Transcatheter aortic valve implantation: a new standard of care

Adam J Nelson, Nicholas J Montarello, Claudia S Cosgrove, Ross L Roberts-Thomson, Sinny Delacroix, Ramesh G Chokka, Joseph K Montarello, Stephen G Worthley

Summary

- Aortic stenosis is the most common valvular lesion requiring intervention and with an ageing population, its burden is likely to increase.
- Increasing comorbidity and a desire for less invasive treatment strategies has facilitated the expansion of percutaneous aortic valve therapies.
- Robust clinical trial data are now available to support the role of transcatheter aortic valve implantation (TAVI) in patients of prohibitive, high and now intermediate surgical risk.
- The introduction of a Medicare Benefits Schedule reimbursement is likely to see TAVI use grow exponentially in Australia over the next 5 years.
- Clinical trials evaluating low risk patients may be the final frontier to see TAVI become the standard of care for most patients with severe aortic stenosis.

Aortic stenosis (AS) is the most common valvular lesion requiring intervention in the developed world. Inexorably linked to advancing age, greater life expectancy will increase the burden of clinically significant AS.[1] Developed nations have witnessed a change in epidemiology from rheumatic to calcific deterioration whereby contemporary data suggest up to 5% of adults > 75 years of age will have at least moderate stenosis.[2] The clinical course of AS has been well studied. Seminal work in the 1960s reported a long latency period followed by an abrupt development of symptoms and subsequent death without intervention.[3] The classic triad of exertional dyspnoea, chest pain and syncope can lead to congestive cardiac failure and sudden cardiac death, the mortality rates of which mimic even the most aggressive of cancers and between a third and a half of patients will succumb within 12 months.[4,5] First described in the 1960s by Harken, surgical replacement of the valve (sAVR) became the gold standard for the treatment of AS and is associated with excellent long term outcomes and low peri-operative risk.[6] However, at least one-third of patients considered for surgery are deemed too high risk and another 10% refuse for fears of operative morbidity.[7] Initially targeting this unmet clinical need,[8] interest in minimally invasive interventions has grown exponentially.

Transcatheter aortic valve implantation (TAVI), or transcatheter aortic valve replacement (TAVR) as it is referred to in North America, is a technique in which a stented bioprosthetic valve is inserted via a catheter and implanted within the native valve, leaving the native leaflets in situ but pushed out of the way. In 2002, the first TAVI in a human was performed by French cardiologist Alain Cribier on an inoperable patient with severe AS and cardiogenic shock.[9] Initially performed with septostomy via the femoral vein, the subsequent development of simpler, direct femoral arterial access (similar to how a percutaneous coronary intervention [PCI] is performed) drove the rapid uptake of the procedure. TAVI can now be performed using various approaches, with the femoral arterial (also known as transfemoral) approach used in most cases (> 90%). Direct transaortic or transapical approaches (Box 1) may be considered in patients with difficult femoral access owing to stenosis, calcification, tortuosity or small calibre vessels. These often require general anaesthesia with a mini-sternotomy (transaortic approach) or mini-thoracotomy (transapical).

Valves can be broadly divided into either balloon-expandable or self-expanding types. Large randomised controlled trial (RCT) data currently exist for the Edwards family of balloon-expandable valves (Edwards Lifesciences) and the CoreValve family of self-expanding valves (Medtronic). In Australia, these valve types and the Portico valve (Abbott) are approved for implantation (Box 2), although many others are accessible via clinical trials.

For this narrative review, we used PubMed to identify original papers and review articles from 1960 to 2018 as well as society guidelines and industry sources to formulate an evidence-based overview of the use of TAVI in clinical practice.

