**REPLY FROM THE
AUTHORS: BIG DATA
AND BETA BLOCKERS:
THE BEST OF TIMES,
THE WORST OF TIMES**

Reply to the Editor:

We are pleased to see an exciting debate unfold regarding our recent manuscript examining the potential risks of beta-blocker administration before surgical aortic valve replacement.¹ A number of potential concerns were brought up regarding the conclusions. Welcome to the world of big data! Only the data available can be analyzed and unfortunately the Society of Thoracic Surgeons (STS) is simultaneously criticized for collecting too many variables or not enough. As all commentators and our limitations section note, the beta-blocker type, dose, and duration were not available.²⁻⁷ As Mazzeffi and colleagues⁴ correctly point out, there is large variability in beta selectivity among the different agents. We can only make assumptions, and a reasonable one would be that prescribing practices mirror the general population, for whom the majority receive nonselective agents. Future studies with data not collected in the current STS database will be needed to ensure generalizable conclusions.

The next concern is whether the beta-blocker cohort is simply a sicker group of patients with expected greater rates of complications.^{2,3,6,7} The propensity matching was able to define a remarkably homogenous and similar group of patients. The STS-predicted risk of mortality was exactly 2.1% in both matched groups. We believe the concerns about coronary artery disease, previous coronary artery bypass grafting, dialysis, and cerebral vascular accidents to be incremental differences. Both univariate comparisons and standardized mean differences (SMDs) suggest all of these factors were well balanced between groups ($P > .05$ and $SMD < 0.1$). Even variables that were different by univariate analysis due to sample size were actually well balanced: body mass index $SMD = 0.03$, preoperative lipid-lowering agent $SMD = 0.09$, and crossclamp time $SMD = 0.09$. Finally, the results did not change when adjusted for body mass index and lipid-lowering agent use (Table 1).

The final major concern raised was the possibility of a type I error due to number of analyses.^{4,5} Ioannidis⁸ has given the research community great reason to view all retrospective studies with a healthy degree of skepticism. Although it is true that there is a 64% false-positive rate for every 20 tests performed, this is based on a .05 P -value threshold. The commenter's own citation warns against simple corrections for multiple comparisons.^{4,9} This is precisely why *The Journal* requires transparency in reporting data. It is up to the reader to incorporate the P value, effect sizes, and confidence intervals into a clinically meaningful conclusion. Although retrospective

TABLE 1. Sensitivity analyses adjusting outcomes of interest for BMI and lipid-lowering agent use

Effect	Point estimate (95% Wald confidence limits)
Odds ratio estimates for cardiac arrest	
preop_BB 0 vs 1	0.557 (0.326-0.95)
preop_lipid_lowering 0 vs 1	0.907 (0.543-1.517)
BMI	1.002 (0.986-1.018)
Odds ratio estimates for atrial fibrillation	
preop_BB 0 vs 1	0.815 (0.69-0.962)
preop_lipid_lowering 0 vs 1	0.954 (0.807-1.126)
BMI	1.002 (0.996-1.008)
Odds ratio estimates for dialysis-dependent renal failure	
preop_BB 0 vs 1	0.48 (0.263-0.876)
preop_lipid_lowering 0 vs 1	0.835 (0.472-1.476)
BMI	1.012 (1.004-1.019)
Odds ratio estimates for any blood transfusion	
preop_BB 0 vs 1	0.823 (0.709-0.955)
preop_lipid_lowering 0 vs 1	1.096 (0.944-1.271)
BMI	0.969 (0.958-0.98)
Odds ratio estimates for RBC transfusion	
preop_BB 0 vs 1	0.817 (0.701-0.953)
preop_lipid_lowering 0 vs 1	1.116 (0.957-1.302)
BMI	0.968 (0.956-0.98)

Variable	Parameter estimate	Standard error	Pr > t
Parameter estimates for postoperative LOS			
Intercept	6.53548	0.36327	<.0001
preop_BB	0.40707	0.24961	.103
preop_lipid_lowering	-0.046	0.25037	.8543
BMI	0.02616	0.00971	.0071
Parameter estimates for ICU hours			
Intercept	54.45809	7.17001	<.0001
preop_BB	9.94151	4.95372	.0449
preop_lipid_lowering	-1.98622	4.96931	.6894
BMI	0.58455	0.19042	.0022

BB, Beta-blocker; BMI, body mass index; RBC, red blood cell; LOS, length of stay; ICU, intensive care unit.

in nature, the data were rigorously analyzed with clinically meaningful effect sizes that were robust across multiple sensitivity analyses. To summarize, thoughtfulness and caution are warranted before the rote administration of beta blockers before an isolated aortic valve replacement.

Robert B. Hawkins, MD, MSc

Gorav Ailawadi, MD, MBA

Division of Thoracic and Cardiovascular Surgery

University of Virginia

Charlottesville, Va

Dr Ailawadi discloses consulting fees from Edwards Lifesciences, Medtronic, Abbott Laboratories, Admedus, W. L. Gore & Associates, Inc, and Cephea Valve Technologies, Inc. Dr Hawkins has nothing to disclose with regard to commercial support.

References

1. Schubert SA, Hawkins RB, Mehaffey JH, Fonner CE, Rich JB, Speir AM, et al. Preoperative beta-blocker use correlates with worse outcomes in patients undergoing aortic valve replacement. *J Thorac Cardiovasc Surg.* 2019;158:1589-97.
2. Baciewicz FA Jr. Commentary: All members of beta-blocker house on probation! *J Thorac Cardiovasc Surg.* 2019;158:1598-9.
3. Levy G, Conti VR. Commentary: Preoperative beta-blockers; One size does not fit all when considering management. *J Thorac Cardiovasc Surg.* 2019;158:1600-1.
4. Mazzeffi MA, Evans CF. Beta-blockers in aortic valve surgery: beta safe than sorry? *J Thorac Cardiovasc Surg.* 2020;159:e42-3.
5. Conti V, Levy G. Beta or worse: more work needed to determine benefit or harm in aortic valve surgery. *J Thorac Cardiovasc Surg.* 2020;159:e43.
6. Rocha RV, Tam DY, Fremes SE. Do we need to block beta-blockers in aortic valve replacement? *J Thorac Cardiovasc Surg.* 2020;159:e41-2.
7. Baciewicz FA Jr. Beta-blocker house revisited! *J Thorac Cardiovasc Surg.* 2020;159:e42-3.
8. Ioannidis JP. Why most published research findings are false. *PLoS Med.* 2005;2:e124.
9. Althouse AD. Adjust for multiple comparisons? It's not that simple. *Ann Thorac Surg.* 2016;101:1644-5.

<https://doi.org/10.1016/j.jtcvs.2019.07.129>