The author reported no conflicts of interest.

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compared with TAVR in terms of 30-day mortality, permanent pacemaker implantation, infections, vascular complications, paravalvular leakage, stroke, and 5-year survival. Although it must be acknowledged that, by using the propensity score method, the authors have excluded approximately 40% of the study population from the matched population, hence assuming that a significant number of sicker patients in both groups were excluded from the analysis, it also must be recognized that in the matched population, the early and late results in the 2 groups were clear enough to demonstrate, on the basis of the authors' experience, a greater efficacy of SuAVR compared with TAVR in the intermediate-risk population.

To my knowledge, no clinical study, either randomized or observational, can be considered perfect. Obviously, the rigorous application of statistical methodology increases the quality of any study by avoiding conflicting interpretations of the results obtained. From this standpoint, observational studies are weaker than randomized studies, but many observational studies (like this one) can report important and useful data and results for daily clinical practice.

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REPLY: "TRUTH" IN RESEARCH—THE ROAD TO TRUTH IS PAVED WITH DOUBT

Reply to the Editor:

In this issue of the *Journal*, Tam and colleagues¹ present a critique of the recently published observational study

by Muneretto and colleagues² comparing sutureless aortic valve replacement with transcatheter aortic valve replacement (TAVR) in patients at intermediate surgical risk. Tam and colleagues present several arguments to support their conclusion that despite appropriate propensity-score matching, residual confounding is likely to explain differences in treatment-related end points presented in the aforementioned analysis.

It is always possible, in observational studies, that residual confounding may explain difference in treatment effect when comparing 2 groups of patients. Conversely, the beauty of appropriately powered and executed, prospective enrollment with randomization is that it accounts, by design, for both measured and unmeasured sources of bias.³ The major disadvantage of randomized controlled trials is the lack of generalizability of results to populations excluded by design. For these reasons, both prospective registry and prospective randomized designs are essential to establish our evidence base in cardiac surgery.

Within the constraints of the dataset of the analysis in question, the propensity score-matched analysis resulted in a comparison of 291 matched pairs from a total of 967 available patients. The ability to match only 60% of the original cohort should be our first indication that the 2 groups being compared were quite different at the outset. The matched pairs appear well balanced on the available covariates (standardized mean difference <0.1 for all variables except insulin-dependent diabetes). Of note, surrogates of frailty such as a 5-meter walk test result >7 seconds and serum albumin <3.5 g/dL were included in the model—2 variables also reported in the PARTNER (Placement of Aortic Transcatheter Valves) II trial.⁴

Even with an appropriate propensity-score match, Tam and colleagues¹ are correct in asserting that unmeasured confounding may remain to explain the differences in outcomes between the 2 treatments. Two of the additional tools described—falsification end points and instrumental variables—are methods that can help identify residual confounding but usually require a priori knowledge of possible imbalance. In prospectively collected databases, such as the aforementioned one analyzed—the additional variables required to perform these types of analyses are rarely collected. In longitudinal, electronic medical record-based datasets, these approaches are more feasible, but practically, hard to execute.

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Tam and colleagues¹ compare and contrast the findings of the aforementioned analysis to those of the PARTNER II randomized controlled trial. However, there are key differences in the populations studied in these 2 patient cohorts. The 5-year all-cause mortality in PARTNER II was 42.1% for surgical replacement and 46.0% for TAVR (hazard ratio, 1.09; 95% confidence interval, 0.95-1.25), yet in the aforementioned study, 5-year all-cause mortality was 16.1% for surgical replacement and 28.9% for TAVR ($P = .007$) with 100% complete 5-year follow-up in both studies. The average age in PARTNER II was 81.6 years and STS risk 5.8% compared with 80.5 years and 6% in the study by Muneretto and colleagues, making these differences in event rates difficult to reconcile. One explanation may be the greater average life expectancy in the countries in the study, ie, Italy (83.6 years), France (82.5 years), and Germany (81.2 years), compared with an average life expectancy of 78.9 years in the United States.⁵ In addition, the rate of previous coronary artery bypass grafting was 24.6% in PARTNER II and 4.3% in Muneretto and colleagues, signifying different patient populations, not directly comparable. There may be more to all-cause mortality in this age range than meets the eye.

Regardless of differences in patient cohorts, the overall 30-day mortality of 5.5% in the matched TAVR patients, along with 11-day mean length of stay, 1.7% tracheostomy rate, 7.9% vascular complication rate, are all quite high and likely due to the fact that only 66.2% of TAVRs were implanted via transfemoral approach for anatomic reasons.² Newer-generation TAVR devices have brought smaller sheath sizes enabling transfemoral approach for most patients, and technical expertise has improved, leading to much lower procedural complication rates in the most recent low-risk trials.

Context is critical in the interpretation of study results. Tam and colleagues have brought important additional insight into the discussion of the aforementioned results, and their thoughtful appraisal of the manuscript is undoubtedly appreciated by the readership of the *Journal*.

Truth be told, no design or methodology is perfect—and we, as surgeon–scientists, should always be cautious to accept “truths” or “certainty,” regardless of the old adage:

“a surgeon may be sometimes wrong, but never in doubt.”
As scientists, we must always be in doubt.

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**REPLY FROM
AUTHORS: THE TRUTH
LIES:
TRANSCATHETER
AORTIC VALVE
IMPLANTATION
TRIALS ON PATIENTS
AT INTERMEDIATE
RISK
Reply to the Editor:**

We read with great interest the commentary of Tam and colleagues¹ and we appreciate the opportunity to discuss it. Our study² gave a new perspective about the comparison between surgery and transcatheter valve, analyzing the impact of the new technologies of sutureless valves on the outcome of patients with aortic stenosis with an intermediate- to high-risk profile. Tam and colleagues pointed out some criticism in terms of study design, concluding that propensity match observational studies cannot replace randomized controlled trials (RCTs).¹

Theoretically we agree about the role of RCTs, but we must point out that RCTs can themselves introduce several biases. The weakest point of any RCT may be the selection biases at the entry point of the study. Sponsored RCTs on transcatheter aortic valve implantation (TAVI) enroll only a small percentage (2%-8%) of patients treated either by TAVI or surgical aortic valve replacement (SAVR), leading to several selection biases. Specific risk factors for surgery (redo operation, patent internal mammary graft, chronic