



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1603 – Transcatheter Aortic Valve Implantation (TAVI) using SAPIen 3 balloon-expandable valve system

Applicant: Edwards Lifesciences Pty Ltd

Date of MSAC consideration: MSAC 80th Meeting, 26-27 November 2020

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of transcatheter aortic valve implantation (TAVI) using a balloon-expandable valve (BEV) system for patients with symptomatic severe aortic stenosis (AS) at intermediate risk for surgery was received from Edwards Lifesciences Pty Ltd by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the creation of a new Medicare Benefits Schedule (MBS) item for transcatheter aortic valve implantation (TAVI) using a balloon-expandable valve (BEV) system for patients with symptomatic severe aortic stenosis (AS) at intermediate risk for surgery on the grounds of acceptable safety, effectiveness and cost effectiveness compared with surgical aortic valve replacement (SAVR). Consistent with the current MBS item for TAVI (item 38495), MSAC supported an MBS item agnostic of the type of TAVI device, noting that this advice would be re-assessed at the March 2021 MSAC meeting consideration of the TAVI device agnostic application in intermediate risk for surgery (MSAC Application 1652).

Consumer summary

Edwards Lifesciences Pty Ltd applied for public funding via the Medicare Benefits Schedule (MBS) for transcatheter aortic valve implantation (TAVI) using a balloon-expandable valve in patients with symptomatic severe aortic stenosis who are at intermediate risk for surgery.

Severe aortic stenosis is a condition that stops blood from flowing easily throughout the body. Eventually this can lead to heart failure because the aortic valve in the heart develops a severe build-up of calcium, which makes it difficult for the valve to open and close.

Consumer summary

TAVI is a procedure that helps to improve a damaged aortic valve. During a TAVI procedure, an artificial valve made of natural animal heart tissue (usually from a cow or a pig) is implanted into the heart. But instead of standard open-heart surgery (where the chest cavity is opened during surgery), in TAVI, a catheter is placed in the femoral artery (in the groin) and guided into the heart.

MSAC accepted that TAVI is safer, more effective and more cost-effective than surgical aortic valve replacement. However, there was not enough evidence to determine whether the use of a balloon-expandable valve was better than a TAVI procedure that uses a self-expanding valve. For that reason, MSAC supported the listing of an MBS item for a TAVI device without specifying which type of valve should be used.

MSAC's advice to the Commonwealth Minister for Health

MSAC supported an MBS item that does not name the type of TAVI device. MSAC based its decision on the fact that it considered TAVI to be effective, safe and cost-effective. MSAC noted that this advice would be re-assessed at the March/April 2021 MSAC meeting, when it would consider the TAVI device agnostic application in intermediate risk for surgery.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that TAVI is currently listed on the MBS for high-risk/inoperable surgical patients with symptomatic severe AS under item 38495. This item is agnostic of the type of TAVI device. MSAC noted that this device specific application for TAVI-BEV is seeking to expand MBS listing to include intermediate-risk surgical patients. MSAC noted that the applicant originally pursued a TAVI device agnostic application ([Application 1552](#)), but due to BEVs perceived different clinical and economic outcomes in intermediate-risk patients, chose to pursue this TAVI-BEV specific application (1603).

MSAC noted that the applicant-developed assessment report (ADAR) appropriately nominated SAVR as the main comparator and TAVI self-expandable valves (TAVI-SEV) as the secondary comparator (as requested by the PICO¹ Advisory Sub-committee [PASC]).

MSAC noted there was no feedback from consumers, but consultation feedback was received which did not support a TAVI device specific application and considered a MBS item should be generic and cover TAVI with all Therapeutic Goods Administration (TGA) approved devices.

MSAC noted there was no direct randomised controlled trial (RCT) evidence assessing the current generation TAVI-BEV (SAPIEN 3) vs. the primary comparator, SAVR. Rather, the ADAR's primary clinical evidence relied on comparing TAVI-BEV with SAVR via a propensity score-adjusted comparison (PARTNER S3i) of two sub-populations from two clinical studies. However, MSAC noted there was direct RCT evidence for the comparison of an older generation TAVI-SEV (CoreValve) vs. SAVR, which was used to inform the indirect comparison of TAVI-BEV with TAVI-SEV, via the common comparator SAVR.

¹ Population, Intervention, Comparator, Outcome

MSAC noted the issues raised by ESC for the use of propensity score-adjustment to compare TAVI-BEV with SAVR. MSAC agreed with the ESC that while the propensity score adjustment process controlled for all relevant observed characteristics for the primary outcomes (the composite endpoint of all-cause mortality, stroke, moderate or severe paravalvular regurgitation at 1 year) there was potential for bias due to potential differences in unobserved variables. MSAC noted that the pre-MSAC response also acknowledged this limitation of the study when discussing the 5-year outcomes from the PARTNER 3Si study, and also that more patients were lost to follow up in the TAVI cohort compared with SAVR cohort. For all secondary outcomes, MSAC also noted that the ADAR acknowledged the high uncertainty from the unadjusted (naïve) comparisons.

In terms of comparative safety of TAVI-BEV *vs.* SAVR, MSAC noted patients treated with TAVI-BEV had a higher rate of moderate or severe aortic regurgitation than patients treated with SAVR at 12 months follow-up. Unadjusted comparisons showed that patients treated with TAVI-BEV had significantly lower rates of re-hospitalisations, fewer new cases of atrial fibrillation, lower rates of myocardial infarction, and lower rates of life-threatening or disabling bleeding than patients treated with SAVR, although MSAC noted that these results are highly uncertain. MSAC noted the 5-year outcomes of PARTNER 3Si presented in the pre-MSAC response showed:

- similar rates of endocarditis, aortic valve re-intervention and valve thrombosis
- lower rates of new pacemakers favouring SAVR.

In terms of effectiveness of TAVI-BEV *vs.* SAVR, MSAC noted that the propensity score-adjustment showed that TAVI-BEV is superior for the outcomes of death and stroke at 12 months. However, MSAC noted the 5-year (unpublished) outcomes presented in the pre-MSAC response showed:

- similar rates of mortality and all strokes (disabling + non-disabling stroke)
- similar rates of the composite of mortality or disabling stroke, and disabling stroke (noting results numerically favoured TAVI-BEV but was not statistically significant as the confidence interval of the hazard ratio of disabling stroke included 1)
- lower rates of non-disabling stroke favouring SAVR.

Overall, MSAC concluded that superiority of TAVI-BEV *vs.* SAVR was not adequately justified over the longer-term results from propensity score analysis.

