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EDITORIAL COMMENT

Transcatheter Aortic Valve Replacement

Not for Everyone Yet?*

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Since its inception, indications for transcatheter aortic valve replacement (TAVR) for patients with severe symptomatic aortic stenosis (SAS) have expanded to include all risk categories. Indications have been based on results from RCTs (randomized controlled trials) demonstrating either superior or equivalent results to surgical aortic valve replacement (SAVR).[1-5] Given patient preference for a less invasive therapy, patients with indications originally excluded from RCTs are now being offered TAVR when deemed appropriate by the heart team. Though there are no RCTs comparing outcomes of TAVR for off-label vs on label indications, there are several early observational studies that raised concerns. Frerker et al[6] reported that the 156 patients who received off-label TAVR at a single center between 2008 and 2012 had a higher mortality at 30 days compared with 435 patients who received on label TAVR. Another study using data from the multicenter TVT registry demonstrated that the 2,272 patients who received off-label TAVR between 2011 and 2014 had a higher adjusted 30-day mortality compared with 21,575 patients who received on label TAVR.[7] However, there was no difference in the adjusted 1-year mortality.[7] Importantly, these studies only included a few off-label TAVR indications and also represented earlier experience with TAVR and older generation devices. Since then, TAVR valves and delivery systems have undergone several iterations and improvements with smaller sheaths, better skirt seal to reduce paravalvular leak (PVL), and better techniques of implantation to reduce pacemaker risk and one may expect better outcomes with these. Moreover, not all off-label TAVR can be considered equal and the question remains whether certain off-label indications may do better than others when treated with TAVR.

In this issue of *JACC: Advances*, Ullah et al[8] performed a propensity score-matched (PSM) analysis using data from the National Readmission Database (NRD) between 2015 and 2019 to calculate the adjusted odds ratio (aOR) of net adverse clinical events (NACE) (composite of mortality, stroke, and major bleeding) in patients undergoing clinical trial excluded (CTE) vs clinical trial included (CTI)-TAVR. The CTE-TAVR group included 41,408 patients who underwent TAVR for 15 off-label conditions (bicuspid aortic valve [BAV], aortic insufficiency, mitral valve disease, hypertrophic obstructive cardiomyopathy, bioprosthetic aortic valves [BPVs], cardiac masses, infective endocarditis, recent use of mechanical circulatory support, end-stage renal disease [ESRD], end-stage liver disease, active peptic ulcer disease [PUD], central arterial disease, morbid obesity, leukopenia, and coagulopathy) that were excluded from RCTs and are relative or absolute contraindications to TAVR. The average patients' age was ~75 years with an even distribution of male (~50% in each group) and female (~45% in each group) patients in both groups. Results showed an increase in the annual CTE-TAVR volumes during the study period with numerical decline in the proportion of major outcomes. However, in any given year, the outcomes of NACE and its individual components in the CTE-TAVR group were worse than those of CTI-TAVR. Overall, the adjusted odds of NACE [aOR: 1.83; 95% CI: 1.73-1.95] and its individual components were significantly higher in CTE-TAVR compared with

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CTI-TAVR at index hospitalization. Complications such as valve leak (aOR: 1.68; 95% CI: 1.39-2.02), valve migration (aOR: 2.79; 95% CI: 2.22-3.52), and device thrombosis (aOR: 2.49; 95% CI: 1.59-2.49) were all higher in the CTE-TAVR group. Outcomes varied among individual contraindications to clinical trial enrollment. At index hospitalization, all contraindicated conditions except BAV, mechanical circulatory support, PUD, and leukopenia had higher NACE compared with CTI-TAVR. The 30- and 180-day readmission rates were similar for BAV, PUD, and leukopenia while they were higher for ESRD, BPV, and coagulopathy compared with CTI-TAVR. These results suggest, though TAVR for 15 off-label indications as a group has worse outcomes compared with TAVR for on label indications, certain off-label indications such as BAV, PUD, and coagulopathy may individually do well with TAVR.