How TAVI is performed

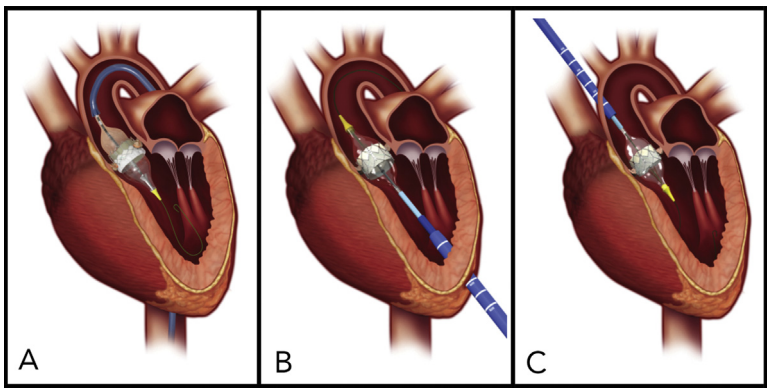
TAVI is usually performed by two specially trained proceduralists — often two interventional cardiologists or a cardiologist and a cardiothoracic surgeon. The procedure is performed with anaesthetic support either with general anaesthesia or via conscious sedation. Large sheaths (14–19 Fr; 4.5–6.5 mm diameter) are inserted into the femoral artery to permit access for the TAVI device into the peripheral arterial system. The native aortic valve is crossed and a balloon catheter is used to pre-dilate the aortic valve (balloon aortic valvuloplasty) under burst pacing (180–200 bpm). The stented bioprosthetic device is then positioned across the native valve using fluoroscopy. Balloon-expandable valves are deployed under rapid pacing to markedly attenuate cardiac output and prevent valve movement during deployment. Self-expanding valves are recapturable through significant steps of their deployment. The femoral sheath is removed and the artery is closed using a pre-closure device. Modern day care following TAVI is minimalist, with most patients returning from the procedure suite with little more than an intravenous cannula and cardiac telemetry. Length of stay is rarely longer than 72 hours, with increasing numbers of patients in our institution discharged the day after TAVI.

Current data

The evolution of a large volume of randomised data in the last decade has supported the use of TAVI in a variety of patient groups and resulted in changes to the guidelines for the management of symptomatic, severe AS (Box 3). Unlike PCI, TAVI has attempted to demonstrate benefit in the highest risk individuals initially, before extension into lower risk cohorts. In order to provide comparable groups to randomise in trials, patients have been stratified according to their surgical risk using the Society of Thoracic Surgeons (STS) score.[10] The score

Royal Adelaide Hospital, Adelaide, SA. adam.nelson@adelaide.edu.au • doi: 10.5694/mja17.01255

1 Balloon-expandable transcatheter aortic valve implantation via transfemoral (A), transapical (B) and direct transaortic (C) routes



comprises binary and continuous variables derived from a large outcomes database of patients undergoing cardiothoracic surgery. In general, an STS score predicting mortality > 8% or risk of major morbidity > 50% is considered high risk, while those predicting mortality of 4–8% are considered intermediate risk and those < 4% are low risk.[11]

Inoperable

The Placement of Aortic Transcatheter Valves (PARTNER) IB trial was the first RCT[5] conducted in a cohort of patients with severe, symptomatic AS who were high risk (STS score > 10%) and adjudicated by two surgeons to be inoperable (risk of death or irreversible morbidity > 50%). The trial was powered for non-inferiority and randomised 358 individuals of mean age 83 years to either transfemoral TAVI of a first generation balloon-expandable valve or to best medical therapy, which could include balloon aortic valvuloplasty. Individuals were followed to 5 years with the primary endpoint of all-cause mortality and a number of safety measures. At 1 year there was a 20% absolute survival advantage of TAVI over best medical therapy, which reached non-inferiority criteria (hazard ratio, 0.55; 95% CI, 0.40–0.74; $P < 0.001$) and was sustained at 5 years.[12] Similar results were seen in a first generation self-expanding valve trial comparing outcomes with a performance goal derived from the PARTNER 1B cohort.[13] From a safety perspective at 12 months, there was an increased incidence of major strokes (7.8% *v* 3.9%; $P = 0.18$), major bleeding (22.3% *v* 11.2%; $P = 0.007$) and major vascular complications such as aortic dissection, ventricular perforation and limb ischaemia (16.8% *v* 2.2%; $P < 0.001$) in the TAVI arm. The high procedural complication rate reflected the cohort's frailty and comorbidity (> 50% mortality in the placebo arm) as well as the comparatively primitive valve delivery technology and procedural learning curve. A recent study of a contemporary, inoperable cohort showed much improved complication rates: major stroke (0.9%), major bleeding (14%) and major vascular complications (5.1%).[14]

