Authors have nothing to disclose with regard to commercial support.

β -BLOCKERS IN AORTIC VALVE SURGERY: BETA SAFE THAN SORRY?

To the Editor:

We recently read with interest the article by Schubert and colleagues¹ on β -blocker use in patients undergoing aortic valve replacement surgery. This study is provocative and timely, given the increased emphasis on quality reporting in cardiac surgery and recent uncertainties about perioperative β -blocker use. In their analysis, Schubert and colleagues¹ found that patients taking β -blockers had increased risks of postoperative atrial fibrillation, allogeneic transfusion, and renal failure requiring dialysis. These findings should be interpreted cautiously for several reasons.

First, Schubert and colleagues¹ analyzed 19 study outcomes, which substantially increases the probability of a false-positive finding. When 20 statistical comparisons are made, the incidence of type 1 error, finding a significant difference that does not actually exist, is 64%.² Considering the study's findings from a Bayesian perspective, it is unlikely that preoperative β -blocker use actually increases postoperative atrial fibrillation.

Second, Schubert and colleagues¹ did not have data on β_1 selectivity. Because β -blockers have diverse pharmacology, categorizing them together almost certainly introduces bias. For example, nebivolol has 40:1 β_1 to β_2 selectivity, whereas carvedilol has 0.6:1.³ Drugs that have β_1 selectivity are associated with better perioperative outcomes, but they tend to be more expensive and less prescribed.⁴ Alternatively, blockade of β_2 receptors reduces renal blood flow and cerebral oxygen delivery, particularly in the setting of hemodilution.⁵ If a high percentage of patients in the study of Schubert and colleagues¹ received nonselective β -blockers, this could explain the study's outcomes; however, it may also limit its generalizability, because β -blocker prescribing practices change with time.

Finally, the Society of Thoracic Surgeons definition for preoperative β -blocker use is too narrow to draw

meaningful conclusions from a large, multicenter database. The Society of Thoracic Surgeons defines preoperative β -blocker use as receiving any β -blocker within 24 hours of surgery. There is no accounting for whether β -blocker use was long-standing or initiated just before surgery. This is important, because long-term β -blocker use is more likely to be beneficial in patients with severe aortic stenosis than a single dose of a β -blocker given just before surgery.

In summary, the study by Schubert and colleagues¹ highlights the need for more studies on β -blockers in cardiac surgery. It has significant limitations, however, which need to be considered before drawing general conclusions about β -blocker use in patients with aortic stenosis who require aortic valve replacement surgery.

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<https://doi.org/10.1016/j.jtcvs.2019.05.060>

REPLY: DO WE NEED TO BLOCK β -BLOCKERS IN AORTIC VALVE REPLACEMENT?

Reply to the Editor:

Preoperative β -blocker therapy has been used as a quality measure for patients undergoing coronary artery bypass grafting surgery to decrease postoperative mortality and adverse events. In 2013, LaPar and colleagues¹ questioned the use of β -blocker as a quality metric, after comparing the early outcomes after coronary

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Dr Rocha has nothing to disclose with regard to commercial support. Dr Tam is supported by a CIHR Fellowship, Canada. Dr Fremes is supported by the Bernard S. Goldman Chair in Cardiovascular Surgery Toronto, Ontario, Canada.

artery bypass grafting in patients with versus without preoperative β -blocker therapy. No differences in mortality, morbidity, or length of stay were observed between groups. On the basis of the lack of early β -blockade benefit in coronary artery bypass grafting cases, Schubert and associates² evaluated the role of β -blocker therapy in patients requiring surgical aortic valve replacement (SAVR), in which its potential benefit was less certain. They compared the short-term outcomes of 4592 propensity score-matched patients undergoing isolated SAVR with versus without preoperative β -blockade, from 18 cardiac surgery centers across the Commonwealth of Virginia during a period of 14 years.² In their comparison, preoperative β -blocker use was associated with increased rates of postoperative renal failure requiring dialysis, transfusion, atrial fibrillation, and cardiac arrest, and with a longer intensive care unit stay. The investigators concluded that β -blocking agents should not be used as a quality metric in SAVR.

In their letter to the Editor, Mazzeffi and colleagues³ appropriately highlight their concerns with the conclusions of the study of Schubert and colleagues.² Limitations of administrative database studies include data granularity and, in this case, a paucity of information regarding the duration, indication, dosage, and type of β -blocker therapy. Mazzeffi and colleagues³ have highlighted the differences in pharmacology related to different β -blockers, which may have an important effect on outcome. Importantly, the retrospective nature of the data inevitably introduces confounding into the analysis. Despite the use of propensity score matching to balance multiple preoperative variables, there may still be residual unmeasured confounders in the results after matching. For instance, the longer aortic crossclamp time in the group of patients receiving β -blockers, despite similar incidence of aortic annular enlargement, suggests that the procedures in this group may have been more complex. Increased cardiopulmonary bypass time has been shown to be an independent risk factor for postoperative complications, such as renal failure requiring dialysis and transfusion.^{4,5} Moreover, the higher rate of postoperative atrial fibrillation, despite β -blockade, may likely reflect a potentially sicker group of patients. Echocardiographic data, on risk factors for atrial fibrillation, such as left ventricular or atrial dimensions, were not available.⁶

After propensity score matching, 19 comparisons were performed, which poses a risk for multiplicity and type I error. Common strategies to address multiplicity are the Bonferroni correction or false discovery rate. These techniques could have been considered when performing such a high number of comparisons. Nevertheless, this hypothesis-generating study adds important data to the cardiac surgery literature and sets the stage for a randomized, controlled trial, which may properly address the question of whether patients undergoing SAVR should receive preoperative β -blockers.

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<https://doi.org/10.1016/j.jtcvs.2019.05.076>

REPLY: BETA-BLOCKER HOUSE REVISITED!

Reply to the Editor:

Mazzeffi and Evans¹ raise several red flags regarding the conclusions offered by Schubert and colleagues.²

As I mentioned in my own comment,³ the duration and selectivity of the preoperative beta-blocker were not documented. The percentage of patients receiving preoperative beta-blocker therapy solely as a quality metric was also not noted. It is likely that a majority of patients received nonselective beta-blockers, a factor that