MSAC considered the secondary comparison of TAVI-BEV *vs.* SEV, noting that:

- the ESC and the ADAR appropriately concluded there was too much clinical heterogeneity between trials to draw conclusions from the indirect comparison. However, MSAC noted the ADAR assumed superiority of TAVI-BEV *vs.* SEV, as it did not make a clinical claim for its comparison of TAVI-BEV *vs.* SEV
- the direct randomised trial, SOLVE-TAVI, which was the only head to head comparison using new generation TAVI-BEV (SAPIEN 3) *vs.* SEV (Evolut-R) as currently used in Australia, and included by the Commentary, suggested that TAVI-BEV and SEV were similar in terms of the composite primary endpoint: all-cause mortality, stroke, moderate or severe paravalvular leakage, and permanent pacemaker implantation at 30-day follow-up. MSAC also agreed with ESC who considered there were applicability concerns with the trial population (high risk) and that the results were limited to 30-days, and as such did not inform longer term outcomes. However, MSAC noted that consultation feedback provided (unpublished) updated results from SOLVE-TAVI showing that no difference in the primary composite outcome was maintained at 1-year follow-up

- the pre-MSAC response acknowledged that evidence from RCTs of TAVI-BEV *vs.* SEV is limited but considered it favoured TAVI-BEV on the basis of a recent non-inferiority trial (SCOPE-1). However, MSAC noted there was applicability concerns with the trial population as patients were not selected on the basis of surgical risk (56% intermediate risk) and that the TAVI-SEV device used in the trial was not currently registered on the Australian Register of Therapeutic Goods (ARTG).
- the pre-MSAC response considered there is no evidence to suggest that there is ‘no difference’ between TAVI-BEV *vs.* SEV in intermediate risk but that there is evidence existing of the superiority of TAVI-BEV *vs.* SAVR and the non-inferiority of TAVI-SEV *vs.* SAVR. However, MSAC noted some concerns with the conclusions from propensity score analysis and that the comparison of TAVI-SEV *vs.* SAVR was informed from a direct RCT (discussed above).

Overall, MSAC considered that superiority of TAVI-BEV *vs.* SEV was not adequately justified.

MSAC noted that the revised modelling provided in the pre-MSAC response showed that TAVI-BEV is dominant (i.e. cheaper and more effective), even with a TAVI device cost of **\$redacted**. However, MSAC noted that the higher Prosthesis List benefit (proposed **\$redacted** for TAVI-BEV compared with the current benchmark of \$22,932 for TAVI-BEV and SEV) is not justified as the 5-year follow-up results from propensity score analysis were not a sufficient basis to conclude superiority of TAVI-BEV over SAVR. In addition, MSAC noted there is the precedent set for similar clinical performance and thus the same benefit across TAVI device options in high risk populations should be the default position in the intermediate risk population. MSAC considered there was no basis to award a higher benefit for one device when the Prostheses List had other devices at a lower benefit. MSAC noted that the pre-MSAC response indicated that the **\$redacted** includes consumables so there would be no net change to price within the private sector (previously purchased by private hospitals and/or patients).

MSAC noted that TAVI-BEV may result in cost savings in both the public and private hospital settings if TAVI-BEVs are to replace SAVR in intermediate-risk. However, MSAC noted that the Commentary considered that TAVI-BEV may also replace medical management as some intermediate-risk patients would prefer to not undergo major open-heart surgery with SAVR but would opt for minimally invasive surgery with TAVI-BEV. MSAC also noted that introducing TAVI-BEV on the Prostheses List would significantly increase private health insurance expenditure.

MSAC noted that the advantage of having a separate item number for intermediate-risk patients in addition to the current MBS item numbers for high-risk/inoperable surgical patients is that this can be used to monitor practice when data from the Australasian Cardiac Outcomes Registry (ACOR) TAVI registry is analysed.

MSAC noted that there is no need to be more specific/explicit about defining “intermediate” risk. Registry reports should provide details about the clinical reasons why patients are categorised at higher risk level than surgical risk score. MSAC noted that the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) has been recently revised and should not be included in the item descriptor.

MSAC advised that providers should be restricted from claiming transthoracic echocardiogram items that would potentially cover pre-procedure and immediate post-procedure echocardiography on the same day as the TAVI procedure. However, MSAC

advised that this should not restrict intraoperative imaging by a different provider conducting/claiming transoesophageal echocardiography under MBS item 55135 as it assists the procedure.

MSAC concluded that this item should be device agnostic, similar with the current MBS item for TAVI (and SAVR). MSAC recommended that the item should be reviewed after 12-24 months.

MSAC supported the following item descriptor:

TAVI, ~~using a balloon-expandable system~~, for treatment of symptomatic severe aortic stenosis, performed via transfemoral delivery, unless transfemoral delivery is contraindicated or not feasible, in a TAVI Hospital on a TAVI Patient by a TAVI Practitioner – includes all intraoperative diagnostic imaging that the TAVI Practitioner performs upon the TAVI Patient.

(Not payable more than once per patient in a five-year period.)

Notes: The Health Insurance (Section 3C General Medical Services - Transcatheter Aortic Valve Implantation) Determination 2017(Cth) (Department of Health 2017) outlines the definitions of a TAVI Patient, TAVI Hospital and TAVI Practitioner.

*TAVI Patient is a patient who, as a result of a TAVI Case Conference, has been assessed as having an **intermediate risk** for surgical aortic valve replacement and is recommended as being suitable to receive the service described in Item XXXXX.*

TAVI Hospital means a hospital, as defined by subsection 121-5(5) of the Private Health Insurance Act 2007, that is clinically accepted as being a suitable hospital in which the service described in Item XXXXX may be performed.

TAVI Practitioner is either a cardiothoracic surgeon or interventional cardiologist who is accredited by the Cardiac Accreditation Services Limited.

Fee: \$1,455.10 Benefit: 75% = \$1,091.35 85% = \$1,370.40

MSAC noted the need for consistency in MSAC’s advice for applications 1652 (TAVI device agnostic application) and 1603 (TAVI-BEV). MSAC considered it would re-assess the decision to support an MBS item agnostic of the type of TAVI after its March 2021 meeting, depending on the outcome of the TAVI device agnostic application in intermediate risk for surgery (MSAC [Application 1652](#)). MSAC noted that the process allows MSAC to deal with each application on its merits while acknowledging future applications.

4. Background

This is the first submission for TAVI-BEV for patients with symptomatic severe aortic AS at intermediate risk for surgery. MSAC has not previously considered this application.

MSAC application 1552 was a TAVI agnostic application for patients at intermediate risk for surgery ([1552 Ratified PICO Confirmation](#)). This was placed on hold by the applicant to pursue this TAVI-BEV specific application (MSAC application 1603). The applicant’s rationale for this was that the PARTNER II trial showed BEVs have different clinical and economic outcomes in intermediate-risk patients. PASC advised that these “different clinical

& economic outcomes” should be clarified during the assessment phase, including what they were compared to. [[1603 Ratified PICO confirmation](#), p3].