This study has several strengths. It includes a large sample size of ~80,000 PSM matched real-world patients with SAS from multiple centers in the United States who were treated with TAVR. Thus, it informs us about real world TAVR practices in the United States. The majority of these procedures, ~90%, were performed in large metropolitan teaching hospitals where one may expect to see experienced high volume operators, well defined heart teams, and TAVR pathways indicating that the data is robust. It includes 15 off-label TAVR indications in the CTE group, a number greater than what was included in previously published observational studies, making this the most comprehensive study on the topic. Using PSM analysis, balanced and matched groups of patients were obtained in the CTE vs CTI-TAVR groups as well as each individual component of CTE-TAVR vs CTI groups, thereby minimizing confounding. The comparison of individual components of CTE vs CTI-TAVI helps in understanding which off-label indications may or may not benefit from TAVR. Since the study included data from 2015 to 2019, a time period prior to approval of TAVR for low-risk patients, the STS risk score of these patients would approximate to 4% or greater. Though greater than the mortality in the CTI group, the observed mortality rate at 30-day readmission in the CTE group was 4.4% which is reflective of the population included in this study. The rate of stroke remained low in both groups, ~1.5% and need for permanent pacemaker, though high at ~9% to 10%, was not different between groups. These are somewhat reassuring as those patients who may not have gotten surgery for their SAS did as was expected with TAVR. Though this data do not inform practice just yet, it provides a basis to plan future RCTs to compare select off-label TAVR indications that had comparable outcomes to CTI-TAVI such as BAV, PUD, leukopenia with SAVR.

Despite these strengths, there are several limitations to this study. The results of this trial must be interpreted with caution as it is observational in nature utilizing registry data and carries the inherent biases of the NRD database including a risk of unmeasured confounders. It includes site reported data without any adjudication of the events by a core lab. Moreover, events that occurred outside the hospital, at home, or in the community are not captured resulting in underreporting of some outcomes. Although the study included an estimate of the risk of mortality, the actual STS risk scores, and frailty are missing, thus making it hard to compare the actual surgical risks of the CTE and CTI groups. The patients in the CTE group may have been sicker to begin with because they were offered TAVR instead of surgery for an off-label indication which may have translated into worse outcomes. Moreover, the exact etiology of mortality, whether related to the procedure itself or to patients' comorbidities is unknown. The NRD database does not provide information regarding the valve type or size and hence we cannot establish if one valve type is better than the other for off-label TAVR. In addition, there is no echocardiographic, coronary tomography, or post procedure antithrombotic data to understand the reason for the worse procedural outcomes such as device thrombosis or device embolization. Finally, there are no details regarding the complexity of the procedure or the access site used that could throw light on the reasons for the worse outcomes.

Overall, the safety of TAVR procedure has increased and due to its less invasive nature compared to SAVR, it has become an attractive option for patients and heart teams, including off-label indications. However, not all off-label indications for TAVR are the same with regards to the risks of the actual procedure and ensuing short- and long-term outcomes. In some conditions, SAVR still remains the first line therapy.[9] Although there are no RCTs comparing outcomes of TAVR and SAVR for each of these CTE indications, there are observational data for TAVR in some of these CTE indications. For instance, outcomes of TAVR in selected patients with BAV is comparable to TAVR in tricuspid valves[10] or SAVR[11] while in other conditions like ESRD and BPV, patients may have good results with the TAVR procedure but have a high long-term mortality due to the underlying comorbidities.[12,13] Some of these patients may do worse with surgery due to their comorbidities. Thus, the role of the heart team is extremely

important in deciding between treatment options.[14] In addition to surgical risk scores which provide an estimate of short-term mortality and anatomy of the annulus, aorta, and peripheral vasculature, heart teams must consider the risks and benefits of other available options, estimated long term outcomes, and patient preferences for quality of life when making treatment decisions for patients with SAS. Operating teams must exert caution while performing TAVR in patients with off-label indications and follow the heart team approach for case selection.

In summary, this 4-year NRD database study informs us that outcomes of CTE-TAVR are worse than CTI-TAVR. However, the proportion of these outcomes is decreasing over the study period indicating increasing operator experience, better patient selection, and device improvements. In addition, these outcomes may reflect the poor underlying prognosis in some of these conditions. Although registry data are not a substitute for RCTs, this data will serve as a useful guide to plan more robust studies in future comparing TAVR vs SAVR vs medical therapy for CTE indications. Until then, TAVR is not for all and SAVR still plays a role in some conditions[8] as first line therapy with a need for careful patient selection by heart teams considering all options and patients' quality of life.

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