High risk

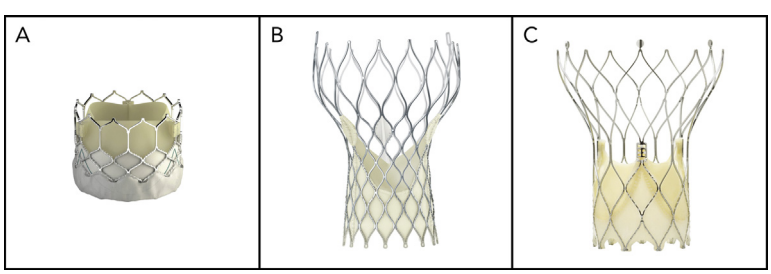
In parallel with PARTNER 1B, the PARTNER 1A trial evaluated 699 individuals with symptomatic, severe AS who were still high risk but were deemed operable.[15] The patients were randomised to either TAVI or sAVR, with the primary outcome of all-cause mortality powered for non-inferiority. The 1-year mortality was 24.2% for TAVI compared with 26.8% for sAVR, meeting non-inferiority criteria confirmed at 5 years with Kaplan–Meier curves continuing to track together.[16] Although there were more strokes in the TAVI arm at 1 year (8.3% *v* 4.3%; $P = 0.04$), there was no difference by 3 and 5 years, censuring this early safety signal. Comparatively, a trial of a self-expanding valve in high risk individuals ($n = 795$) showed a 1-year mortality of 14.2% for TAVI compared with 19.1% for sAVR, meeting pre-specified non-inferiority and superiority criteria ($P = 0.04$).[17] Two-year follow-up confirmed this overall benefit and also demonstrated a favourable stroke rate in the TAVI arm of 10.9% compared with 16.6% for sAVR ($P < 0.05$).[18]

Intermediate risk

Two recent studies have been published in patients deemed intermediate risk based on their STS score: PARTNER 2A for a balloon-expandable valve[19] and SURTAVI for a self-expanding valve.[20] These trials both involved second generation, lower profile delivery systems and superior valve technology. The PARTNER 2A trial randomised 2032 patients at intermediate risk (mean STS score, 5.8%).[19] At the landmark 2-year analysis, all-cause mortality was similar between groups: 19.3% for TAVI compared with 21.1% for sAVR, meeting criteria for non-inferiority. Within the pre-specified transfemoral TAVI cohort there was a statistically significant difference in the as-treated arm at 2 years: 16.3% *v* 20.0% for sAVR (hazard ratio, 0.78; 95% CI, 0.61–0.99; $P = 0.04$), suggesting superiority. From a safety perspective, there were more major vascular complications with TAVI (7.9% *v* 5.0%; $P = 0.008$) at 30 days; however, there was significantly less life-threatening bleeding (10.4% *v* 43.4%; $P < 0.001$), acute kidney injury (1.3% *v* 3.1%; $P = 0.006$) and new atrial fibrillation (9.1% *v* 26.4%; $P < 0.001$).

Similar outcomes were observed in the SURTAVI trial,[20] which randomised 1746 participants of similar risk and age (mean STS score, 4.4%) to self-expanding TAVI or sAVR. Using Bayesian analysis, the primary endpoint of all-cause death or disabling stroke at 2 years favoured TAVI (TAVI, 12.6% *v* sAVR, 14.0%). Similar to the PARTNER 2A trial, the TAVI arm had significantly less acute kidney injury (1.7% *v* 4.4%) and atrial fibrillation (12.9% *v* 43.4%); however, unlike the PARTNER 2A trial, the stroke trend was reversed, favouring TAVI (TAVI, 3.4% *v* sAVR, 5.6%).

2 Representative images of balloon-expandable and self-expanding devices



A: Trileaflet bovine pericardial valve mounted on a balloon-expandable cobalt chromium stent: third generation, Sapien 3 (Edwards Lifesciences). **B:** Self-expanding nitinol stent containing a trileaflet porcine pericardial valve: second generation, CoreValve Evolut R (Medtronic). **C:** Self-expanding nitinol stent containing a trileaflet bovine pericardial valve: Portico (Abbott). ◆

3 American and European guidelines for management of severe symptomatic aortic stenosis[23,24]

	Calculated (or adjudicated) surgical risk			
	Inoperable	High	Intermediate	Low
American guidelines*	TAVI: Class I sAVR: na	TAVI: Class I sAVR: Class I	TAVI: Class IIa sAVR: Class I	TAVI: not recommended sAVR: Class I
	Class I recommendation to engage the heart team to incorporate assessment of risk, frailty and comorbid conditions together with patient preferences and values			
European guidelines†	TAVI: Class I sAVR: na	STS score > 4% (or non-quantified characteristics such as frailty, porcelain aorta); decision by heart team based on individual characteristics, with TAVI favoured in older patients suitable for TF access		TAVI: not recommended sAVR: Class I

