et al., we specifically examined the prognostic effect of mutant *IDH* alleles. The rate of event-free survival did not differ significantly between the group of patients without these mutations and the group of patients with *IDH1*^{R132} mutations (hazard ratio for refractory disease, relapse, or death, 1.04; 95% confidence interval [CI], 0.57 to 1.88), *IDH2*^{R140} mutations (hazard ratio, 0.72; 95% CI, 0.40 to 1.30), or *IDH2*^{R172} mutations (hazard ratio, 0.72; 95% CI, 0.30 to 1.76). Thus, these results from a large randomized clinical trial do not suggest that ATRA has specific clinical activity in patients who have AML with *IDH1*/*2* mutations.

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Since publication of their article, the authors report no further potential conflict of interest.

DOI: 10.1056/NEJMc1608739

Perioperative Rosuvastatin in Cardiac Surgery

TO THE EDITOR: In the Statin Therapy in Cardiac Surgery (STICS) trial, Zheng et al. (May 5 issue)[1] found that the initiation of rosuvastatin before cardiac surgery did not reduce the risk of postoperative atrial fibrillation. A meta-analysis of randomized trials, including this trial, showed that the risk of postoperative atrial fibrillation was lower among patients who received atorvastatin than among those who received placebo (odds ratio, 0.35; 95% confidence interval [CI], 0.25 to 0.50; P<0.001). This meta-analysis, which did not have evidence of publication bias, did not show a significant benefit with rosuvastatin as compared with placebo (odds ratio, 0.69; 95% CI, 0.28 to 1.71; P=0.42).[2] These findings suggest a possible difference in pleiotropic effects among the various statins.[3,4]

In the STICS trial, treatment with rosuvastatin was initiated close to the time of surgery (up to and including 2 days before the day of surgery in 59% of the patients). Some studies have suggested that statins exert their full pleiotropic effect in 14 days.[3] In a meta-regression analysis, statins were associated with a 3% reduction in the risk of postoperative atrial fibrillation per day of therapy.[5] Although the STICS trial showed no benefit of rosuvastatin, the results cannot be extrapolated to other statins (e.g., atorvastatin) if these drugs are initiated within a sufficient duration (i.e., at least 14 days) before cardiac surgery.

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No potential conflict of interest relevant to this letter was reported.

1. Zheng Z, Jayaram R, Jiang L, et al. Perioperative rosuvastatin in cardiac surgery. N Engl J Med 2016;374:1744-53.
2. Elgendy IY, Mahmoud A, Huo T, Beaver TM, Bavry AA. Meta-analysis of 12 trials evaluating the effects of statins on decreasing atrial fibrillation after coronary artery bypass grafting. Am J Cardiol 2015;115:1523-8.
3. Barakat AF, Saad M, Abuzaid A, Mentias A, Mahmoud A, Elgendy IY. Perioperative statin therapy for patients undergoing coronary artery bypass grafting. Ann Thorac Surg 2016;101:818-25.
4. Turner NA, Midgley L, O'Regan DJ, Porter KE. Comparison of the efficacies of five different statins on inhibition of human saphenous vein smooth muscle cell proliferation and invasion. J Cardiovasc Pharmacol 2007;50:458-61.
5. Chen WT, Krishnan GM, Sood N, Kluger J, Coleman CI. Effect of statins on atrial fibrillation after cardiac surgery: a duration- and dose-response meta-analysis. J Thorac Cardiovasc Surg 2010;140:364-72.

