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REPLY: OBSERVATIONAL STUDIES VERSUS RANDOMIZED CONTROL TRIALS: A BIG MATCH!

Reply to the Editor:

I read with great interest the letter by Tam and colleagues¹ regarding the application of the statistical methodol-

ogy in propensity score matching studies such as in the recent study by Muneretto and colleagues.² Tam and colleagues correctly raised an important statistical issue inherent in many retrospective clinical trials. They pointed out that in several clinical studies, the confounding variables could lead to improper results owing to inadequate selection of the confounding variables. In particular, Tam and colleagues deeply criticized some aspects of the study of Muneretto and colleagues, stating that the use of propensity score matching was inadequate, for several reasons. According to their criticism, the patient selection period (2008-2015) was improper, because transcatheter aortic valve replacement (TAVR) was not commonly used in patients at intermediate risk, all the patients included in the study were age >75 years, and more than one-quarter of the matched patients had a Society of Thoracic Surgeons Predicted Risk of Mortality <4%. In addition, the 5-year relative mortality rate was 15% in the sutureless aortic valve replacement (SuAVR) patients, compared with 23% in the TAVR patients (relative risk, 1.5). Tam and colleagues doubted that the TAVR patients were sicker than the SuAVR patients, however.

Randomized controlled trials (RCTs) represent the cornerstone when comparing 2 treatments; however, RCTs are somewhat affected by inclusion and exclusion criteria, which are sometimes very rigid, so that such patients recruited in RCTs do not always reflect daily clinical practice. In contrast, retrospective studies allow analysis of the clinical results coming from “real-life” data, but such studies are affected by an excessive number of confounding variables and bias. That said, Tam and colleagues’ statements and criticisms about Muneretto and colleagues’ study are very shareable, as are the suggestions regarding the application of even more effective statistical methods than propensity score matching when adjusting for confounding.

In a recent Commentary published in the *Journal*,³ I highlighted that the patients included in this study had a lower incidence of preoperative risk factors compared with the PARTNER-2⁴ and SUR-TAVI⁵ trials, and I stated that it can be assumed the heart team followed a careful patient selection process to address the patients either to SuAVR or TAVR.

However, we cannot absolutely deny that the clinical results reported by Muneretto and colleagues demonstrate better efficacy and safety for conventional surgery

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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.