Perspective

Aortic valve replacement *vs.* transcatheter aortic valve implantation: Patient selection

Jian Ye[1], Jia Lin Soon[2], John Webb[3]

[1]Division of Cardiac Surgery, St. Paul's Hospital, University of British Columbia, Canada; [2]Division of Cardiothoracic Surgery, National Heart Center, Singapore; [3]Division of Cardiology, St. Paul's Hospital, University of British Columbia, Canada

Corresponding to: Jian Ye, MD, FRCSC. Division of Cardiovascular Surgery, St. Paul's Hospital, B493-1081 Burrard Street, Vancouver, BC, Canada. Email: jye@providencehealth.bc.ca.

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Introduction

Conventional aortic valve replacement (AVR) with cardiopulmonary bypass (CPB) is the treatment of choice for patients with symptomatic severe degenerative aortic stenosis, as it offers both symptomatic relief and the potential for improved long-term survival (1). Surgical intervention is based on standardized guidelines, which have resulted in excellent outcomes using conventional AVR, especially in patients with a relatively low-risk profile (2-4). Even in octogenarians, recently published data indicates good patient outcomes (5-7). However, since a considerable number of elderly patients with symptomatic severe aortic stenosis have significant co-morbidities, conventional AVR with CPB can be associated with an unacceptable risk of perioperative mortality and morbidity. A significant number of patients with aortic stenosis are not referred for surgical assessment because of advanced age and other significant comorbidities (8,9). Therapeutic options for these patients are limited, and neither medical therapy nor balloon valvuloplasty offers survival benefit (9). Minimally-invasive transcatheter aortic valve implantation (TAVI) has therefore been developed as a treatment alternative for this cohort of patients (10-16). Since the first reports of transfemoral TAVI (14) and the first successful transapical TAVI without CPB using the Cribier-Edwards balloon expandable valve (Edwards Lifesciences, Irvine, California, USA) in humans were reported in 2006 (15,16), there have been dramatic advances in TAVI technology and procedure (17-24). The clinical application of TAVI has also significantly broadened. The criteria for patient selection for TAVI continue evolving, and vary significantly among cardiac surgical institutions.

Conventional AVR *vs.* TAVI

High risk inoperable patients

It has been demonstrated in many publications that patients with symptomatic aortic stenosis who are deemed to be "inoperable" may benefit significantly from TAVI as an alternative to medical management. In "inoperable" patients reported 30-day mortality is typically <10% and 1-year survival following TAVI has ranged from 65% and 80%. In the European SOURCE registry the 1-year survival of very high risk patients (logistic EuroSCORE of ≥40%) were 59.2% and 72.5% following transapical and transfemoral TAVI respectively (25). Our study has demonstrated 71.9±5.5%, 66.3±6.4% and 58.0±9.5% survival rates at 1, 2, and 3 years in high risk inoperable patients undergoing transapical TAVI (26). In comparison a similar cohort of inoperable patients who received conservative management had survival rates of approximately 50%, 25% and 10% at 1, 2 and 3 years (27). The PARTNER (Placement of AoRTic traNscathetER valves) cohort B randomized trial recruited high-risk inoperable patients with severe aortic stenosis and an overall STS score of 11.6±6.0% (28). A significant proportion of patients were considered unsuitable for surgical AVR because of factors unaccounted for by the STS score. These included patients with porcelain aorta, thoracic irradiation, severe chest wall deformity, oxygen-dependent respiratory insufficiency and frailty. The 30-day mortality for TAVI (transfemoral TAVI exclusively) was 6.4%. 1-year Kaplan-Meier all-cause mortality was 30.7% with TAVI

versus 50.7% with standard therapy (28). The two year follow up continued to demonstrate incremental benefit with TAVI, with an overall survival of 56.7% compared to 32.0% with standard medical therapy (29). As the result of these encouraging outcomes from the PARTNER trial and many other nonrandomized studies, the SAPIEN™ valve was approved for commercial use in inoperable patients with symptomatic aortic stenosis by the United States Department of Food and Drug Administration and the Canadian Department of Health and Welfare.

