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EDITORIAL COMMENT

Sealing the Achilles Heel of Transcatheter Aortic Valve Replacement?*

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Transcatheter aortic valve replacement (TAVR) has made a remarkable development during the past decade from a treatment option considered as last resort for inoperable patients with severe symptomatic aortic stenosis to the preferred therapy for those at increased risk for surgical aortic valve replacement (SAVR) (1-3). As a result, the use of TAVR continues to expand in lower risk and younger patients with a longer life expectancy. Thus, some of the remaining limitations of TAVR may gain further prominence in the long run, notably paravalvular regurgitation (PVR), atrioventricular conduction disturbances, and prosthetic valve degeneration.

Moderate or severe PVR has been more frequent after TAVR than SAVR and consistently shown to increase short- and long-term device-related morbidity and mortality (2-6). Hence PVR has been regarded as the Achilles heel of TAVR, and numerous efforts aimed to reduce its incidence to improve clinical outcomes. Patient characteristics, the anatomy of the aortic valvar complex, pre-procedural planning, procedural factors, and device-specific features all impact the risk of PVR. In this context the routine use of multislice computed tomography, which enables precise annular sizing and procedural planning, has importantly contributed to reduce the rate of relevant PVR in recent years (7). However, the most important advances to mitigate the risk of PVR with a high degree of reproducibility constitute device iterations.

In the only randomized trial comparing a self-expanding with a balloon-expandable device, implantation of the early-generation CoreValve (Medtronic, Minneapolis, Minnesota) was associated with significantly higher rates of moderate or severe aortic regurgitation as assessed by post-procedural angiography (18.3% vs. 4.1%; $p < 0.001$) and new pacemaker implantation (37.6% vs. 17.3%; $p = 0.001$) as compared with the SAPIEN prosthesis (Edwards Lifesciences, Irvine, California) (8). Stent frame modifications, the addition of a higher inner polyethylene terephthalate skirt (Sapien XT [Edwards Lifesciences]), and an outer polyethylene terephthalate sealing cuff (SAPIEN 3 [Edwards Lifesciences]) have since reduced the incidence of moderate or severe PVR with the balloon-expandable device to 3% to 4% based on echocardiographic assessment (3,5,9,10).

As it relates to the CoreValve prosthesis, 30-day rates of moderate or severe PVR amounted to 11.4% and 9.0% and rates of new pacemaker implantation to 21.6% and 19.8% in the extreme- and high-risk landmark trials, respectively (1,4). Its successor, the Evolut R valve (Medtronic) comprises a shortened frame redesigned to improve anatomical fit while preserving the inner porcine pericardial skirt and allows for recapturability to fine tune implantation depth. In 2 recent prospective studies evaluating the Evolut R prosthesis, the rate of moderate or severe PVR amounted to 5.7% (at 30 days) and 1.9% (at discharge), and rates of new pacemaker implantation to 16.4% (at 30 days) and 19.3% (at discharge), respectively (11,12). The Evolut PRO (Medtronic) constitutes the latest iteration of this self-expanding prosthesis and features an external pericardial wrap that covers the lower 2 rows of stent frame cells with the aim to fill the space between the structures of the stent frame and the landing zone to further reduce the rate of PVR. The addition of this skirt results in a

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2F increase in delivery catheter size compared with the Evolut R. In this issue of *JACC: Cardiovascular Interventions*, Forrest et al. (13) present the results of TAVR performed in 60 patients at increased risk for SAVR using the Evolut PRO prosthesis. Sizing was based on multislice computed tomography, outcomes were reported according to the definitions of the Valve Academic Research Consortium-2, and echocardiography endpoints assessed by an independent core laboratory.

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Implant success was 100%, although in 35% of the cases the valve had to be resheathed or recaptured. The vast majority (98.3%) of the devices were delivered via iliofemoral access. The primary efficacy endpoint was defined as the proportion of patients with less-than-mild prosthetic valve regurgitation at 30 days and amounted to 72.4%, with no patient showing evidence for moderate or severe regurgitation. Of the patients without a pacemaker at baseline, 11.8% required implantation of a permanent pacemaker within 30 days after TAVR. The mean transprosthetic gradient was low with 6.4 mm Hg as typical for a supra-annular valve design, though acknowledging that no patient requiring a 23-mm device was included. The pre-defined primary safety endpoints, all-cause mortality and disabling stroke at 30 days, amounted to 1.7% each in a patient population with a mean Society of Thoracic Surgeons score of 6.4%. Thirty-day rates of major vascular complications and life-threatening or disabling bleeding were 10.0% and 11.7%, respectively.

The presented data are promising and support the concept to mimic surgical-like outcomes as it relates to PVR by the addition of an external seal that compensates for incomplete stent-landing zone apposition, in particular in heavily calcified regions. Of note, the benefit in terms of PVR reduction did not appear to be associated with an increase of other adverse event rates. Notwithstanding, conclusive evidence and the interpretation of the primary safety and other clinical endpoints are precluded by the small sample size of the present cohort. Moreover, the categorization of patients with mild PVR as not meeting efficacy is not well founded in view of the lack of consistent evidence that mild PVR has an independent impact on clinical outcomes (1,3,5,10). Despite similar baseline characteristics, the comparison of PVR rates to the ones observed in the previously mentioned studies evaluating the CoreValve or Evolut R prostheses is difficult in view of unmeasured confounders and the degree of selection bias frequently inherent to small-scale studies documenting the clinical introduction of new devices. Hence, open questions such as the impact of the sealing wrap on the balance between mitigation of PVR and the rate of new pacemaker implantation in various anatomies as well as the effect of the larger introducer sheath on the risk of vascular and bleeding complications would need to be addressed in large registries or even head-to-head trials. Conceptually and in analogy to other devices comprising an outer seal, the Evolut PRO can be assumed to be a step forward, but confirmation in real-world practice is needed.

Next to external sealing wraps other features may be desired to achieve surgical-like PVR and pacemaker rates with self-expanding valves. Full retrievability, a lower stent frame minimizing interaction with the outflow tract (and allowing straight-forward coronary access), and an optimal balance among the ability to adapt to the landing zone, radial strength, and mechanical stress on the atrioventricular conduction system. With a larger selection of valve platforms becoming available in the next years, experience and familiarity with an array of different devices will allow a tailored approach to device selection for the individual patient based on the integration of patient characteristics, anatomical factors, and after balancing the advantages and disadvantages of the different transcatheter valve systems.

We conclude that with the improvement in patient selection, procedural planning, implantation technique, and more recently the advent of external seals, the rate of relevant PVR has been lowered considerably and in view of the results of the most current devices the prospects to definitely seal the Achilles heel of TAVR are promising.

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