* American College of Cardiology and American Heart Association.[23] † European Society of Cardiology and European Association for Cardio-Thoracic Surgery.[24] na = not applicable; sAVR = surgical aortic valve implantation; STS = Society of Thoracic Surgery; TAVI = transcatheter aortic valve implantation; TF = transfemoral. ◆

Low risk

The only published randomised data on low risk individuals comes from the Scandinavian NOTION trial, which included 280 patients with a mean STS score of 3%.[21] These patients were randomised to either a self-expanding TAVI or sAVR and, although the trial was aimed at showing superiority, it was underpowered. The trial instead demonstrated similar rates of the composite endpoint of all-cause death, stroke or myocardial infarction at 2 years (TAVI, 15.8% *v* sAVR, 18.8%; $P = 0.43$). Valve area and gradients were similar, if not superior in TAVI compared with sAVR. Of note, there was a higher rate of moderate or severe paravalvular leak (15.4% *v* 0.9%; $P < 0.001$) and permanent pacemaker implantation (41.3% *v* 4.2%; $P < 0.001$). The PARTNER 3 trial will report next year on the outcomes for over 1300 low STS score risk patients randomised to either a third generation balloon-expandable TAVI or sAVR.

Patient selection and suitability

The choice of sAVR or TAVI is not simply based on the anatomical (eg, height of the coronary ostia) or technical (eg, sheath size) aspects of a procedure but the careful consideration of a number of complex, often competing patient factors (eg, frailty, renal dysfunction). A multidisciplinary team for decision making around these interrelated and specialised issues seems intuitive and obvious, as occurs in other areas of medicine such as cancer; however, a definition of its exact role and constituent members is nebulous and lacks a robust evidence base. Since the "heart team" appeared in the literature as part of the SYNTAX trial (the seminal trial comparing PCI with coronary artery bypass grafting for multivessel coronary disease),[22] increasing awareness of patient complexity has broadened team membership to include geriatricians, peri-operative physicians, anaesthetists, specialist nursing staff, TAVI coordinators and imaging cardiologists. Vascular surgeons and intensivists are often invited. The presentation of each TAVI candidate at a heart team meeting has become a Class I recommendation in both the American[23] and European[24] guidelines (Box 3) despite only level C evidence.

Although each institution's heart team is likely to be different, discussion is centred around three key issues: does the patient have severe AS?; is AS causing the patient's symptoms?; and what is the most appropriate management strategy?

Technical suitability

Determining patients' technical suitability for TAVI takes into account aortic valve morphology, annular size and availability of suitable arterial access. Anatomical features such as low coronary height, coronary sinus capacity and bulky basal septal hypertrophy can dictate choice of valve. Similarly, left- and right-sided heart catheterisations are performed to assess the presence of coronary artery disease and pulmonary hypertension.

General suitability

Peri-operative and general physicians make an important contribution to the selection of TAVI candidates. Respiratory illness, obesity, frailty and diastolic dysfunction all confound the accurate assessment of AS symptom burden. Competing risk from lung disease, malignancy and dementia can limit clinical improvement following a technically successful TAVI and thus a heart team assessment of anticipated benefit is critical. As TAVI becomes more available and less technically challenging, an increasing focus of the heart team is to identify patients for whom the procedure may be futile — whether we can perform TAVI is rapidly being replaced with whether we should. Futility is defined by the combination of two criteria: the lack of medical efficacy judged by the physician, and a lack of meaningful survival as judged by the patient.[25] The assessment of futility, therefore, is inherently value driven and requires critical physician–patient–family engagement, particularly with respect to understanding the potentially dynamic health care goals of patients and their families. If the procedure is deemed futile, this needs to be sensitively conveyed to patients and families, as well as the referring cardiologist, and plans for symptom management should be instituted.

Frailty

Frailty contributes significantly towards a patient's risk of adverse events and outcomes following the procedure,[26] but it is not well reflected in the current risk-predictive models. Core domains such as malnutrition and wasting, inactivity and weakness all capture frailty but are challenging to quantitate.[27] Reproducible, standardised tests of physical performance such as gait speed and grip strength are performed, along with baseline cognitive testing. Quantitation of the traditional eyeball test[28] remains elusive and most centres therefore include photos or videos as adjuncts to case presentations to inform functional status.