TAVI high-risk and inoperable applications 1361

MSAC previously considered the MBS listing of TAVI for use in patients who are symptomatic severe AS at high risk for SAVR or non-operable at its March 2016, October 2015 ([Stakeholder meeting](#)) July 2015, and April 2015 meetings. At its March 2016 meeting, MSAC supported MBS listing of the TAVI procedure for the aforementioned patient population ([Public Summary Document \[PSD\] Application No. 1361.2](#)). Note, the summary of the MSAC consideration for deriving the hospitalisation estimates associated with TAVI vs. SAVR and final modelled approach is summarised below. TAVI was listed on the MBS (MBS item 38495, and case conference items 6080, 6081) for patients assessed as having an unacceptably high risk for surgical aortic valve replacement on 1 November 2017.

Hospitalisation

MSAC noted that the hospital cost for TAVI was assumed proportional based on TAVI/SAVR length of stay ratio of 1:2 derived from an unpublished data set from Western Australia presented by Yong (2012). MSAC questioned the validity of applying this ratio as it reduces the internal validity of the model as being based directly on the PARTNER trial. Given that all other clinical inputs into the model were derived from the PARTNER trial, the PARTNER-based ratio of 1:1.5 using data from Smith et al (2011) or 1:1.6 using data from Reynolds et al (2012) were therefore suggested as more appropriate. MSAC noted that this approach still favoured TAVI because this calculation assumes that the cost of hospitalisation will be evenly distributed across the length of the hospital stay, whereas it is known that the reductions in hospital stay are typically for the cheaper days that do not incur the costs of the procedure (PSD Application No. 1361.2, p3).

Clinical claim to justify modelled approach

MSAC did not consider that the claim of an improved overall survival was substantiated in order to justify the incremental cost-effectiveness and incremental cost-utility ratios presented in the comparison of TAVI with SAVR. MSAC instead recommended that this aspect of TAVI use be negotiated on a cost-minimisation basis. Further, as much of the incremental cost in the model was driven by the cost of the prosthesis, MSAC advised that negotiation of a reduced benefit for the relevant prostheses when considered for the Prostheses List would address this concern. MSAC advised that the cost-minimisation basis for this negotiation should be that the benefit for any TAVI prosthesis should be no greater than would exceed the current SAVR prosthesis benefit, plus the current AR-DRG cost for the procedure to implant the SAVR prosthesis, minus the application of the 1:1.5 ratio to reduce this AR-DRG cost to implant the TAVI prosthesis. MSAC further advised that this reduced benefit should also apply to the use of TAVI in the other cohort of currently inoperable patients ([PSD Application No. 1361.2](#), p4).

Note, earlier at its April 2015 MSAC meeting, MSAC supported the item to be agnostic to TAVI device, “MSAC preferred not to specify any particular TAVI device, for example by brand name or by specifying any particular device characteristic, such as a balloon-expandable device (to signal a preference for the applicant’s SAPIEN device) or a self-expandable device (to signal a preference for Medtronic’s CoreValve device). As noted below, the existing evidence does not justify discriminating against any particular device on clinical grounds, and there was no reason to inhibit price competition across device alternatives [[PSD Application No. 1361](#), p2].

Comparison of 1603 vs. 1361 series

A comparison of the key similarities and differences between the economic model proposed by the current Applicant Developed Assessment Report (ADAR) and the previous application (MSAC 1361) for TAVI-BEV and TAVI-SEV in high-risk patients is provided in Table 1.

Table 1 Comparison between TAVI-BEV for intermediate-risk patients (MSAC 1603) and TAVI for high-risk patients (MSAC 1361 and resubmission 1361.2). MSAC 1552, TAVI-SEV is on hold to pursue the BEV application.

	MSAC1603 (current application)	MSAC 1361 (April 2015)	MSAC 1361.2 (March 2016)																								
Intervention	TAVI-BEV	TAVI-BEV-and TAVI-SEV	TAVI-BEV-and TAVI-SEV																								
Patient population	Intermediate risk patients as determined by Heart Team	High risk or inoperable as determined by the patient's clinician.	High-risk and inoperable patients (not described)																								
Comparator	SAVR and TAVI-SEV	SAVR and medical management	SAVR and medical management																								
Clinical evidence used for economic model	1-year outcomes from PARTNER 3Si	2-year data from PARTNER trial. 5-year data published and considered by MSAC (April 2015). Revised economic model using 5-year mortality from PARTNER trial presented in pre-ESC response prior to July 2015 consideration of 1361.1.	5-year data from the PARTNER trial. The numerically different overall survival estimates following TAVI and SAVR were not statistically significantly																								
Clinical claim	Superior effectiveness vs SAVR (composite outcome: death, stroke, aortic regurgitation) No claim vs TAVI-SEV		Superior safety and clinical effectiveness for TAVI versus SAVR																								
Health states	3 states 1) Alive, no disabling stroke 2) Alive, disabling stroke 3) Dead The model adjusted for baseline cerebrovascular disease (9.4%) to account for the likelihood that patients have had a prior stroke.	5 states 1) Alive, no complications 2) Alive, other complications 3) Alive, with major stroke 4) Alive, with heart failure 5) Dead No adjustment for pre-existing complications was made.	3 states 1) Alive, standard follow-up 2) Alive, with major stroke 3) Dead No adjustment for pre-existing complications was made.																								
Time horizon	10 years (base-case). 5 and 20-year time horizon presented in sensitivity analyses	10-years. MSAC considered that both a 5-year and 10-year time horizon would be informative.	5-years presented in the base-case and 10-years was presented in sensitivity analyses																								
Prostheses cost of TAVI-BEV	ADAR included prosthesis costs for public patients only	ADAR included prosthesis costs for all patients	ADAR included prosthesis costs for all patients																								
Prosthesis cost	TAVI-BEV: \$redacted SAVR: \$9,079	-	TAVI: \$33,348 SAVR: \$6,738																								
Length of stay	<table border="1"> <thead> <tr> <th>Source</th> <th>TAVI</th> <th>SAVR</th> <th>Diff./Ratio</th> </tr> </thead> <tbody> <tr> <td>BEV: Partner 3Si naïve comparison</td> <td>Median: 4 days</td> <td>Median: 9 days</td> <td>5 days 1: 2.25</td> </tr> <tr> <td>SEV: SURTA VI RCT</td> <td>Mean: 5.75 days ±4.85</td> <td>Mean: 9.75 days ±8.03</td> <td>4 days 1:1.7</td> </tr> </tbody> </table>	Source	TAVI	SAVR	Diff./Ratio	BEV: Partner 3Si naïve comparison	Median: 4 days	Median: 9 days	5 days 1: 2.25	SEV: SURTA VI RCT	Mean: 5.75 days ±4.85	Mean: 9.75 days ±8.03	4 days 1:1.7	-	<table border="1"> <thead> <tr> <th>Source</th> <th>TAVI</th> <th>SAVR</th> <th>Diff./Ratio</th> </tr> </thead> <tbody> <tr> <td>Yong 2012</td> <td>6.2 days</td> <td>12 days</td> <td>5.8 days 1: 2.0</td> </tr> <tr> <td>PARTNER trial</td> <td>8 days</td> <td>12 days</td> <td>4 days 1:1.5</td> </tr> </tbody> </table> <p>MSAC accepted estimate from PARTNER trial (Smith 2011).</p>	Source	TAVI	SAVR	Diff./Ratio	Yong 2012	6.2 days	12 days	5.8 days 1: 2.0	PARTNER trial	8 days	12 days	4 days 1:1.5
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Yong 2012	6.2 days	12 days	5.8 days 1: 2.0																								
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Hospitalisation cost	TAVI: \$21,944 SAVR: \$49,375	-	TAVI: \$24,328 SAVR: \$48,655																								
Hospital costs (use in model)	ADAR included hospital costs for public patients using AR-DRG codes. MBS costs were applied to private patients.	Hospital costs (derived from AR-DRG codes) and MBS costs were applied to all patients	Hospital costs (derived from AR-DRG codes) and MBS costs were applied to all patients																								
Hospital costs for TAVI-BEV	44% of the costs of SAVR. Based on the median length of hospital stay for TAVI-BEV (4-days) vs.	50% of the costs of SAVR. Based on the length of stay in hospitals (ADAR proposed: 6 days for TAVI-BEV vs. 12 days for SAVR).	No change in hospital costs from 1361. The critique noted that the model was most sensitive to hospitalisation costs for TAVI-BEV.																								