DOI: 10.1056/NEJMc1608082

TO THE EDITOR: In the STICS trial, perioperative statin therapy did not prevent perioperative myocardial damage in Chinese patients undergoing elective cardiac surgery. This result differs from that of a previous study that involved European patients.[1]

Of note, the mean (±SE) low-density lipoprotein

(LDL) cholesterol level at baseline in the STICS trial was 82.6±0.9 mg per deciliter; this was significantly lower than the mean (±SD) LDL level of 121±28 mg per deciliter in the previous trial.[1] A subgroup analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE-IT–TIMI 22) trial showed that the benefit of statin therapy was dependent on the baseline LDL cholesterol level. The protective effect of 80 mg of atorvastatin daily over 40 mg of pravastatin daily was not significant in patients in the lowest quartile of baseline LDL cholesterol level (with a median LDL cholesterol level of 81 mg per deciliter).[2]

A lack of response to intensive periprocedural statin therapy has also been reported in Chinese patients undergoing percutaneous coronary intervention.[3,4] This finding is contrary to the results of the Atorvastatin for Reduction of Myocardial Damage during Angioplasty serial trials.[5] Thus, the negative result of the STICS trial with respect to myocardial injury may be attributed to the baseline LDL cholesterol levels, which are lower in the Chinese population than in the European population. A subgroup analysis involving patients stratified according to LDL cholesterol level may help to rule out this possibility.

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No potential conflict of interest relevant to this letter was reported.

1. Mannacio VA, Iorio D, De Amicis V, Di Lello F, Musumeci F. Effect of rosuvastatin pretreatment on myocardial damage after coronary surgery: a randomized trial. J Thorac Cardiovasc Surg 2008;136:1541-8.
2. Giraldez RR, Giugliano RP, Mohanavelu S, et al. Baseline low-density lipoprotein cholesterol is an important predictor of the benefit of intensive lipid-lowering therapy: a PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) analysis. J Am Coll Cardiol 2008;52:914-20.
3. Jang Y, Zhu J, Ge J, Kim YJ, Ji C, Lam W. Preloading with atorvastatin before percutaneous coronary intervention in statin-naïve Asian patients with non-ST elevation acute coronary syndromes: a randomized study. J Cardiol 2014;63:335-43.
4. Hao PP, Chen YG, Wang JL, et al. Meta-analysis of the role of high-dose statins administered prior to percutaneous coronary intervention in reducing major adverse cardiac events in patients with coronary artery disease. Clin Exp Pharmacol Physiol 2010; 37:496-500.
5. Pasceri V, Patti G, Nusca A, et al. Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: results from the ARMYDA (Atorvastatin for Reduction of MYocardial Damage during Angioplasty) study. Circulation 2004;110:674-8.

DOI: 10.1056/NEJMc1608082

TO THE EDITOR: Zheng et al. report that perioperative statin therapy did not prevent postoperative atrial fibrillation, but acute kidney injury was significantly more common among patients who received rosuvastatin than among those who received placebo (P=0.005). The pathogenesis of the acute kidney injury is not discussed. The most plausible cause of acute kidney injury after the administration of a statin is rhabdomyolysis.

The participants in the trial were recruited in China. Asians have more side effects from drugs than do non-Asians.[1] Plasma exposure to rosuvastatin and its metabolites is significantly higher for a given dose in Asian persons (especially in Chinese persons) than in whites.[2] In a trial of lipid-lowering drugs, the risk of myopathy with niacin (at a dose of 2 g) plus laropiprant (at a dose of 40 mg once daily) added to simvastatin (at a dose of 40 mg daily) was 10 times greater among Chinese patients than among European patients.[3]

In the current trial, participants received rosuvastatin at a dose of 20 mg daily, whereas a modest dose of rosuvastatin (10 mg daily) did not result in excess myopathy among Chinese participants in another trial.[4] In Japan, the on-label recommended daily dosage of rosuvastatin is 5 mg. Acute kidney injury may have been caused by the use of rosuvastatin at an excess dose for Asians.

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No potential conflict of interest relevant to this letter was reported.

1. Hori M, Matsumoto M, Tanahashi N, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation — the J-ROCKET AF study. Circ J 2012;76:2104-11.
2. Lee E, Ryan S, Birmingham B, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. Clin Pharmacol Ther 2005;78: 330-41.
3. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. Eur Heart J 2013;34:1279-91.
4. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;374:2021-31.