High risk patients

In general, patients with STS score of >10% or EuroSCORE of >20% are considered to be high risk. In the European SOURCE registry, the 1-year Kaplan-Meier survivals of patients with logistic EuroSCORE of 20-40% were 73.5% and 83.5% following transapical and transfemoral TAVI respectively (25). We used propensity scoring based on logistic regression modelling of 16 pre-operative patient characteristics to identify a group (46 patients) of very high-risk isolated conventional AVR patients comparable to those patients (46 patients) undergoing transapical AVI. There were no statistically significant differences in rates of peri-operative death, cerebrovascular accidents, wound infections, re-operation for bleeding, or length of post-operative hospital stay between the AVR and TAVI groups (30). In the PARTNER cohort A high-risk AVR-eligible patients, the 30-day all-cause mortality was 3.4% in the combined transfemoral and transapical TAVI group *vs.* 6.5% in the AVR group (P=0.07) (31). Major vascular complications at 30-days were more prominent in TAVI patients (11.0%) compared to 3.2% in AVR patients (P<0.001) (31). The 1-year all-cause mortality was 24.2% in the TAVI group and 26.8% in the AVR group respectively (P=0.44) (31). The 2-year results from the PARTNER cohort A randomized trial now also support the use of the SAPIEN valve as an alternative to high risk AVR with comparable survival: 66.1% (TAVI) *vs.* 65% (AVR) (32). These data suggest that TAVI at least provides comparable benefits in the high-risk patients compared to AVR although the long-term outcome following TAVI has not been determined. There is general agreement that TAVI is a reasonable alternative treatment to AVR in high-risk patients and may have advantages over AVR in selected patients, particularly those with advanced age >80 years, morbid obesity, small aortic annulus, severe COPD, ascending aortic calcification, reoperation, and cerebral vascular disease. In younger (particularly <65 years) high-risk patients AVR may be preferred given the unknown durability of TAVI and a high incidence of paravalvular leaks. At present, experience and follow up with transcatheter valve-in-valve implantation in the setting of failed tissue valves remains extremely limited.

Moderate-risk patients (STS 5-10%)

There have been no studies directly comparing TAVI and AVR in moderate-risk patients. A single centre report showed 30-day mortality of 2.4%, stroke of 2.4%, major adverse cerebrovascular and cardiac events (MACCE) of 5.9%, and pacemaker implantation in 21.4% in moderate risk patients (age 80±5 years) with predicted mortality of 12.6±6.5% by EuroSCORE and 5.0±2% by STS (33). This perioperative mortality and morbidity with TAVI is probably higher, at least not better than those with conventional AVR (34). A recent study of the Society of Thoracic Surgeons National Database over the last 10 years has provided results on 108,867 patients. In 2006, the overall mortality rate was 2.6% and the stroke rate 1.3%. The operative mortality rate even in octogenarians had declined to 4.5% in 2006 (34). In one study, the observed 30-day mortality and stroke rates both were 0% in the moderate risk elderly patients (age ≥80 years), with estimated mortality of 6.0±3.4 by STS calculator following isolated conventional AVR (35). The limited results that are available do not support that TAVI provides better early mortality or stroke benefits in the moderate-risk patients who require isolated AVR. Furthermore, mid and long term outcomes of TAVI are not yet available. Further study is required before TAVI is extended to the moderate-risk patients, particularly to younger patients (<65 years).

Low-risk patients (STS <5%)

To date, no studies directly compare TAVI and AVR in low-risk patients. It is well documented that the perioperative mortality and morbidity are extremely low following isolated AVR in low-risk patients. In one report 30-day mortality and stroke were both 0% in patients of <80 years with a STS estimated mortality of 2.9±3.0 (33). In the 2006 STS database mortality from AVR was <1.0% for patients younger than 60 years and 1.3% for those of 60-70 years; stroke risk was <0.5% for patients of younger than 60 years and <1.0% for those of 60-70 years (34). Currently, it is unlikely that TAVI would provide better early and late

outcomes than AVR in low-risk patients. Furthermore, transcatheter valves are unlikely to have durability comparable to the best surgical tissue valves. Currently, conventional AVR is the standard treatment for aortic stenosis in low-risk patients.