	MSAC1603 (current application)			MSAC 1361 (April 2015)			MSAC 1361.2 (March 2016)		
	SAVR patients (9-days) from PARTNER S3i								
Utility	Utility values	TAVI-BEV	SAVR	Utility values	TAVI	SAVR	Utility values	TAVI	SAVR
	Alive, no disabling stroke	Pop norms (73-81)	Pop Norms (73-81)	Baseline (trial data)	0.67	0.67	Baseline (trial data)	0.66	0.66
	Alive, disabling stroke	0.50	0.50	Alive, no complications	0.702	0.702	No-complication (trial data)	0.75	0.74
	Disutility major event (once off)	0	0	Alive, with stroke	-0.147	-0.147	Disutility major event (once off)	-0.10	-0.10
				Alive, with heart failure	-0.188	-0.188	Alive, with major stroke	0.65	0.65
				Other complications - first cycle	-0.10	-0.10	Alive, with heart failure	0.636	0.636
				- ongoing	-0.056	-0.056			
				Other adverse events	-0.10	-0.10			
Transition probabilities	Transition probabilities were calculated from trial data assuming a constant rate of treatment effectiveness between TAVI-BEV and SAVR for 1-year. After this, no treatment benefit was assumed.			Trial data were extrapolated beyond the duration of the trials assuming the constant rate of treatment effectiveness.			The revised economic model used overall survival transition probabilities from the Kaplan Meier curves published in the key clinical trials ((Mack <i>et al.</i> , 2015) and (Kapadia <i>et al.</i> , 2015)). Point estimates were retrieved by digitalizing the curves, running a regression analysis for point estimates and deriving probabilities by calculating the ratio of the point estimate at t with t+1.		

Abbreviations: SAVR = surgical aortic valve replacement; TAVI-BEV = transcatheter aortic valve implantation – balloon-expandable valve system; TAVI-SEV = transcatheter aortic valve implantation – self-expandable valve system. CMA?
Source: Table 37, pp67-68 of the Commentary, and added in by Department

TAVI low risk application

An application for TAVI-BEV for patient at low risk of surgery (MSAC application 1635) was considered at the August 2020 PASC meeting.

TAVI + cerebral embolic protection (CEP) application

MSAC application 1605- transradial delivery of a dual filter CEP system, performed as an adjunct during TAVI, will also be reviewed by ESC and MSAC at the October 2020 and November 2020 meetings, respectively.

Redacted.

5. Prerequisites to implementation of any funding advice

The SAPIEN 3 TAVI-BEV device is Australian Register of Therapeutic Goods (ARTG) registered (ARTG no. 284496) and is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a Heart Team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy. The TAVI-SEV devices (CoreValve Evolut devices) by Medtronic are also ARTG registered (ARTG no. 284003, 319850) for all patients with symptomatic severe AS, regardless of surgical risk (Table 2).

Table 2 ARTG registration status for Edwards SAPIEN 3 (i.e. TAVI-BEV) and near market comparators (i.e. TAVI-SEV): Medtronic CoreValve, Medtronic CoreValve Evolut R System and Abbott Portico system

ARTG no.	Product Name	Product Description	Intended Purpose	Sponsor
TAVI-BEV				
284496	60245 Aortic transcatheter heart valve bioprosthesis, stent-like framework	The Edwards SAPIEN 3 transcatheter heart valve is comprised of a balloon-expandable, radiopaque, cobalt-chromium alloy frame, a trileaflet bovine pericardial tissue valve, a polyethylene terephthalate (PET) inner skirt, and a PET outer skirt. The Commander Delivery system components are intended for use via transfemoral access.	The Edwards SAPIEN 3 Transcatheter Heart Valve System is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a Heart Team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy.	Edwards Lifesciences Pty Ltd
TAVI-SEV				
254835	Portico Transcatheter Heart Valve – Aortic – Aortic transcatheter heart valve bioprosthesis, stent-like framework	The Portico valve is a pericardial, tri-leaflet valve, mounted inside a self-expanding stent designed for intra-annular placement using minimally invasive techniques. The valve is designed to be implanted in the native aortic heart valve without open-heart surgery and without concomitant surgical removal of the failed native valve.	The Portico valve is indicated for transcatheter delivery in patients with symptomatic severe native aortic stenosis who are considered <u>high surgical risk</u> .	Abbott Medical Australia Pty Ltd
284003	Medtronic CoreValve Evolut R System – Aortic transcatheter heart valve bioprosthesis, stent-like framework	The Medtronic CoreValve™ Evolut™ R system is a recapturable transcatheter aortic valve <u>implantation</u> system, which includes the CoreValve™ Evolut™ R transcatheter aortic valve, the EnVeo™ R delivery catheter system, and the EnVeo™ R loading system. The support frame is manufactured from Nitinol, which has multilevel, self-expanding properties and is radiopaque. The bioprosthesis is manufactured by suturing valve leaflets and a skirt from porcine pericardium into a tri-leaflet configuration.	The Medtronic CoreValve Evolut R system is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis <u>who are judged by a heart team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy</u> .	Medtronic Australasia Pty Ltd
319850	CoreValve Evolut PRO system – Aortic transcatheter heart valve bioprosthesis, stent-like framework	The Medtronic Evolut PRO system is a recapturable transcatheter aortic valve <u>replacement</u> system, which includes the CoreValve Evolut PRO transcatheter aortic valve, the EnVeo R delivery catheter system, and the EnVeo R loading system. The support frame is manufactured from Nitinol, which has multilevel, self-expanding properties and is radiopaque. The bioprosthesis is manufactured by suturing valve leaflets and an inner skirt from porcine pericardium into a tri-leaflet configuration.	The Medtronic CoreValve Evolut PRO system is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis <u>who are judged by a heart team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy</u> .	Medtronic Australasia Pty Ltd

