Reply to the Editor:

We appreciate the comment and update from Takagi and colleagues. They previously reported the results of a meta-analysis of controlled studies, showing that preoperative statin use was associated with reduced all-cause mortality after cardiac surgery.¹ At this time, they added recently published studies, including ours,² in the meta-analysis and showed that preoperative statin therapy was associated with a 33% reduction in postoperative mortality (pooled odds ratio, 0.67; 95% confidence interval, 0.54–0.83; $P = .0002$), which supports a beneficial effect of preoperative statin use in patients undergoing cardiac surgery. Their pooled analysis included 24,039 patients from 13 controlled studies. However, the generalizability of their finding is still not high.

Most patients included in their pooled analysis underwent coronary artery bypass surgery. Statins have been shown to be effective in the prevention of major cardiac events in coronary artery disease.^{3,4} Perhaps most patients undergoing coronary artery bypass surgery are expected to be taking a statin before surgery, although routine statin therapy regardless of low-density lipoprotein cholesterol level is still controversial. All patients included in our study had no coronary artery disease.² Our study has indicated a potential benefit of preoperative statin in patients undergoing cardiac surgery without coronary artery disease. However, the study has limitations of observational studies. A randomized controlled study is necessary to confirm the finding.

To generalize the beneficial effect of preoperative statin use in patients undergoing cardiac surgery, further investigations are necessary in patients without coronary artery disease or those without hypercholesterolemia.

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GRAFT PATENCY IN CORONARY ARTERY BYPASS VERSUS OFF-PUMP CORONARY ARTERY BYPASS

To the Editor:

We read with great interest the article by Angelini and associates¹ regarding effects of coronary artery

bypass grafting with cardiopulmonary bypass (CABG-CPB) versus off-pump coronary artery bypass (OPCAB) grafting on graft patency from long-term (7-year) follow-up of 2 randomized controlled trials (Beating Heart Against Cardioplegic Arrest Study [BHACAS] 1 and 2). The likelihood of graft occlusion was not different between OPCAB (10.6%) and CABG-CPB (11.0%) groups (odds ratio, 1.00; 95% confidence interval [CI], 0.55–1.81; $P > .99$).¹ Meanwhile, our previous meta-analysis² of randomized controlled trials (not including the study by Angelini and collaborators¹) demonstrated a statistically significant increase in venous graft occlusion (risk ratio [RR], 1.28; 95% CI, 1.06–1.54; $P = .0094$) and overall graft occlusion (RR, 1.27; 95% CI, 1.03–1.56; $P = .0234$) with OPCAB relative to CABG-CPB in the random-effects model. We herein updated the meta-analysis,² including the study by Angelini and colleagues.¹

Our comprehensive search identified 7 studies reporting ≥ 3 -month graft patency. Pooled analysis of all

FIGURE 1. Forest plot of venous graft occlusion risk among patients randomized to off-pump coronary artery bypass (OPCAB) grafting versus coronary artery bypass grafting with cardiopulmonary bypass (CABG-CPB) in all studies (A) and studies reporting ≥ 1 -year patency (B). IV, Inverse variance; CI, confidence interval.

7 studies demonstrated no statistically significant difference in arterial graft occlusion (RR, 1.01; 95% CI, 0.63–1.60; $P = .98$; P for heterogeneity = .16) between OPCAB and CABG-CPB but a statistically significant increase in venous graft occlusion (RR, 1.29; 95% CI, 1.08–1.54; $P = .006$; P for heterogeneity = .98; Figure 1, A)^{1,3-7} and overall graft occlusion (RR, 1.29; 95% CI, 1.00 [1.0028]–1.42; $P = .05$ [.0465]; P for heterogeneity = .27) with OPCAB relative to CABG-CPB in the fixed-effects model. Two of the 7 studies stated 3-month graft patency, whereas the remaining 5 studies reported ≥ 1 -year patency. In a sensitivity analysis, pooled analysis of the 5 studies reporting ≥ 1 -year graft patency demonstrated no statistically significant difference in arterial graft occlusion (RR, 0.98; 95% CI, 0.58–1.68; $P = .95$; P for heterogeneity = .36) and overall graft occlusion (RR, 1.16; 95% CI, 0.97–1.40; $P = .11$; P for heterogeneity = .83) between OPCAB and CABG-CPB but a statistically significant increase in venous graft occlusion (RR, 1.27; 95% CI, 1.06–1.53; $P = .01$; P for heterogeneity = .94; Figure 1, B)^{1,5-7} with OPCAB relative to CABG-CPB in the fixed-effect model.

The results of our analysis suggest that OPCAB may attenuate venous graft patency over CABG-CPB. Four of the 5 studies included in the sensitivity analysis, however, had merely 1-year follow-up duration as contrasted with 7-year follow-up in the study by Angelini and coworkers.¹ Further long-term follow-up results of randomized controlled trials are needed to confirm our results.

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Reply to the Editor:

In this issue, Takagi and Umemoto¹ report a meta-analysis of patency after coronary artery bypass (CABG) and off-pump CABG (OPCAB) that we and others declined to conduct.^{2,3} We have 4 comments on the appropriateness of both their revised and original analyses.⁴

The authors make the mistake that we described in our article³—that is, they assumed statistical independence of multiple grafts in the same patients. We reiterate that this “could seriously undermine statistical inferences.”³ In our own primary patency analysis, ignoring the dependency between grafts within patients would have narrowed the confidence interval by 40%. Underestimating the standard errors by this amount would make all of their

pooled estimates not statistically significant.

Meta-analysts should write a protocol in advance,⁵ including specifying the planned analyses. Can Takagi and Umemoto confirm that the subgroup analysis by different conduit type was prespecified? In the Beating Heart Against Cardioplegic Arrest Study (BHACAS) follow-up, the 2 groups had very similar overall occlusion rates, but the proportions of vein and arterial grafts occluded in the OPCAB compared with the CABG group happened to be in the directions observed in the original meta-analysis.⁴ We had no prior hypothesis that veins should be more at risk of occlusion with OPCAB and concluded that our nonsignificant findings arose by chance. Did Takagi and Umemoto report the subgroup analyses because it showed statistical significance, without a prior intention to do so?

Although updating a meta-analysis is always worthwhile, one should not expect the addition of a single new result to overturn a previous conclusion unless the new trial contributes an overwhelming amount of new information (depicted by the size of a “blob” in a forest plot) or a substantially different estimate (which might cause concern about heterogeneity). Neither was the case here.

Inspection of the blobs does, however, show that one trial contributes most of the statistical weight.⁶ Interestingly, the PRAGUE-4 trial reported patency findings for a similar number of patients (255) as the BHACAS trials (199), highlighting that the large weight is due to a high rate of overall occlusion (45%) compared with the other trials (7%–17%). Meta-analysts need to judge whether it makes sense to pool data.⁵ We question whether the PRAGUE trial should be pooled with the others, even in the absence of statistical heterogeneity and without obvious major design differences between studies. Moreover, there are other important sources of heterogeneity between trials,