Dr Muneretto reported consultant for LivaNova. Dr Di Bacco reported no conflicts of interest.

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REPLY: 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 colleagues[1] and we appreciate the opportuinity to discuss it. Our study[2] 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 obstructive pulmonary disease, etc) may be overexpressed in a "selected" study population, while unfavorable characteristics for TAVI (extent of calcification, the heart valve–vessel anatomy) may be underexpressed. Once the patient is enrolled in the study, subsequent randomization cannot reverse these selection biases, which affect the entire population. These biases may obviously deeply affect the study results and reliability of the conclusion. To date, important RCTs supported from transcatheter valves manufacturers, showed the noninferiority of TAVI when compared with surgery in patients at intermediate risk.[3,4] Moreover, those trials reported an unusually high rate of strokes in the surgical population (30-day outcome: 5.6% SURTAVI, 6.1% PARTNER II). However, major international registries, which collect hundred thousands of patients (Society of Thoracic Surgeons, GARY Registries), report an incidence of stroke significantly lower in the same subset population (GARY Registry 1.0% stroke rate[5]). Furthermore, Brennan and colleagues[6] analyzed data from the Transcatheter Therapy Registry and the Society of Thoracic Surgeons Registry (9464 propensity-matched patients with intermediate-high risk) and found that TAVR and SAVR resulted in an identical rate of stroke at 30 days (2.8%). The "uncommon" high incidence of stroke in the surgical group may have affected the reliability of SURTAVI and PARTNER II results.

Patients included in the surgical cohort of the aforementioned trials had several and specific risk factors such as previous coronary artery bypass grafting (PARTNER II 25%) and major associated surgical procedure (9.1%). The impact of these risk factors in the surgical group have not been adequately taken into consideration.[3] Particularly, patients undergoing reoperation for SAVR with a patent mammary artery have a very high surgical risk (surgical mortality, range: 4% - 16%). In addition, the high rate of patients with previous CABG enrolled in those trials does not reflect the standard worldwide population undergoing SAVR.[5,7]

Finally, there are several warnings about the negative impact of permanent pacemaker implant on survival and new hospitalization rate.[8,9] Only in the PARTNER I a dedicated analysis on this topic was performed,[10] but there is a lack of data from PARTNER II and SURTAVI trials on patients at intermediate risk over 2 years' follow-up.

The impact on the patient outcome of conduction disturbances and aortic regurgitation after TAVI needs to be better investigated at long term, before jumping to any conclusions.

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