for statins to exert the maximum pleiotropic effect. Although statins, particularly atorvastatin, have been shown to exert a rapid anti-oxidant effect in patients undergoing elective CABG (13), studies have suggested that 14 days of statin therapy are usually required to achieve the full anti-inflammatory effect (14,15). This finding was supported by a meta-regression analysis, in which statins were associated with a 3% reduction in the risk of postoperative AF per day of therapy, which highlights the incremental benefit with earlier initiation of preoperative therapy (9). In the STICS trial, 58% of the patients were started on rosuvastatin only 2 days or less prior to the surgery and the maximum duration of therapy preoperatively was 8 days (11). This relatively short duration of preoperative treatment might have diminished the pleiotropic effects of statin therapy. Finally, genetic polymorphisms are known to affect the pharmacokinetics and pharmacodynamics of statins,
resulting in inter-individual and inter-ethnic variability in the response to the drug (16). In the STICS trial, all patients were recruited from China, which might affect generalization of these results to other ethnicities.

An unexpected finding of the STICS trial was the higher incidence of acute kidney injury (AKI) with rosuvastatin, driven mainly by stage 1 AKI (11). The effect of perioperative statin therapy on renal function after cardiac surgery has been an area of debate. Earlier observational studies suggested a “renoprotective” effect for statins (17–19). These findings were disputed in a recent randomized trial, which showed no benefit with high dose atorvastatin on the risk of AKI after cardiac surgery (20). In fact, there was an increased risk of AKI in statin-naive patients with preexisting chronic kidney disease. In the STICS trial, almost two-thirds of the patients were statin-naive, which suggests a possibly higher risk of renal adverse events with de-novo initiation of therapy. Furthermore, some studies had suggested that East Asian subjects, as compared with Caucasians, have higher plasma exposure to rosuvastatin and its metabolites with the same dose, probably secondary to genetic polymorphism (21).

In summary, the STICS trial demonstrated no benefit for short-term perioperative rosuvastatin therapy in the prevention of postoperative AF in patients undergoing elective CABG, and a possible increased risk of AKI. The findings also support the hypothesis that early smaller studies could magnify the benefit of a treatment effect, which are oftentimes challenged by the results of large scale randomized trials (22). However, the results of the STICS trial may not be extrapolated to other statins (most importantly atorvastatin) if initiated earlier (i.e., ≥14 days prior to the surgery).

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Footnote

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