Current indications

Indications for TAVI will continue to grow as trial populations expand and valve durability is confirmed. Current international guidelines[23,24] based on the above-mentioned RCTs are detailed in Box 3 and continue to stratify recommendations by STS score. In the absence of local guidelines, and while awaiting contemporary

Australian TAVI registry data, our expert opinion is that the majority of patients receiving TAVI in Australia are inoperable or high surgical risk and are reviewed by a heart team. Increasingly, patients of intermediate risk are undergoing TAVI after heart team review on the strength of RCT data, and low risk patients are considered on a case-by-case basis when the heart team determines that the STS score has not adequately captured perceived surgical risk.

Complications following TAVI

Stroke

Ischaemic cerebrovascular events are a feared complication of TAVI. Cerebral magnetic resonance imaging studies have revealed a high incidence (up to 85%) of new ischaemic lesions following TAVI.[29] Most are silent, with clinically overt stroke occurring in only 3% of cases.[30] Current guidelines for antithrombotic therapy following TAVI recommend dual antiplatelet therapy, with aspirin and clopidogrel for 1–6 months after the procedure, followed by aspirin alone.[31] About half of strokes within the first 30 days after TAVI occur within the first 24 hours[30] and likely relate to the formation of thrombi on intravascular equipment, as well as dislodgement of tissue debris during instrumentation of the aorta and valve.[32,33] Peri-procedural embolic protection devices used to capture this debris have shown some benefit radiologically (eg, smaller ischaemic volumes on magnetic resonance imaging[34]), although these have not translated to clinically meaningful differences and are not in mainstream guidance.[35] Strokes occurring in the subacute period (Days 1–30) are often cardio-embolic relating to atrial fibrillation, for which antiplatelet therapy is known to be inadequate.[30]

Valve durability

Until recently, TAVI has been performed exclusively in older patients or those with significant comorbidities in whom valve longevity has not been a priority. The adoption of TAVI for patients who are younger and therefore have longer life expectancy will depend largely on long term durability. Currently, there are published data for TAVI valve function up to 5 years after implantation. The ADVANCE study followed 996 high surgical risk patients implanted with a self-expanding valve and reported valve dysfunction in 2.6% at 5 years.[36] Foroutan and colleagues performed a meta-analysis of observational studies with a median follow-up of 1.6–5 years, and reported an incidence of valve deterioration of 0–1.34 per 100 patient years.[37] The 5-year outcomes of the PARTNER 1 trial showed no cases of structural valve deterioration requiring surgical valve replacement.[16] Although the results of mid-term durability of TAVI prostheses are encouraging, long term follow-up is eagerly awaited.

Paravalvular leak

Paravalvular leak (PVL) is more frequently observed in TAVI than sAVR, and in early trials was associated with increased mortality rates.[38,39] However, the more recent PARTNER 2A trial with a contemporary valve demonstrated even moderate PVL in TAVI to be well tolerated, although moderate to severe PVL still conferred an increased risk of all-cause mortality.[19,40] Causes of PVL dictate management strategies: valve-in-valve procedures for malplacement or incorrect sizing, as well as balloon post-dilatation or paravalvular plugs for incomplete sealing, are all available.[41,42] Further, evolution in prosthesis design (eg, skirt technology) and high fidelity pre-procedural planning (eg, computed tomography, 3D modelling) has produced a marked reduction in incident PVL.

Pacemakers

Given the proximity of the aortic valve to both atrioventricular nodal and infra-nodal conduction tissue, aortic valve intervention is associated with the development of conduction disease (high degree atrioventricular block and new onset left bundle branch block) and permanent pacemaker implantation. In the TAVI setting, this is secondary to a combination of trauma, ischaemia and oedema generated during and after the implantation procedure.[43] The largest datasets from the contemporary balloon-expandable and self-expanding valves suggest rates of permanent pacemaker insertion to be, respectively, 12%[44] and 18%[45] in registries and 8.5%[19] and 26%[20] in the recent RCTs. The comparator arms have consistently reported rates in sAVR of 5–7% at 30 days.[5,17] In a lower risk and younger population, the development of permanent pacemaker dependency or persistent dyssynchrony may be more relevant and will need close observation.

