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EDITORIAL COMMENT

Additional Perspectives on the Prognostic Significance of Tricuspid Regurgitation

More Lessons From the Study of Patients With Low-Flow Aortic Stenosis*

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Collective appreciation of low-flow, low-gradient (LF-LG) aortic stenosis (AS) has increased significantly in recent times. Clinical practice guidelines (1,2) provide concordant recommendations for the evaluation and treatment of patients with LF-LG AS with either low left ventricular (LV) ejection fraction (EF) or normal LV EF. Patients with LF-LG AS constitute an increasing percentage of patients currently seen in multidisciplinary heart valve centers, and they pose challenging management issues that relate to the accuracy of the assessment of flow, AS severity, and LV function. Observational studies have consistently reported reduced survival for patients with low- compared with normal-flow AS and for patients with low-flow AS managed conservatively compared with those receiving aortic valve replacement (AVR) (3,4). Transcatheter aortic valve replacement (TAVR) is often preferred over surgical AVR for such patients, but the decision-making process is complex and must be individualized. Because survival and functional outcomes for patients with low-flow AS are compromised, improved methods of risk stratification are needed to target therapies more effectively.

In this issue of *JACC: Cardiovascular Interventions*, Dahou et al. (5) add to the many observations their group has made regarding the presentation, natural history, evaluation, management, and outcomes of patients with severe LF-LG AS. Among 211 patients with severe LF-LG AS and low EF prospectively enrolled in the TOPAS (True or Pseudo-severe Aortic Stenosis) study, the presence of more than mild, functional tricuspid regurgitation (TR) was independently associated with all-cause and cardiovascular mortality over a mean follow-up of 2.4 years. Increasing degrees of TR were associated with higher mortality risk, even after multivariable adjustment.

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Patients with more than moderate TR had lower 30-day survival following AVR than those with lesser degrees of TR. Whether more than mild TR should be routinely addressed at the time of surgical AVR in such high-risk patients cannot be answered by this study. Surgical practice has already moved aggressively toward tricuspid valve repair at the time of left-sided valve surgery for mild or greater degrees of TR, particularly in the setting of tricuspid annular dilation (>40 mm) (1,2,6,7). Transcatheter treatment of functional TR at the time of TAVR is not currently available. Alternatively, whether moderate or greater degrees of TR should be considered a relative contraindication to aortic valve intervention deserves further scrutiny and debate. It seems doubtful that patients would be excluded from AVR on this basis alone. Randomized controlled trials to answer these questions, however, would be significantly challenged by a lack of equipoise among both surgeons and cardiologists.

It is not intuitively obvious how functional TR independently contributes to the excess mortality risk observed in patients with severe LF-LG AS and low EF. As the authors note (5), their study was limited by the relatively small number of patients, the

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confounding effects of unmeasured variables, the difficulties inherent in assessing TR severity, and the lack of more precise, quantitative information regarding right ventricular function. A single-center study of 518 TAVR patients reported a 15% prevalence of moderate or severe TR (8). The fate of TR following TAVR was extremely variable and could not be predicted beforehand. Significant TR was significantly associated with 2-year mortality only in a subgroup of patients with EF >0.40. Hutter et al. (9) reported that ≥ moderate TR was not an independent predictor of 1-year all-cause mortality among 29 TAVR patients. In contrast, among 553 patients in the inoperable cohort of the PARTNER (Placement of Aortic Transcatheter Valves) II trial, moderate/severe TR was significantly associated with 1-year all-cause mortality, whereas qualitatively-assessed right ventricular dysfunction was not (10). The effect of TR on survival was not assessed in a PARTNER trial analysis of the predictors of mortality and outcome in 530 inoperable or high-risk patients with low-flow severe AS (4).

The adverse effects of TR on long-term outcomes have been reported for other patient cohorts. In a study of 5,223 Veterans Affairs patients followed over 4 years, increasing TR severity was independently associated with worse survival (11). The presence of any degree of TR was independently associated with reduced long-term survival among 117 patients with ischemic or dilated cardiomyopathy referred for transplant evaluation (12). Similarly, severe TR was identified as an independent predictor of mortality among 1,421 patients with LV EF ≤0.35 (13). A subgroup analysis from a study of 576 heart failure patients showed that moderate or severe TR was linked to worse survival among patients with mild or moderate LV systolic dysfunction, but not for patients with severely depressed LV systolic function or with elevated amino-terminal brain natriuretic peptide levels (14).

It is now more apparent that functional TR is not as innocuous as previously assumed. Further study is clearly needed to unravel the mechanism(s) by which TR worsens survival and to verify the preliminary observations made in these several, methodologically-limited studies regarding its independent contribution to outcomes in various patient cohorts. Our surgical colleagues have been aware for many years of the adverse long-term consequences of not addressing functional TR at the time of left-sided valve surgery, related in part to the high morbidity and mortality risks associated with reoperative tricuspid valve surgery. It may be fair to say that the tricuspid valve is no longer the "forgotten valve." Accurate and quantitative assessment of its function, as well as that of the supporting right ventricle, with whose fate it is intertwined, remains a challenge that may complicate the design and execution of interventional trials with hard clinical endpoints. Dahou et al. (5) rightfully question whether functional TR is a risk marker or risk factor for mortality in patients with LF-LG AS and low EF. The same question could be posed for patients with other types of heart disease and functional TR. It is hoped that this resurgent respect for TR will spur additional investigations to help establish best practices for risk assessment and treatment.

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