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Challenges and Future Opportunities for Transcatheter Aortic Valve Therapy

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ABSTRACT

Background: Transcatheter aortic valve replacement (TAVR) is a novel less-invasive therapy for high-risk patients with severe aortic stenosis (AS). Despite the impressive clinical growth of TAVR, there are many challenges as well as future opportunities.

Results: The heart valve team serves as the central vehicle for determining appropriate case selection. Considerations which impact clinical therapy decisions include frailty assessments and defining clinical "futility". There are many controversial procedural issues; choice of vascular access site, valve sizing, adjunctive imaging, and post-dilatation strategies. Complications associated with TAVR (strokes, vascular and bleeding events, para-valvular regurgitation, and conduction abnormalities) must be improved and will require procedural and/or technology enhancements. TAVR site training mandates a rigorous commitment to established society and sponsor guidelines. In the future, TAVR clinical indications should extend to bioprosthetic valve failure, intermediate risk patients, and other clinical scenarios, based upon well conducted clinical trials. New TAVR systems have been developed which should further optimize clinical outcomes, by reducing device profile, providing retrievable features, and preventing para-valvular regurgitation. Other accessory devices, such as cerebral protection to prevent strokes, are also being developed and evaluated in clinical studies.

Summary: TAVR is a worthwhile addition to the armamentarium of therapies for patients with AS. Current limitations are important to recognize and future opportunities to improve clinical outcomes are being explored.

Background

In the past decade, after initial proof-of-concept and subsequent feasibility studies, the application of less-invasive catheter-based approaches to functionally replace diseased aortic valves has been incorporated into the clinical treatment armamentarium in symptomatic high-risk patients with severe aortic stenosis (AS). Since 2007, in more than 50 countries, over 750 cardiovascular centers have treated almost 100,000 aortic stenosis patients using transcatheter aortic valve replacement (TAVR) technologies. Despite the rapid acceptance and clinical appeal of TAVR, as with any new and novel medical therapy, there are still many challenges to be addressed and future opportunities to be

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Abbreviations and Acronyms

AS = aortic stenosis

CT = computerized tomography

ICE = intra-cardiac echocardiography

LBBB = left bundle branch block

LV = left ventricular

PARTNER = Placement of Aortic Transcatheter Valves

PVR = para-valvular regurgitation

RV = right ventricular

STS = Society for Thoracic Surgeons

TA = transapical

TAo = transaortic

TAVR = transcatheter aortic valve replacement

TEE = transesophageal echocardiography

TF = transfemoral

TVT = transcatheter valve therapy

US = United States

VARC = Valve Academic Research Consortium

explored. The purpose of this manuscript is to selectively highlight the crucial challenges of TAVR which are presently under investigation and to direct attention towards expanding clinical applications and new technologies which constitute important future opportunities.

Challenges

Case selection

Identifying "high-risk" patients

Patient selection under the auspices of a multidisciplinary "Heart Team" is crucial to achieve optimal clinical outcomes after TAVR. The differentiation between high-risk, "inoperable" (or extreme risk), and prohibitive risk AS patients has been actively debated since regulatory approval of TAVR and especially during the formulation of the Placement of Aortic Transcatheter Valves (PARTNER) clinical trial.[1] Risk assessment has often been guided by standard surgical scoring systems, including the Society of Thoracic Surgery (STS) and EuroSCORE models, which were not fully validated in this high-risk patient population. These on-line risk scores, as designed for everyday use, do not include important co-morbidities such as severe pulmonary hypertension, right ventricular (RV) dysfunction, severe liver disease, home supplemental oxygen, prohibitive anatomy (such as chest deformity or severe aortic calcification), disability, or frailty. Characterization of surgical risk requires direct involvement of experienced surgeons who usually include a number of important co-morbidities when considering the highest risk patients for TAVR: malnutrition and cachexia, physical deconditioning or wheelchair bound, chronic kidney disease on dialysis, history of particular solid tumor malignancies, neurological disorders such as dementia and stroke, and other debilitating conditions that preclude patients from returning to a reasonable functional status. One of the biggest challenges in assessment of patient risk status is developing a validated quantitative algorithm that best defines patient risk from the standpoint of predicting early and late mortality as well as functional recovery in the setting of TAVR. The combined analyses of the PARTNER trials or the new United States (US) Transcatheter Valve Therapies (TVT) National Registry will hopefully provide sufficient patient data to offer the possibility of a TAVR specific risk algorithm at some point in the future.[2]

Frailty and futility

Not entirely captured in current risk stratification metrics is the attribute of frailty, which has been associated with worse TAVR outcomes. The concept of frailty is crudely defined as an impairment in multiple systems that leads to a decline in resiliency and homeostatic reserve. It is influenced by physical disability and medical co-morbidities, but is not adequately described by just these attributes.[3] Green et al have devised a frailty score for TAVR patients, based loosely on criteria established by Fried et al.[4] The frailty phenotype, including impairments in gait speed and grip strength, reduced serum albumin, and diminished Katz activities of daily living, was associated with a longer post-TAVR hospital stay, as well as increased 1-year mortality.[5] The multicenter FRAILTY-AVR study will compare outcomes of surgical aortic valve replacement (SAVR) and TAVR using several frailty assessment tools in the effort to define which factors are the most predictive of mortality and morbidity in elderly patients. The results of the US CoreValve Pivotal Trial Extreme Risk cohort highlight the need to define and quantify the significance of this interaction, as the only two significant predictors of all-cause mortality or major stroke (the primary endpoint), were STS score of >15% ($p = 0.02$) and residence in an assisted living facility ($p < 0.01$).[6]

A careful frailty assessment plays a key role in the differentiation of "futility" ("no hope" patients) and high-risk utility patients and should be incorporated into all TAVR risk stratification analyses. The term "Cohort C" describes this subset of futile inoperable patients who have both poor survival (i.e. less than 1 year) and poor quality of life, despite successful TAVR. Simply stated, "Cohort C" or futile patients represent those patients who are dying *with* aortic stenosis but not *from* AS. Common clinical characteristics most associated with futile risk patients include extreme co-morbidities (e.g. STS score >15%), extreme frailty usually with a dependent social status, severe pulmonary or liver disease, severe dementia, chronic kidney disease (e.g. dialysis dependent), and hemodynamic instability (especially requiring vasopressors). What remains to be defined is the quantitative interplay of frailty metrics and existing risk stratification models based on age and co-morbid conditions, in accurately determining a "Cohort C" patient.

Procedural considerations

Access alternatives

Factors which may determine preferred TAVR vascular access include peripheral arterial disease (inadequate vessel diameter, severe calcification or extreme tortuosity of the iliofemoral vessels), the presence of extensive calcification of the ascending aorta (i.e. porcelain aorta), hostile chest wall anatomy (either due to ortho-voltage radiation exposure or chest wall deformities), previous coronary bypass graft surgery with mammary conduits adherent to the chest wall,