Source: Compiled from Table 11 p25; and Table 12, pp26-27 of the Commentary

Abbreviations: ARTG = Australian Register of Therapeutic Goods; SEV = self-expanding valves; TAVI = transcatheter aortic valve

6. Proposal for public funding

The proposed MBS item descriptors are summarised in Table 3.

Table 3 Proposed MBS item descriptor

Category X – XXXXX
<p>TAVI, using a balloon-expandable system, for treatment of symptomatic severe aortic stenosis, performed via transfemoral delivery, unless transfemoral delivery is contraindicated or not feasible, in a TAVI Hospital on a TAVI Patient by a TAVI Practitioner – includes all intraoperative diagnostic imaging that the TAVI Practitioner performs upon the TAVI Patient.</p> <p>(Not payable more than once per patient in a five-year period.)</p>
<p><i>Notes: The Health Insurance (Section 3C General Medical Services - Transcatheter Aortic Valve Implantation) Determination 2017(Cth) (Department of Health 2017) outlines the definitions of a TAVI Patient, TAVI Hospital and TAVI Practitioner.</i></p> <p>TAVI Patient is a patient who, as a result of a TAVI Case Conference, has been assessed as having an intermediate risk for surgical aortic valve replacement and is recommended as being suitable to receive the service described in Item XXXXX.</p> <p>TAVI Hospital means a hospital, as defined by subsection 121-5(5) of the Private Health Insurance Act 2007, that is clinically accepted as being a suitable hospital in which the service described in Item XXXXX may be performed.</p> <p>TAVI Practitioner is either a cardiothoracic surgeon or interventional cardiologist who is accredited by the Cardiac Accreditation Services Limited.</p>
<p><i>Fee: \$1,455.10^a Benefit: 75% = \$1,091.35 85% = \$1,370.40</i></p>

^a The ADAR's proposed item fee differed from the fee in the ratified PICO (\$1,432.30) and the current MBS fee for item 38495 (\$1,476.95). This is likely due updates made to the MBS fee schedule.

Source: Table 2, px of the Commentary

The Commentary considered that consistent with MBS item 38495 (for patients assessed as having an unacceptably high risk for surgical aortic valve replacement), the proposed item does not provide an objective definition of a patient who 'has been assessed by the Heart Team as having an intermediate risk for SAVR' but noted that PASC requested that 'intermediate risk' be clearly defined in the new MBS item to prevent clinicians using their own judgment to define 'intermediate risk' and to avoid leakage into low-risk patients [[1603 Ratified PICO confirmation](#), 2]. The ADAR and primary clinical evidence defined 'intermediate risk' as someone who has a Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score of 4-8%. In the Pre-ESC response (p1), stated that the STS-PROM comprises just one aspect of risk stratification and that there are a number of other eligibility criteria for TAVI, including clinical and personal factors. The pre-ESC response (p1) considered that current best practice involves a multidisciplinary Heart Team assessing patients on an individual basis. Therefore, specifying a definition of intermediate risk in the MBS descriptor is unnecessary and arbitrary.

Prosthesis

The ADAR proposed a higher prosthesis benefit of **\$redacted** for TAVI-BEV than the July 2020 Prostheses List benefit of \$22,932 for TAVI-BEV and TAVI-SEV devices. The Commentary highlighted that the ADAR did not justify the higher price or make an explicit clinical claim that TAVI-BEV delivers superior clinical outcomes relative to TAVI-SEV in the intermediate risk population.

7. Summary of public consultation feedback/consumer Issues

Feedback was received from a TAVI manufacturer and a single specialist, which did not support a device specific (and brand) application and considered it should be generic and cover TAVI with all TGA approved devices. They both considered there is no major difference between BEV and SEV.

The feedback from the TAVI manufacturer also considered that the device specific application would limit treatment options for patients, as prostheses selection is based on the most appropriate device for the patient. Furthermore, this feedback considered that all TAVI devices and all relevant evidence should be assessed noting that:

- outcomes, particularly mortality have always been comparable between BEVs and SEVs highlighting the results from two direct randomised controlled trials (RCTs) (SOLVE-TAVI² in intermediate risk and CHOICE trial³ in high risk)
- the pivotal RCTs (highest quality evidence) of an intermediate risk population demonstrate TAVI is non-inferior to SAVR at all timepoints (PARTNER 2A⁴, SURTAVI⁵)
- the application's superiority claim for TAVI-BEV vs. SAVR is based on observational studies which are subject to inherent biases due to the nature of the study design.

The feedback from a single specialist also considered that the proposed fee is inadequate for the complexity, regulatory requirements and time involved with the procedure.

8. Proposed intervention's place in clinical management

Description of Proposed Intervention

TAVI involving the SAPIEN 3 (i.e. newer generation device) BEV system involves minimally-invasive transfemoral insertion of a prosthetic heart valve, positioned within the native aortic annulus. Once in situ, the valve is expanded while the heart is rapidly paced. The procedure is performed using fluoroscopic and transoesophageal guidance, under general or local anaesthesia.

Description of Medical Condition(s)

Severe AS is characterised by narrowing of the aortic valve, leading to restriction of blood flow. The proposed population for the intervention is defined as patients with symptomatic⁶ severe AS⁷ at intermediate risk for surgical aortic valve replacement (SAVR), with no more than mild frailty and fulfilling any one of the following criteria:

- STS score 4-8% OR

² Thiele H, Kurz T, Feistritz HJ, Stachel G, Hartung P, Eitel I, et al. 2020. Comparison of newer generation self-expandable vs. balloon-expandable valves in transcatheter aortic valve implantation: the randomized SOLVE-TAVI trial. *Eur Heart J* 41: 1890-1899

³ Abdel-Wahab M, Mehilli J, Frerker C et al. Comparison of balloon-expandable versus self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. *JAMA*. 2014;311:1503.

