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In Reply:

Thank you for your interest in our study assessing the association between withholding angiotensin receptor blockers (ARBs) in the early postoperative period and 30-day mortality after noncardiac surgery. We agree that the availability of intraoperative indicators would have been an asset to our study. However, due to the complexity of the data structures across the nation for anesthesia record keeping,[1,2] intraoperative vital signs are currently unavailable on a national level for research analysis within the Veterans Affairs healthcare system. There are numerous researchers throughout the Veterans Affairs, including the authors of this study, working to enable the analysis of nationwide intraoperative data for research. We look forward to improved modeling once this functionality becomes available. Despite this limitation, we have made our best efforts to adjust for early postoperative sequelae of potentially confounding intraoperative events, and we have accounted for major confounders such as hypotension and blood loss. Both immediate postoperative blood pressure (day of surgery) and blood pressure on postoperative day (POD) 1 are included in the models and are likely stronger determinants of ARB resumption than intraoperative blood pressure because medication resumption is often decided by surgeons or hospitalists on the basis of current status, without regard to previous intraoperative vital signs. Early postoperative creatinine and troponin increases are likewise included in our models and would reflect end-organ consequences of intraoperative hypoperfusion. Blood transfusions on POD 0 to 2 are also incorporated to adjust for significant perioperative bleeding.

With respect to our intentional exclusion of late postoperative complications from our models, we deliberately did not include complications that occurred after POD 2 because doing so would have resulted in adjusting for possible mediators, leaving us only with the direct effect rather than the total effect.[3] We were primarily interested in the total effect of the association between ARB withholding and 30-day postoperative mortality (*i.e.*, all-cause mortality), which composed of both the indirect effects (those mediated by measured postoperative complications) and the direct effects (those mediated by unmeasured factors). Thus, if any of the complications we measured were along the causal pathway to death, adjusting for them would have given us only the direct effect. Adjusting for mediators can be misleading because if we had measured all complications perfectly, we might have adjusted away the entire effect. We illustrate this with a simplified directed acyclic graph,[4] which is shown in figure 1. We do agree that early complications (POD 0 to 2) that occurred before the decision to resume ARB could certainly represent confounding by indication,[5] and thus, all were initially included in our models as potential confounders. However, due to predetermined model selection criteria, some were not incorporated into the final models. Early postoperative events that were included in the multivariable logistic regression model (on which the propensity score was generated) were increase in creatinine level; increase in troponin level; and new diagnoses of renal failure, sepsis, or cerebral ischemia on POD 0 to 1. We used the change-in-coefficient approach during Cox model selection, so some variables were not selected for inclusion in the model because their addition did not appreciably change the hazard ratio (by 5%); therefore, we do not believe a large degree of residual confounding resulted from their exclusion. Of course, we do mention in our limitations that the complications were often bundled with admissions, discharges, and procedures, and thus, the exact timing of complications compared with ARB restart was not always clear; thus, some residual confounding may still be present.

We hope that in our response we have addressed Dr. Xue's concerns and fully explained our rationale for dealing with the limitations posed by large administrative data sets.

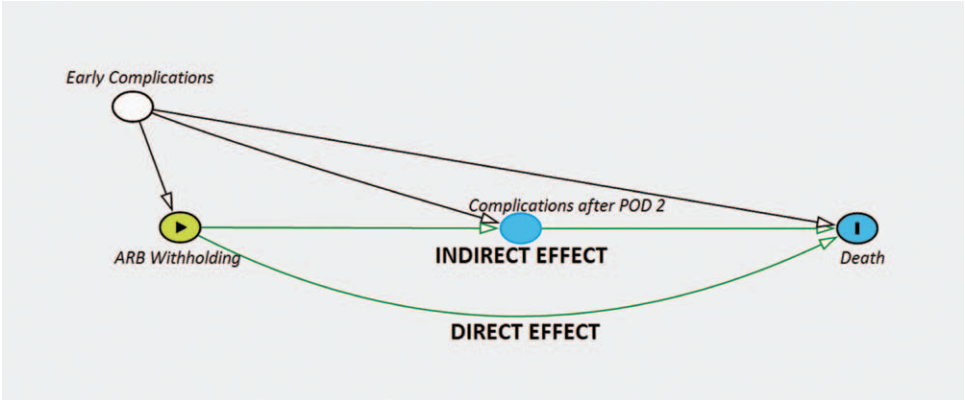

Fig. 1. In this directed acyclic graph, early complications are confounders, whereas late complications are mediators. Therefore, to determine the total effect of angiotensin receptor blocker (ARB) withholding, adjustment is only necessary for early complications. To determine the direct effect, that is, the effect of ARB withholding directly on death, without being causally mediated by complications, one would need to adjust for all complications (both early and after postoperative day [POD] 2). In our study, we were primarily interested in the association between ARB withholding and all-cause mortality (including deaths caused by complications after POD 2, which may have been due to ARB withholding). Therefore, we did not adjust for complications after POD 2, but we did adjust for early complications, which could have been a common reason for withholding ARBs and mortality.

Competing Interests

Dr. Takemoto receives consulting funds from the Durham Veterans Affairs Medical Center, Durham, North Carolina, and receives salary support from the Veterans Health Administration Office of Informatics and Analytics, Washington, D.C. Drs. Lee and Wallace are salaried anesthesiologists at the San Francisco Veterans Affairs Medical Center, San Francisco, California.

Susan M. Lee, M.D., F.R.C.P.C., M.A.S., Steven Takemoto, Ph.D., Arthur W. Wallace, M.D., Ph.D. University of California, San Francisco, San Francisco Veterans Affairs Medical Center, San Francisco, California (S.M.L.). susan.lee5@va.gov or suze.lee@utoronto.ca

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