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EDITORIAL COMMENT

Coming Closer to Personalized Medicine in Transcatheter Aortic Valve Replacement*

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Transcatheter aortic valve replacement (TAVR) has become increasingly the treatment of choice in patients with symptomatic severe aortic stenosis being at high risk for perioperative mortality. Recently, it has been shown that TAVR is also an option for patients at intermediate risk (1,2). At present, surgical aortic valve replacement (SAVR) is a recommended standard procedure for low-risk patients, that is, STS score <4 or EuroSCORE II <4 (3). Currently, several trials are examining whether TAVR is also noninferior to SAVR in those patients at lower perioperative mortality risk, such as the NOTION-2 (Comparison of Transcatheter Versus Surgical Aortic Valve Replacement in Younger Low Surgical Risk Patients With Severe Aortic Stenosis; NCT02825134), LRT (Feasibility of Transcatheter Aortic Valve Replacement in Low-Risk Patients With Symptomatic, Severe Aortic Stenosis; NCT02628899), PARTNER 3 (The Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis; NCT02675114), or Medtronic TAVR in Transcatheter Aortic Valve Replacement Low Risk Patients (NCT02701283) trials. However, the long-term durability of TAVR valves remains an important unanswered question, especially in younger patients with longer life expectancy; therefore, this issue will be addressed in these ongoing trials. Improvements of first-generation transcatheter heart valves, development of novel technologies, and increasing center and operator experience have resulted in a significant increase in short- and long-term survival rates and in a decrease in complication rates over time (4).

One of the new-generation prostheses is the ACURATE neo (Boston Scientific, Marlborough, Massachusetts), a self-expanding device, which received CE mark approval in 2014 (5). It consists of a nitinol frame with a porcine pericardial leaflet valve placed in a supra-annular position and a pericardial sealing skirt on both the outer and the inner surface of the stent body. It is characterized by an X-shaped stent design with a unique 2-step top-down mechanism of deployment. Observational studies demonstrated very favorable outcomes with a high procedural success rate (up to 98%) and very low 30-day mortality rate (1.4% to 2.3%) (6,7). Although 1-year outcome data were published only recently (8), little is known about predictors of periprocedural outcome with the ACURATE neo prosthesis.

SEE PAGE 1721

In this issue of *JACC: Cardiovascular Interventions*, Kim et al. (9) present a German single-center analysis of procedural outcome in 500 patients undergoing transfemoral aortic valve replacement with the ACURATE neo prosthesis implanted between 2012 and 2017. The study population reflects a usual TAVR population (average age >80 years, predominantly women). Pre- and post-dilation were performed in 75% and 40%, respectively, and the procedure time was very short (median 36 min). Device success was achieved in 90%. Moderate or severe paravalvular leek (PVL) was noted in 6% and 0.6% of cases, respectively.

Several issues of the study by Kim et al. (9) merit discussion to put these results into perspective.

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Most importantly, the study gives us an important early glimpse into the tailored approach for TAVI procedure with a focus on careful patient selection based on anatomic characteristics. The best outcomes with the ACURATE neo prosthesis with only trace-to-mild PVL were achieved in mild (0.8%) to moderate (5%) calcification of the device landing zone (DLZ), respectively. In line, the presence of annular plaque protrusions and of increased perianular calcification (>97.0 mm^3) were independent predictors of at least moderate PVL. This indicates that calcium deposits and annular plaque protrusions may impair proper expansion of the ACURATE neo prosthesis. This valve has a relatively low radial force being advantageous for the low rate of permanent pacemaker implantation (PPI). Moreover, less oversizing of the device (in other words prosthesis implantation according to the official sizing recommendations) also independently predicted PVL. This important early observation led to another very important contribution of the study, that is, the novel sizing recommendation. Official sizing recommendations of the manufacturer (S for annulus 21.0 to 23.0 mm; M for 23.0 to 25.0 mm; and L for 25.0 to 27.0 mm) were not validated with real-word clinical data. The study of Kim at al. (9) proposes a clinically meaningful modified sizing chart with roughly 1.0-mm oversizing to avoid PVL (i.e., perimeter-derived annulus size in diastole: S for 20.0 to 22.0 mm; M for 22.1 to 23.9 mm; and L for 24.0 to 25.8 mm). The current study underscores, therefore, that the DLZ calcification and proposed oversizing should be carefully considered in the decision-making process regarding valve selection (prosthesis type and size).