⁴ Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. 2016. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med* 374: 1609-1620.

⁵ Søndergaard L, Popma JJ, Reardon MJ, et al. Comparison of a complete percutaneous versus surgical approach to aortic valve replacement and revascularization in patients at intermediate surgical risk results from the randomized SURTAVI trial. *Circulation* 2019;140:1296-305.

⁶ Defined as NYHA functional Class II or greater and symptoms of symptoms of dyspnoea, angina or syncope,

⁷ Defined as an aortic valve area <0.8 cm²

- one major organ system compromise not to be improved postoperatively OR
- possible procedure-specific impediment.

Clinical place

The current clinical management algorithm and the proposed clinical management algorithm present the intended use of TAVI in the intermediate risk population following a listing on the MBS are provided in Figure 1 and 2, respectively. The key difference between the current and proposed clinical management pathway is the addition of TAVI-BEV (and TAVI-SEV) as a treatment option for intermediate-risk patients. The ADAR stated that currently in Australia, patients with symptomatic, severe AS and who are at intermediate risk of surgery either undergo curative surgery with surgical aortic valve implantation (SAVR) or are managed medically with pharmacological treatment, with or without balloon valvuloplasty, to relieve symptoms. However, the Commentary noted that the ADAR did not consider medical management as a viable treatment option for intermediate-risk patients as only SAVR (and TAVI) is curative.

The Commentary noted that the proposed algorithms also did not consider the patient's age as an important factor in the choice between SAVR and TAVI-BEV. European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (EACTS) Guidelines for Valvular Heart Disease⁸ note that SAVR is generally preferred in patients under 75 years and TAVI-BEV in patients 75 years and older. This is because the long-term durability of TAVI devices is unknown, with only preliminary data showing TAVI devices may last at least five-years without any signs of early degeneration. In comparison, SAVR valves are estimated to last 10 to 15 years.

⁸ Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 38: 2739-2791.

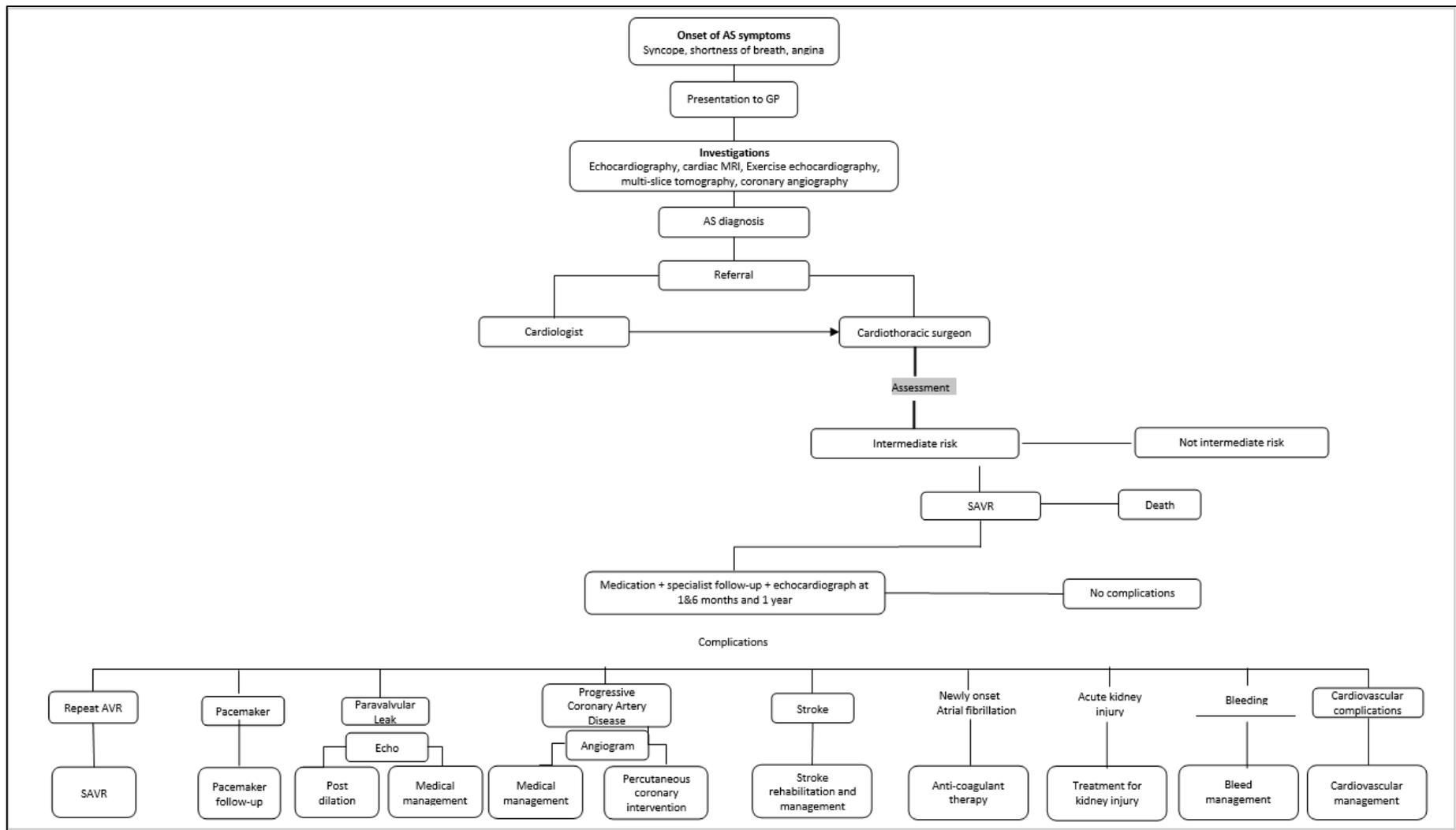


Figure 1 Current clinical management algorithm for the identified population without listing TAV-BEV

