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EDITORIAL COMMENT

Prosthesis-Patient Mismatch After "High-Risk" Aortic Valve Replacement*

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Since the initial description of prosthesis-patient mismatch (PPM) more than 3 decades ago (1), the clinical import of PPM after surgical aortic valve replacement (SAVR) has been debated in the surgical published data. The phenotypic manifestation of PPM is an elevated aortic valve gradient after valve implantation. Although a number of indices have been used to characterize the frequency of PPM after valve replacement, the most common parameter used to describe its magnitude is the effective orifice area index (EOAi), which accounts for the body surface area (BSA) and, presumptively, the cardiac output. PPM is defined as moderate when the EOAi is $\leq$0.85 cm^2/m^2 but $\geq$0.65 cm^2/m^2, and severe when the EOAi is $<$0.65 cm^2/m^2.

PPM has been associated with higher early (2-5) and late mortality (4,6-10) after aortic valve surgery. In a meta-analysis comprising 34 studies that included 27,186 patients and 133,141 patient-years, both moderate and severe PPM increased all-cause mortality (hazard ratio: 1.19 and 1.84, respectively) and cardiac-related mortality (hazard ratio: 1.32 and 6.46, respectively); these relationships were consistent over time (11). The impact of PPM on late mortality may be influenced by the presence of older age, left ventricular (LV) dysfunction, New York Heart Association functional class III or IV symptoms, and concomitant coronary artery bypass grafting (12,13).

PPM has been associated with a number of other untoward outcomes, including longer time in the intensive care unit (3); a reduction in functional improvement and exercise capacity (14,15); less regression of LV mass after valve surgery (16,17), particularly in patients with LV hypertrophy (18); increased neurologic events (19); and more late structural valve deterioration (20). PPM may have an even more profound impact on outcomes in patients with low gradient aortic stenosis (21,22). PPM was independently associated with increased rates of congestive heart failure, impaired LV mass regression, and a trend toward increased late mortality in patients with low gradient aortic stenosis (22).

Transcatheter aortic valve replacement (TAVR) has provided another option for reducing PPM in patients undergoing aortic valve replacement because of the lower profile of the transcatheter valve without a sewing ring (23). A matched analysis of patients with aortic stenosis compared 50 patients treated using a balloon-expandable transcatheter valve with 2 groups of 50 patients who underwent surgery with a stented valve (Edwards Perimount Magna, Edwards Lifesciences Corp., Irvine, California) or a stentless valve (Medtronic Freestyle, Medtronic Inc., Minneapolis, Minnesota) (23). The mean transprosthetic gradient at discharge was lower in the TAVR group (10 $\pm$ 4 mm Hg) compared with the stented (13 $\pm$ 5 mm Hg) and stentless (14 $\pm$ 6 mm Hg) surgical groups. The incidence of severe PPM was significantly lower in the TAVR group (6%) than in the stented (28%) or stentless (20%) surgical groups, albeit with a higher rate of moderate paravalvular regurgitation with TAVR (8%) than surgery (0%) (23).

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In this issue of the *Journal*, Pibarot et al. (24) report the impact of PPM on late outcomes in 699 patients at "high risk" for surgery who were randomized to

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surgery or TAVR in the PARTNER (Placement of AoRTic TraNscathetER Valves) trial. Patients in the TAVR group were exclusively treated with the balloon-expandable Edwards SAPIEN bioprosthesis using transfemoral or transapical access. Approximately 90% of patients in the surgical group were treated with an Edwards bovine bioprosthetic valve by protocol; only 2 patients also underwent a root enlargement procedure (24). Echocardiograms 7 to 30 days after aortic valve replacement were reviewed at an independent core laboratory using echocardiographic criteria for determining PPM, which is the preferred method compared with in vitro measurements or calculated orifice area from standardized tables (6,25).