Accordingly, the study underlines and confirms a learning curve with TAVR, and specifically with the ACURATE neo prosthesis, where in this center many of the earliest patients were treated. The authors show now, that over time, patient selection changed with more distinct oversizing and less calcified DLZ resulting in a decline of 30-day mortality, device failure, and relevant PVL.

This highly relevant analysis (9) also adds much-needed evidence regarding TAVR outcomes in lower-risk populations. The median STS score in the paper by Kim et al. was 4.4% with an interquartile range of 3.1% to 6.6%, indicating that low- to intermediate-risk patients were included into this registry (9). Whereas other data with the ACURATE neo prosthesis were reported in intermediate-risk populations (STS score 6% to 6.8%) (6–8), the early experience with this new device shows also a favorable outcome with a 30-day mortality of 3.3% in these low- to intermediate-risk patients. Therefore, these data add important insights into the ongoing debate concerning expansion of TAVR indication in younger and/or lower-risk patients. This is particularly important because excellent efficacy and safety outcomes were reported in patients with longer life expectancy for SAVR (10). Accordingly, the first trial in low-risk patients (STS score 3.0%, EuroSCORE II: 2.0%), the NOTION (Nordic Aortic Valve Intervention) trial, randomized 280 patients to TAVR or SAVR and showed promising results. It reported no difference for the composite rate of death from any cause, stroke, or myocardial infarction at 1 and 2 years (11,12). Although these results are encouraging, more data from 4 ongoing trials are urgently awaited before TAVR can be offered to low-risk patients with a life expectancy of decades.

Indeed, TAVR is associated with higher rates of PPI as compared with SAVR, which has been shown to be a clinically disadvantageous complication in TAVR (1,12,13). In addition, although higher rates of PPI after TAVR are associated with increased cost, overall, TAVR is more cost effective than SAVR (14). Importantly, in the present analysis, PPI was implanted in only 10.2% of patients, which is in the range of previous studies with the ACURATE neo (6–8,13), and one of the lowest observed with TAVR (2,8). These multiple registry data, therefore, help to make clinical decisions (i.e., valve type and size) according to the individual's anatomic and clinical characteristics, much in the sense of a "personalized medicine." In this view, the ACURATE neo valve is placed in the lowest range for PPI of new TAVR devices. Also in line with previous reports (15), a pre-existing right bundle branch block was a predictor of a new PPI. Another important contribution of this study is the observation that some device-related factors, such as more aggressive pre-dilatation and more oversizing, were associated with a higher rate of new PPI, but others were not, such as implantation depth and post-dilatation.

Nevertheless, like other registry studies, this study (9) has limitations that were properly addressed by the authors. Among others, the single center design and a post hoc-type analysis deserve to be mentioned. Although this study gives important insights into the anatomic and technical predictors of procedural outcome, these results should be validated in further investigations. It needs to be mentioned that within the SCOPE trial program, we are awaiting the results of 2 ongoing randomized controlled trials in which the comparative effectiveness of the ACURATE neo valve is examined, the balloon-expandable (Edwards SAPIEN 3, Safety

and Efficacy of the Symetis ACURATE Neo/TF Compared to the Edwards SAPIEN 3 Bioprosthesis [SCOPE I]; NCT03011346) and self-expanding (Medtronic Evolut R, Safety and Efficacy Comparison of Two TAVI Systems in a Prospective Randomized Evaluation II [SCOPE II]; NCT03192813) devices.

Taken together, these observations emphasize that our goal of further improving the procedural outcome can only be reached with our careful consideration of several factors, such as "access" to avoid bleeding complications, "valve type" to fit the individual anatomy to the known characteristics of the different TAVR valves, and "patient selection" to accommodate advantageous results of other treatment options, such as SAVR (minimally invasive, combined valve and coronary artery bypass grafting, or else). If results of randomized controlled trials, such as the SCOPE I and II trials, are able to properly characterize patient- and procedure-related factors, which predict device and procedural success as well as long-term outcome, this would represent a major step forward to precision medicine in TAVR.

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