Off-label indications

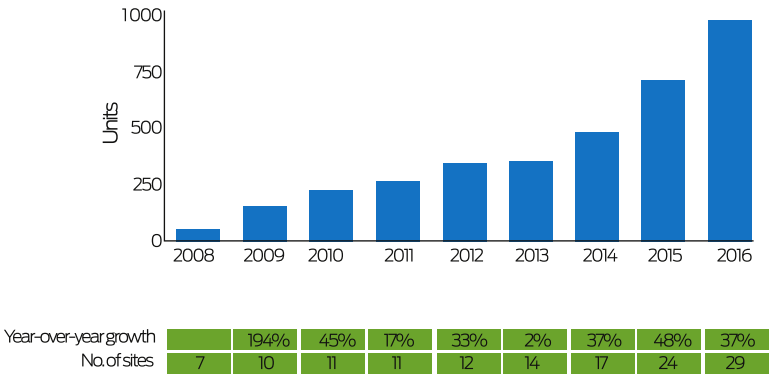
The durability of a bioprosthetic valve is associated with implanted age; a younger patient will not only expose the valve to greater haemodynamic demand but also a more vigorous immune system. This can result in pannus formation, calcification and thrombosis, all of which can lead to re-stenosis and, potentially, incompetence.[46] An evolving indication is TAVI into a failing surgical bioprosthesis (valve-in-valve), not only in the aortic but also mitral and tricuspid valves. Obviating the need for re-sternotomy, valve-in-valve procedures performed in 365 patients with failed bioprosthetic surgical valves were associated with an impressive 30 day all-cause mortality and stroke rate of 2.7%, modest PVL in 1.9% and all-cause mortality of 12.4% at 12 months.[47] If shown to be durable, this solution is likely to change the landscape of clinical decision making for younger patients.

TAVI uptake in Australia

TAVI was first performed in Australia in 2008, not long after some of the earliest clinical trials started enrolment. Well over 300 000 implants have now been placed worldwide.[48] The introduction of TAVI-specific diagnosis-related groups allowed remuneration as early as 2008 and 2009 in Germany and France, where today almost half of all isolated aortic valve intervention occurs via TAVI.[49] For the past decade, individual hospital or health service funding arrangements, often directly with industry or via clinical trials, have been the only way for clinicians to offer this therapy to deserving patients. Almost 10 years after the first implant in Australia, the Medical Services Advisory Committee recommended the institution of a Medical Benefits Schedule item number, making the procedure rebatable and thus more accessible to patients and providers, both public and private. The wording on the indication includes individuals who have severe symptomatic AS and are of prohibitive or high surgical risk and ultimately deemed suitable for TAVI by a heart team.

Our best understanding of present TAVI volume in Australia comes from industry estimates that about 50 TAVI procedures occurred in 2008 and over 1000 are expected to occur in 2018 (personal communication, Scott Graham, Edwards Lifesciences). For the past 3 years there has been a yearly growth of 30–40%, with over 30 sites in Australia now running TAVI programs (Box 4) (personal communication, Scott Graham, Edwards Lifesciences). In view of this impressive uptake, and the introduction of a Medical Benefits Schedule item number, the Cardiac Society of Australia and New Zealand and the Australia and New Zealand Society of

4 Transcatheter aortic valve implantation in Australia: number of units implanted and sites, 2008–2016*



Year-over-year growth		194%	45%	17%	33%	2%	37%	48%	37%
No. of sites	7	10	11	11	12	14	17	24	29

* Industry estimates provided by Edwards Lifesciences. ◆

Cardiac and Thoracic Surgeons have provided guidance on training requirements for centres contemplating TAVI programs.[50]

Conclusion

The introduction of TAVI has revolutionised the management of aortic valve disease in Australia. Iterative development in valve structure and function, delivery technology and an evolving understanding of patient selection has seen TAVI become a preferred treatment strategy in progressively lower risk cohorts. The focus within heart teams and health systems has shifted from how to technically perform TAVI to how we select individuals most likely to benefit from the intervention. A significant task for future heart teams will be dissecting disease-driven frailty from general sarcopenia and functional decline in older individuals. With the advent of TAVI-specific risk scores and improved quantification of frailty, recommending good palliative care in the face of futility will become a critical part of any robust structural heart team. At the other end of the spectrum, implantation into younger, less comorbid individuals will reduce the level of competing risk for death, and subsequently test prosthesis durability. Further intraprocedural and device-related improvements should continue to drive the technology into the future and ultimately see TAVI become the gold standard for most patients with AS.

Competing interests: Stephen Worthley consults for and has received honoraria from Medtronic and Abbott.

Provenance: Not commissioned; externally peer reviewed. ■ ■

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