

Aortic Regurgitation After Transcatheter Aortic Valve Replacement: Is it a Fall from Grace or Just a Storm in a Teacup?

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A decade of great enthusiasm has emerged after the first-in-man, successful transcatheter aortic valve replacement (TAVR) report in 2002. Subsequently, the results of the pivotal randomized Placement of AoRTic TraNscathetER (PARTNER) trial were instrumental for the TAVR approval as the standard of care for symptomatic inoperable aortic stenosis.¹ This 10-year successful history had major drawbacks that were mostly related to the procedure and overcome, in part, by technique and device refinements. Although the short-term outcomes have improved (< 10%), the long-term mortality post-TAVR has not changed over time.²⁻⁵ Moreover, the high incidence and the association of post-TAVR aortic regurgitation with mortality have been raising concerns.^{6,7} However important methodological considerations across these studies hamper the understanding of whether this phenomenon represents a “fall from grace” or just a “storm in a teacup”.

See page 103

The reported incidence of aortic regurgitation post-TAVR ranges from 50% to 85% and derives mostly from echocardiographic data.⁸ The aortic regurgitation can be either central or paravalvular (leak) in origin and graded according to quantitative or semi-quantitative parameters. But none of these methods were prospectively validated nor consensually standardized by the Valve Academic Research Consortium.⁹ Acknowledging these limitations, apparently more than mild aortic regurgitation post-TAVR has been associated with worse long-term outcomes in different studies with a pooled hazard ratio of 2.27 [95% confidence interval (95%CI): 1.84-2.81] at 1 year.⁷ Nonetheless, the most intriguing data came from PARTNER trial (Cohort A) where even mild

aortic regurgitation post-TAVR was related to a higher mortality and a real gradient effect was demonstrated.⁶

The manuscript published by Lluberas et al.¹⁰ in this issue of **Revista Brasileira de Cardiologia Invasiva** adds important post-TAVR paravalvular aortic regurgitation data based upon a retrospective analysis of 112 (68.8%) symptomatic aortic stenosis patients treated with Medtronic CoreValve[®] (Medtronic, Minneapolis, USA) device, mostly at a single pioneer center in Brazil. The authors reported a frequency of 56% of post-procedural paravalvular aortic regurgitation. Of these, 41% were mild and 11.6% moderate. No severe paravalvular aortic regurgitation was noted. This incidence is similar to the literature but in the lower range for the CoreValve[®] studies (9% to 21%).¹¹ The incidence of moderate or severe paravalvular aortic regurgitation interesting finding may be related to a more liberal use of balloon post-dilatation (34%). Although underpowered for clinical end-points, no mortality difference was observed at one-year follow-up comparing the moderate paravalvular aortic regurgitation to mild or no aortic regurgitation (7.7% vs. 8.1%, respectively; P = NS).

This finding highlights the conflicting evidence surrounding the post-TAVR aortic regurgitation mortality association. Numerous studies have shown the association of aortic regurgitation post-TAVR and mortality but important analytical and methodological considerations such as the proportional hazard function, the survivorship bias, the lack of standardized definition criteria, the timing and inherent limitations of echocardiographic evaluation and the limited data provided by independent echo core lab diminish the strength of this association. All together, these considerations mitigate the establishment of a direct causal relationship. In other

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Received on: 6/4/2013 • Accepted on: 6/5/2013

words, the link between post-TAVR aortic regurgitation and mortality can be mediated or moderated by either measured or unmeasured confounders and thus is far from being closed. In this arguing line, Lluberas et al.¹⁰ provide a further insight into the theme by modeling the baseline determinants of paravalvular aortic regurgitation post-TAVR. But, the limited event number ($n = 13$) most likely over-fitted the model and the estimates. Interestingly, the only independent echocardiographic baseline predictor was the presence of left ventricular ejection fraction $< 35\%$ [odds ratio (OR): 4.16, CI: 1.01-17.0; $P = 0.048$] which is comparable to the core lab based longitudinal study from PARTNER trial pointing out for a baseline ventricular remodeling difference in patients who develop post-TAVR aortic regurgitation.¹² Moreover, this study has documented that the post-TAVR aortic regurgitation remains mostly unchanged during the 2 years follow-up. This is somehow in line with the native chronic aortic regurgitation natural history studies. The long-term survival of volume overload of chronic moderate aortic regurgitation is remarkably good and the mortality is associated with symptoms development and hinges on the clear documentation of the left ventricular remodeling parameters.¹³ Conversely, the studies that showed a higher mortality aortic regurgitation post-TAVR failed to demonstrate aortic regurgitation progression over time, left ventricular remodeling or worsening of functional class symptoms.

Nevertheless, independent of whether or not the post-TAVR aortic regurgitation is a mediator or moderator of poor outcomes, this data underscores the actual procedural limitation and the window of opportunity to improve the technology. Advances in the new TAVR devices are ongoing and include modifications that will limit effectively or eliminate the aortic regurgitation post-TAVR.¹⁴ For now the best strategy is to adopt preventive measures to reduce the incidence of aortic regurgitation such as selecting the adequate size and prosthesis for each patient. One important developing area is the understanding of aortic-valve complex through the multimodality image analysis.¹⁵ These studies focused on the annulus and against the prior belief of a simple circular, compliant and static structure geometry, the current knowledge about this “virtual” ovoid ring is far beyond the possibility of a single dimension analysis. Recently, the fourth dimension was added to the annulus measurement – the time – and confirmed the dimension variability according to the cardiac cycle phase.¹⁶ Herein, the incorporation of the multidimensional analysis by means of multidetector computer tomography and two dimensional/three dimensional echocardiogram has proven to be useful.

The advent of TAVR has transformed the aortic stenosis treatment and forced the Interventional Cardiology to re-engineering not only our labs but also the way in which we interact with the different components of a functioning heart-team with the aim of improving patient prognosis. Whether the aortic regurgitation

post-TAVR represents a real “fall from grace” or just a “storm in a teacup” is still unknown. Further studies designed specifically to answer this question are warranted to ensure the TAVR future potential application on intermediate and low-risk populations.

CONFLICT OF INTEREST

Augusto D. Pichard is proctor for Edwards Lifesciences. Marco A. Magalhães and Ron Waksman have no conflict of interest to declare.

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