Potential candidates for transcatheter aortic valve implantation

Transcatheter aortic valve implantation should be considered as a program, rather than a simple procedure. A multidisciplinary team, including cardiologists, cardiac surgeons, echocardiologists and anaesthetists, is essential in achieving appropriate patient selection and creating a dedicated and safe procedural environment for the defintive treatment of aortic stenosis. Appropriate patient selection is important to ensure optimal care of patients with aortic stenosis. The following criteria should be considered in determining if a patient is a candidate for TAVI.

Confirmed severe AS

According to 2008 American College of Cardiology (ACC)/American Heart Association (AHA) guideline (36), the criteria to define severe AS include aortic valve area of <1.0 cm^2 and mean transaortic pressure gradient of >40 mmHg or aortic jet velocity >4 m/sec. In some circumstances, the indexed aortic valve area of <0.6 cm^2/m^2 is also considered as severe aortic stenosis despite an absolute aortic valve area of >1.0 cm^2. Patients with severe AS and low cardiac output frequently present with a relatively low transvalvular pressure gradient (i.e., mean gradient <30 mmHg). In selected patients with low-flow/low-gradient AS and LV dysfunction, stress echocardiography (with exercise or dobutamine infusion) may be useful to determine the transvalvular pressure gradient and valve area during baseline and stress states. If stress results in increases in stroke volume and aortic valve area >0.2 cm^2 with little change in pressure gradient, it is likely that the baseline severity of AS is overestimated. In contrast, patients with true severe AS likely have a fixed valve area with increases in stroke volume and pressure gradient during a stress state.

Confirming indications for surgical intervention

Generally recognized indications for conventional AVR are clearly stated in 2008 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (36), which include: (I) symptomatic patients with severe AS, (II) patients with severe AS undergoing other heart operations, and (III) patients with severe AS and LV systolic dysfunction (EF <0.50).

Defining high-risk or inoperable patients

The current consensus is that TAVI should be reserved for patients who meet standard indications for surgical AVR but are defined as high-risk for operative mortality and morbidity with conventional AVR. Transcatheter aortic valve implantation may be recommended in selected patients with moderate operative risk for conventional AVR. However, it is difficult to arrive at a standardised definition of appropriate candidates for TAVI, i.e. patients who are considered too high-risk for conventional AVR and would derive more benefit from the transcatheter approach/procedure. Several predictive risk models developed from large surgical databases have been used to ascribe objective quantitative risks of operative mortality and morbidity for patient selection. The two most commonly used risk models are the European System for Cardiac Operative Risk Evaluation (EuroSCORE), and the STS Risk Calculator. It has been generally agreed that logistic EuroSCORE greater than 20% or STS score higher than 10% is considered to be high-risk for conventional AVR. However, these risk models are not precise or entirely consistent, particularly in the elderly. In general, the logistic EuroSCORE overestimates operative risks, while the STS Risk Calculator may underestimate them. Many risk factors that have been observed in elderly patients are not well reflected by these scoring systems. Such risk factors include end-stage liver disease, prolonged preoperative hospital stay, general deconditioning, frailty, immobility due to other medical conditions, degree of obesity, significant abnormalities of other valves, severity of peripheral vascular and aortic disease, previous chest wall radiation, previous infected sternotomy, porcelain aorta and degree of lung disease. On the other hand, some (particularly younger) patients with high logistic EuroSCORE (>20%) or STS score (>10) may still be reasonable candidates for conventional AVR. We believe that a combination of objective quantitative predictive risk models, objective measurement of frailty and subjective assessments by experienced surgeons is the ideal/best way to characterize individual risks. Patients with porcelain aorta, patent coronary bypass grafts, physical deformities restricting sternal access and frailty are 'special' subgroups for whom TAVI may offer advantages, regardless of the STS risk score.