DOI: 10.1056/NEJMc1608082

THE AUTHORS REPLY: Elgendy et al. suggest that the use of atorvastatin in our trial would have reduced the incidence of postoperative atrial fibrillation. However, as shown by their meta-analysis of previous randomized trials, the odds ratios for the incidence of atrial fibrillation with rosuvastatin versus placebo were almost identical to those for atorvastatin versus placebo: odds ratio, 0.41 (95% CI, 0.21 to 0.78) and odds ratio, 0.35 (95% CI, 0.25 to 0.50), respectively. As we discussed in our article, the previous trials were small and had other major limitations. A Cochrane review also showed evidence of publication bias, with no reduction in the incidence of atrial fibrillation in a trial of atorvastatin (results not published) (Fig. S5 in the Supplementary Appendix of our article). By contrast, our trial involved more cases of atrial fibrillation than the previous trials combined, had high levels of adherence, evaluated prespecified blinded outcomes systematically, and involved intention-to-treat analyses. Thus, differences between the results in our trial and those in the meta-analyses are probably due to methodologic problems with previous trials rather than to the type of statin used.

Regarding the suggestion by Elgendy et al. that the effect of statin therapy on atrial fibrillation would have been larger with longer preoperative therapy: antioxidant and antiinflammatory effects develop rapidly after the initiation of statin therapy. The actual duration of preoperative treatment, as compared with the planned duration of preoperative treatment, was reported in only one previous trial. Treatment was initiated 4 to 8 days before surgery in more than twice as many patients in our trial as in previous trials (Fig. S2 in the Supplementary Appendix of our article), and the odds ratio of 1.35 (95% CI, 0.82 to 2.21) for the incidence of atrial fibrillation after cardiac surgery among these patients was not consistent with a halving of the incidence of postoperative atrial fibrillation with statins as compared with placebo.

Wang and Peng suggest that myocardial damage was not prevented in our trial because the baseline LDL cholesterol level was lower than that in patients in a European trial. However, perioperative statin therapy has also been previously reported to have reduced myocardial damage in a randomized trial conducted in China.[1] The analyses from the STICS trial stratified according to baseline LDL cholesterol level are provided in Figures S2 and S4 in the Supplementary Appendix of our article; in particular, there was no benefit among patients with a baseline LDL cholesterol level higher than 100 mg per deciliter. Wang and Peng also suggest, on the basis of a subgroup analysis in the PROVE-IT trial, that long-term statin therapy is not beneficial in patients with a low LDL cholesterol level (as in our trial). However, the Cholesterol Treatment Trialists' meta-analysis of 26 trials showed that proportional reductions in vascular events for each reduction of 1 mmol per liter in LDL cholesterol level were similar, even if the initial LDL cholesterol levels were lower than 80 mg per deciliter.[2]

In reply to Tomoda: the risk of statin-induced myopathy is higher among Chinese persons than among whites, but the absolute excesses are small (0.06 percentage points vs. 0.02 percentage points[3]). Consequently, an excess of myopathy is unlikely to have caused the absolute (±SE) excess in acute kidney injury (5.4±1.9 percentage points) in our trial. Moreover, a similar excess of acute kidney injury was observed in a North American trial of atorvastatin.[4] In summary, the lack of evidence of beneficial effects combined with the excess of acute kidney injury (albeit mainly mild) does not support the routine use of perioperative statin therapy.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Almansob MA, Xu B, Zhou L, et al. Simvastatin reduces myocardial injury undergoing noncoronary artery cardiac surgery: a randomized controlled trial. Arterioscler Thromb Vasc Biol 2012;32:2304-13.
2. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81.
3. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. Eur Heart J 2013;34:1279-91.
4. Billings FT IV, Hendricks PA, Schildcrout JS, et al. High-dose perioperative atorvastatin and acute kidney injury following cardiac surgery: a randomized clinical trial. JAMA 2016;315:877-88.

DOI: 10.1056/NEJMc1608082