There are a number of important findings from this well-executed analysis. First, the frequencies of moderate and severe PPM were lower after TAVR (26.6% and 19.7%, respectively) than after SAVR (31.9% and 28.1%, respectively) (24), although severe PPM with TAVR was seen more often than in prior registry analyses (6%) (23). The differences in severe PPM between the TAVR and SAVR cohorts were accentuated in those patients with echocardiographically determined annular diameters <20 mm, and the rate of PPM was lower in patients who underwent balloon post-deployment dilation, likely because of further expansion of the transcatheter valve. It is not clear whether the higher frequency of severe PPM after TAVR was related to the use of smaller valve sizes, the independent echocardiographic core laboratory readings, or the large BSA of patients enrolled in the current study.

Likewise, the 60% frequency of moderate or severe PPM in the SAVR group in this series was also slightly higher than the 44.2% aggregate frequency of moderate or severe PPM in a large meta-analysis (11). These higher rates may be attributable to the restricted annular sizing (18 to 25 mm) in the study protocol, although one also wonders whether the near exclusive (90%) use of a stented bovine pericardial valve may have influenced these higher rates of PPM; surgeons may not have been free to use "best practice" surgical techniques that would lower the rate of PPM, including the next generation of stented (26) and stentless (27) surgical valves. In addition, given the relationship between small (19 and 21 mm) surgical valve diameters, PPM in larger patients, and untoward clinical outcomes (28–30), one would also ask whether adjunct surgical root enlargement techniques would have allowed the use of larger surgical valves and less PPM had they been permitted by the protocol (31–33).

The second notable finding of this study is the relationship involving post-operative PPM, 2-year mortality, and LV mass regression. The authors suggest that the higher mortality rate may be attributable to residual LV afterload and failure to normalize coronary flow reserve after surgery, a plausible rationale. It is less clear why a similar effect of PPM on late mortality was not observed in the TAVR group, and the authors have suggested several cogent reasons. However, in contrast to the current findings, an analysis of 165 patients undergoing TAVR, of whom 18.2% patients showed PPM before hospital discharge, found that patients with PPM had limited LV mass regression and left atrial volume reduction over 6 months compared with patients without PPM (34). Of note, a higher proportion of patients with PPM did not have improved New York Heart Association functional class compared with patients without PPM (36.7% vs. 1.5%; $p < 0.001$). PPM may be a particularly challenging issue for TAVR in patients with bioprosthetic valve failure (35).

We find it interesting that the BSA, body mass index, and frequency of obesity were all higher in the patients with PPM in the TAVR group in the current study. A systematic review of the Society of Thoracic Surgeons National Cardiac Database that included 42,310 patients found that although effective orifice area and geometric orifice area were both inversely correlated with operative mortality, BSA was significantly and inversely correlated with operative mortality (36). When patients were stratified by effective orifice area, geometric orifice area, or manufacturer's labeled valve size and type, BSA elevations were associated with a decrease rather than an increase in operative mortality (36). In the current study, the offsetting reduction in mortality with increased body weight in patients with PPM and residual moderate-severe aortic regurgitation adversely affecting outcomes in patients without PPM may have contributed to the absence of an association between PPM and late mortality in the patients undergoing TAVR (37,38). This is supported by the larger nonrandomized Continued Access Registry analysis in which a relationship was shown between PPM and 1-year mortality in patients without confounding post-procedural regurgitation (24). One could conclude from these analyses that PPM is also an important predictor of late mortality in patients undergoing TAVR, particularly in the absence of post-procedural paravalvular regurgitation.

Finally, the clinical implications from this study suggest that the untoward effects of PPM after surgery in patients with a smaller aortic annulus are offset by more frequent moderate-severe

paravalvular regurgitation after TAVR, resulting in similar 2-year mortality rates in the 2 groups (37). Efforts to reduce paravalvular regurgitation after TAVR with next-generation devices and improved valve sizing and implantation techniques may tip this mortality balance more favorably toward TAVR. Likewise, advanced surgical methods and next-generation surgical valves may lessen the frequency of PPM in high-risk patients undergoing SAVR. Efforts should continue to minimize PPM for both patients treated with SAVR and TAVR, because it is likely that severe PPM will be associated with a continued risk irrespective of which technique is used for aortic valve replacement.

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