Assessing benefits of TAVI

The general consensus is that patients considered as candidates for TAVI should have a meaningful quality of life with a minimum life expectancy of greater than 1 year. For patients with end-stage disease, such as end-stage liver disease and COPD, moderate to severe dementia, limited functional capacity (i.e. bed bound), extreme frailty and end-stage malignancy, TAVI may offer no benefit.

Anatomical and technical suitability for TAVI

Currently, TAVI is recommended only for patients with calcified aortic stenosis with or without regurgitation, and is not offered to patients with isolated rheumatic aortic valve disease. After selecting candidates for TAVI, the treating team should assess the anatomical and technical suitability for the procedure. Conventional coronary angiography, transthoracic echocardiography and either conventional angiography or CT imaging of the aortic root and ilio-femoral arteries are recommended. Transesophageal echocardiography (TEE) is performed to determine the aortic annulus size either before or during the procedure. CT provides multiple measurements of the aortic annulus size, including an average diameter delivered from short and long dimensions, a circumference of the annulus, and an area of the aortic annulus. This method likely provides more accurate measurements of aortic annulus size to determine the size of transcatheter valves. With increasing experience in the CT measurement, we believe CT will become a standard method in selecting transcatheter valve sizes. Specific anatomical considerations in patient selection include: (I) degree and distribution of aortic valve calcification, (II) aortic annulus size, (III) morphology of aortic root, (IV) sino-tubular junction dimension and calcification, (V) location of left main, (VI) left ventricular thrombus, (VII) left ventricular outflow tract and (VIII) vascular access.

High-risk or technically challenging patients for TAVI include those with (I) potential risk for coronary ostial obstruction, (II) calcified sino-tubular junction with its diameter smaller than the aortic annulus diameter, (III) bicuspid aortic valve, (IV) prior mitral valve replacement with bioprosthesis, and (V) severe LV dysfunction, particularly LVEF <20%.At present, relative or absolute contraindications for balloon-expandable Edwards Sapien™ valve include: (I) bicuspid aortic valve with minimal or non-uniformly distributed calcification, (II) aortic annulus size of ≥29 mm (currently the largest valve size is 29 mm), (III) pure rheumatic aortic valve disease, (IV) large mobile atheroma in the ascending aorta and/or aortic arch, (V) left ventricular or atrial thrombus, (VI) concomitant significant mitral stenosis with significant mitral annular calcification, (VII) extremely high-risk for coronary ostial obstruction, (VIII) hemodynamic significance of left ventricular outflow tract obstruction, and (IX) infective endocarditis.

Summary

Transcatheter aortic valve implantation is the treatment of choice for symptomatic aortic stenosis in the unacceptably high-risk or inoperable patients, and is a reasonable option for high-risk patients in general. Currently, there is no evidence suggesting that TAVI provides more favorable clinical outcomes than those of conventional AVR in moderate-risk patients. Although the results of the early TAVI experience are promising, longer-term follow-up is necessary before the procedure can be extended to lower risk or younger patients. With current devices and technologies, TAVI is associated with a high incidence of paravalvular leaks, which has been shown to have a negative impact on long-term outcomes. Before this issue is addressed, it is inappropriate to extend/offer TAVI to low-risk or young patients with moderate operative risk. Evidence-based guidelines need to be developed to ensure all patients with aortic stenosis receive optimal therapy. As with percutaneous intervention and coronary artery bypass grafting for coronary artery disease, conventional AVR and TAVI will likely be offered to different groups of patients. For the foreseeable future conventional AVR will be the treatment of the choice in low-risk or younger (<60-65 years) patients, while TAVI will be offered to the moderate- to high-risk and relatively elderly patients.

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