Source: Figure A-1, p 25 of the ADAR

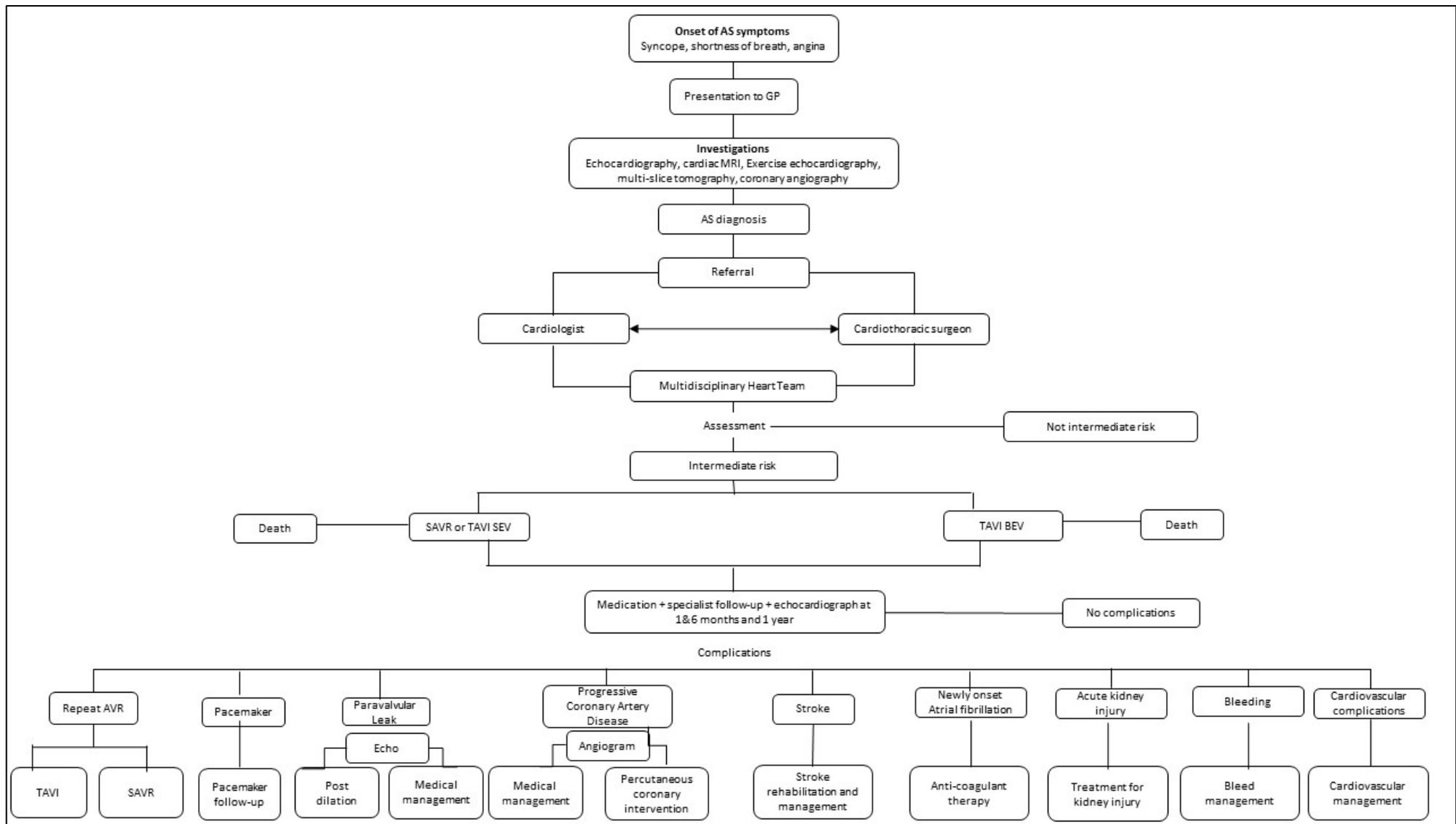


Figure 2 Proposed clinical management algorithm if TAVI-BE V was listed for the identified population

Source: Figure A-2, p 26 of the ADAR

9. Comparator

The ADAR nominated SAVR as the main comparator and TAVI-SEV as a secondary comparator. SAVR is an open-heart surgical procedure to repair or remove the narrowed aortic valve and replace it with a bioprosthetic or mechanical aortic valve. The procedure requires general anaesthetic and extracorporeal circulation, with access via a sternotomy or a less invasive transthoracic approach. The comparators were consistent with the ratified PICO and considered appropriate by the Commentary.

SAVR can be claimed under two existing MBS items (38488, 38489).

10. Comparative safety

There was no direct RCT evidence assessing TAVI-BEV *vs.* the primary comparator, SAVR. The evidential basis of the ADAR consisted of results from:

- PARTNER S3i⁹, a propensity score-adjusted comparison of two sub-populations from two clinical studies: intermediate risk patients (STS-PROM score: 4%-8%) from SAPIEN 3 single-arm observational study¹⁰ (TAVI-BEV arm in PARTNER S3i) and patients treated with SAVR from PARTNER 2A RCT (SAVR arm); and
- an indirect comparison of TAVI-BEV (SAPIEN 3) with TAVI-SEV via the common comparator, SAVR, with data sourced from the PARTNER S3i study and SURTAVI trial respectively.

The Commentary noted that the ADAR did not include a recent RCT (SOLVE-TAVI; Thiele et al., 2020), which directly compared a newer generation TAVI-BEV (SAPIEN 3) to a newer generation TAVI-SEV (Medtronic's Evolut R CoreValve) in patients that were predominantly intermediate risk (median STS-PROM score of 4.7%, interquartile range 3.0%-9.8%). The pre-ESC response highlighted that the population in SOLVE-TAVI was high risk defined by the European System for Cardiac Operative Risk Evaluation (EuroSCORE) of $\geq 20\%$ and/or a Society of Thoracic Surgeons (STS) risk score of $\geq 10\%$, or other high-risk criteria determined by the Heart Team. The results of the SOLVE-TAVI trial were included in the Commentary (Table 4).

The literature search was limited to SAPIEN 3 TAVI-BEV devices as earlier generations of this device are no longer marketed in Australia. The Commentary considered that this was appropriate as several studies have demonstrated the SAPIEN 3 may not be comparable with earlier versions of the device (i.e. SAPIEN XT) (Ando et al., 2016¹¹; Schofer et al., 2016¹²) is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a Heart Team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy.

⁹ Thourani VH, Kodali S, Makkar RR, Herrmann HC, Williams M, Babaliaros V, et al. 2016. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet* 387: 2218-2225.

¹⁰ Kodali S, Thourani VH, White J, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. *Eur Heart J.* 2016;37(28):2252-2262.

¹¹ Ando T, Briasoulis A, Holmes AA, Taub CC, Takagi H, Afonso L. 2016. Sapien 3 versus Sapien XT prosthetic valves in transcatheter aortic valve implantation: A meta-analysis. *Int J Cardiol* 220: 472-478.

