of the everted prosthesis or postoperative hemostasis associated with anastomotic distortion was noted. Thus, the effectiveness of the turn-up method was confirmed with a significantly sized patient cohort and suitable follow-up period.

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Reply to the Editor:

We read with interest the letter of Shimamoto and Komiya comparing our novel technique for aortic anastomosis using telescopic graft inversion¹ with the "turn-up" method.² We appreciate all thoughtful comments and would like to address some of the important points involved.

First of all, Shimamoto and Komiya discussed the time needed for the 2 suture techniques. Both anastomotic techniques are time-consuming. We reported that our method may take about 40% longer than the simple "over-and-over" technique. Both "turn-up" and graft telescopic inversion methods involve 2 layers of sutures for complete anastomosis. However, the easy mattress suture of felt strip in our technique extended the time for anastomosis only slightly. Additionally, there was no need for hemostatic stitches after completing the anastomosis, which might save time. Our method thus reduced the total time for the procedure significantly, mainly because we needed less time

to stop the bleeding. We are convinced that the addition of the technique of Shimamoto and Komiya in selected cases can save overall time and morbidity as well.

In describing our method, we concluded that there is no ridge in the bloodstream in comparison with the "turn-up" method. Inverted Dacron aortic anastomosis results in 1 layer of intraluminal Dacron at the anastomosis level, whereas the "turn-up" technique requires 2 intraluminal layers, which may result in a ridge projecting into the bloodstream. We believe that an anastomotic stenosis or any intraluminal edge can be unfavorable and elicit embolic events. With our method, we try to prevent anastomotic stenosis by completing the anastomosis first, then opening the crossclamp, and carefully tightening and knotting the suture for the external felt with full pressure filling to prevent suspected tourniquet syndrome on the anastomotic side.

We are convinced that both techniques are appropriate for aortic replacement, especially when the arterial wall is highly fragile, as in aortic dissection or in patients with Marfan syndrome. Please allow us to recommend our technique as a worthwhile supplement to the surgical armamentarium that can be used in cases such as those mentioned above.

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IMMORTAL PERSON-TIME BIAS IN OBSERVATIONAL STUDIES IN CARDIAC SURGERY

To the Editor:

We read with great interest the article by Kim and associates¹ in a recent issue of the *Journal of Thoracic and Cardiovascular Surgery*. We find this topic area engaging and relevant to clinical practice, especially in light of expanding indications of dual antiplatelet therapy and recent advances in perioperative management lending to improved acute operative mortality.² However, we have important concerns regarding the methodology and statistical analyses undertaken.

The investigators compared the treatment strategies of aspirin plus clopidogrel with aspirin alone in patients undergoing isolated coronary artery bypass grafting (CABG). Dual therapy was associated with a 50% risk reduction (odds ratio [OR], 0.50; 95% confidence interval [CI], 0.25–0.99) in in-hospital mortality, a 30% risk reduction (OR, 0.70; 95% CI, 0.51–0.97) in bleeding events, and no effect on ischemic/thrombotic events (OR, 0.99; 95% CI, 0.59–1.64). These robust, and seemingly contradictory, findings may be influenced by important biases.

First, the exposure measurement was based on the addition of clopidogrel in days 1 and 2 postoperatively, with primary outcome assessment beginning immediately after the operation. Patients must thus survive (ie, are "immortal") those days into the postoperative period to be defined as exposed to the clopidogrel therapy, whereas patients experiencing an adverse event previously were thus necessarily included in the unexposed group (aspirin alone). Such a classification of exposure to clopidogrel leads to immortal time bias.³ The magnitude of this bias is directly related to the proportion of length of stay (not provided in text) that is immortal, with shorter length of stays resulting in higher bias, and the number

of patients who died in the first 2 days postoperatively.

Second, confounding by contraindication could have been introduced from patients experiencing significant bleeding events (thus prohibiting clopidogrel use) who would be more likely to be in the aspirin monotherapy cohort and with greater risks of major outcomes. Unfortunately, data regarding reasons behind withholding clopidogrel were not included and it appears that surrogates of intraoperative bleeding including transfusion requirements and postoperative chest tube outputs were unmeasured.

Finally, selection bias may also have been introduced with the exclusion of patients who were administered late postoperative clopidogrel (> postoperative day 2), patients who necessarily survived at least the first 3 days. It is unclear whether such exclusions affected the reported rates of in-hospital mortality for on-pump CABGs (1.5%) in this study, which are half the rates reported in the Society of Thoracic Surgeons (STS) national database (3.05%).⁴

The nonrandomized study of pharmacologic treatment effects presents major methodologic challenges, including using current STS definitions of operative outcomes in surgical series. Postdischarge surveillance has recently been suggested to replace current 30-day mortality benchmark.⁵ Given the rapidly changing nature of patient status in the postoperative period, it is imperative that timing of exposure and outcome assessment be accurate. It would be informative for the authors to treat clopidogrel exposure in a time-dependent fashion to more accurately dissect the role of dual antiplatelet therapy after CABG.

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Reply to the Editor:

Vaduganathan and Suissa raised 3 major concerns regarding our recent article.¹ We do not think immortal time bias was present in our study, but we agree with the possibility of confounding by contraindication and selection bias. Although analyzing clopidogrel treatment as a time-varying exposure can be useful, it does not resolve the fundamental issue that arises from the lack of information on the timing of the events. Thus, the causal effect of clopidogrel on ischemic and bleeding events would remain unidentified.

Their first concern was the possibility of immortal time bias if patients needed to have survived 2 days after surgery to be counted in the clopidogrel group. What we did not describe clearly in our article was that survival for at least 2 days after surgery was an eligibility criterion for all patients, irrespective of whether they received clopidogrel or not, since we believed that death in the first 24 to 48 hours after the operation would probably be

related to direct surgical complications rather than to subsequent aspirin or clopidogrel treatment. Therefore, we think that immortal time bias does not apply to our work.

A second concern was confounding by contraindication (or indication) if, for example, physicians were more likely to prescribe clopidogrel to patients who were at a high risk of perioperative ischemic events and less likely to prescribe clopidogrel to those who were at a high risk of bleeding events. This is a common problem with observational pharmacoepidemiologic studies, and we attempted to control for it by using propensity score analysis.² Nonetheless, we recognized it as a possibility in our own work (“it is possible that unmeasured factors might have influenced surgeons to prescribe clopidogrel to patients with lower perceived risk of bleeding,” p. 1382). As we discussed in our article, unavailability of detailed clinical data in the University HealthSystem Consortium database (“...transfusion requirement prior to or during operation, procedural characteristics, and postoperative chest tube output,” p. 1382) was a major limitation that prevented us from drawing any conclusive statement on whether the reduction of in-hospital mortality resulted from lower ischemic events or from lower bleeding events.

The third concern was the possibility of selection bias resulting owing to exclusion of patients who received clopidogrel more than 2 days after surgery. The scientific question that we were interested in was to compare the outcomes between early postoperative clopidogrel use versus aspirin-only treatment. We excluded patients who received clopidogrel after 2 days because clopidogrel might have been administered as a result of an ischemic event. If, in fact, these patients were to be included in the analysis, they should be considered as a downstream consequence of aspirin-only treatment (not clopidogrel). Such