¹² Schofer N, Deuschl F, Vogel B, Pecha S, Seiffert M, Lubos E, et al. 2016. Sapien 3 is Superior to Sapien XT: A Single-Center Analysis of Implanted Balloon Expandable Transcatheter Heart Valves. *The Thoracic and Cardiovascular Surgeon.*

Table 4 Key features of the included evidence comparing TAVI-BEV with SAVR and TAVI-SEV

Trial/Study	N	Design/ duration	Risk of bias	Patient population	Key outcome	Result used in economic model
PARTNER S3i (Thourani et al., 2016)	1037	PSA comparison of two sub-populations from SAPIEN 3 (TAVI-BEV) and PARTNER 2A (SAVR) trials Follow-up: 30 days and 1-year	Low to moderate	Intermediate-risk patients (STS-PROM score (4%-8%)) with severe aortic stenosis	All-cause mortality, stroke, PVR, PPI, reinterventions, HRQoL	Yes
SURTAVI	1657	Design: R, MC, OL, NI, between TAVI-SEV and SAVR. Follow-up: 30-days, 1 and 2 years	Moderate	Intermediate high-risk patients (STS-PROM score (3%-15%)) with severe aortic stenosis	All-cause mortality, stroke, PVR, PPI, reinterventions	No
SOLVE-TAVI ^a (Thiele et al., 2020)	433	Design: R, MC, OL, NI, between TAVI-BEV and TAVI-SEV. Follow-up: 30-days	Low	Baseline demographics suggested patients were predominantly intermediate risk	All-cause mortality, stroke, PVR, and PPI	No

Abbreviations: HRQoL=health-related quality of life; MC=multi-centre; NI = non-inferiority, OL=open label (unblinded); PPI = permanent pacemaker implanted; PSA = propensity score-adjusted; PVR = prosthetic valve regurgitation; R=randomised; SAVR = surgical aortic valve replacement; STS-PROM = Society of Thoracic Surgeons' Predicted Risk of Mortality ; TAVI-BEV = transcatheter aortic valve implantation - balloon-expandable valve; TAVI-SEV = transcatheter aortic valve implantation - self-expandable valve

Notes: a = identified by the evaluation

Source: Table 3, pxii of the Commentary

TAVI-BEV vs. SAVR

The results of the propensity score-adjusted comparison (Table 5) showed that patients treated with TAVI-BEV have higher rate of moderate or severe aortic regurgitation than patients treated with SAVR at 12-months follow-up (weighted differences of proportions [WDP]: 1.2%, 95% confidence interval [CI]: 0.2 to 2.2; p-value = 0.0149).

The unadjusted (i.e. naïve) comparison found that patients treated with TAVI-BEV had significantly higher rates of new permanent pacemaker implantations and numerically higher rates of aortic valve re-intervention over 12-months follow-up. However, patients treated with TAVI-BEV had significantly lower rates of re-hospitalisations, new cases of atrial fibrillation, myocardial infarction and life-threatening or disabling bleeding than patients treated with SAVR. However, as acknowledged in the ADAR, the Commentary considered that the results from the unadjusted (naïve) analyses were highly uncertain.

Table 5 Key safety outcomes reported by the ADAR based on PARTNER S3i- 30 days and 1 year

	TAVI-BEV	SAVR	RD (95% CI)	RR (95% CI)
Propensity score-adjusted comparison				
Moderate to severe aortic regurgitation (12 months)	-	-	1.2%, (0.2 to 2.2) ^a	-
Unadjusted (naïve comparison)				
Life-threatening or disabling bleeding (30 days)	50/1018 (49%)	440/493 (89.2%)	-84.3% (-87.4%; -81.3%)	0.06 (0.04; 0.07)
Aortic valve reintervention (12 months)	6/958 (<1%)	4/794 (<1%)	0.1% (-0.6%; 0.8%)	1.24 (0.35; 4.39)
New permanent pacemakers (30 days)	109/955 (11%)	68/836 (8%)	3.3% (0.5%; 6.0%)	1.40 (1.05; 1.87)
New permanent pacemakers (12 months)	132/842 (6%)	85/721 (2%)	3.9% (0.5%; 7.3%)	1.33 (1.03; 1.71)
Rehospitalisation (30 days)	49/1017 (5%)	62/845 (9%)	-3.8% (-6.1%; -1.5%)	0.56 (0.39; 0.79)
Myocardial infarction (30 days)	3/1060 (<1%)	18/889 (2%)	-1.7% (-2.7%; -0.8%)	0.14 (0.04; 0.47)
New atrial fibrillation (30 days)	54/1012 (5%)	265/649 (41%)	-35.5% (-39.5%; -31.5%)	0.13 (0.10; 0.17)
Stage 3 acute kidney injury (30 days)	5/1058 (<1%)	31/879 (4%)	-3.1% (-4.3%; 1.8%)	0.13 (0.05; 0.34)

Abbreviations: ADAR = ADAR-based assessment; CI = confidence interval; RD = risk difference; RR = relative risk; SAVR = surgical aortic valve replacement TAVI-BEV = transcatheter aortic valve implantation with a balloon-expandable valve

Bold = statistically significant at p-value < 0.05; *Italics* = corrected in the ESC report

Source: Tables 26 – 30, p54-57 of the Commentary

^a Propensity score-adjusted analysis weighted difference of proportions

TAVI-BEV vs. TAVI-SEV

The ADARs indirect comparison between TAVI-BEV and TAVI-SEV suggested:

- TAVI-BEV were significantly less likely to require a permanent pacemaker at 30-days follow-up
- TAVI-BEV patients were significantly less likely to experience atrial fibrillation, myocardial infarction and major vascular complications than TAVI-SEV (see Table B-23 of the ADAR).

However, The ADAR concluded there was too much clinical heterogeneity between trials to draw conclusions from the results of the indirect comparison. Patients in SURTAVI were generally lower risk than patients in PARTNER S3i; SURTAVI patients were generally younger (mean age of 80 years versus 82 years), had lower rates of NYHA class III or IV (58%-60% vs. 73%-76%) and atrial fibrillation (27%-28% versus 35-36%).

The Commentary noted the results from the SOLVE-TAVI trial (Table 6), patients treated with TAVI-BEV had numerically lower rates of moderate to severe prosthetic valve regurgitation (2% vs. 3%) and required fewer new permanent pacemakers (19% vs. 23%) at 30-day follow-up, compared with patients treated with TAVI-SEV. These differences were statistically not significant. Additionally, the Commentary noted that the duration of follow-up in the SOLVE-TAVI trial was only 30-days, and as such the results should be interpreted with caution as there is the potential for additional long-term differences in adverse outcomes. The pre-ESC response considered that the results of SOLVE-TAVI were not relevant as the study authors stated that that “the study included mainly high-risk patients undergoing TAVI. Therefore, the impact of the two different valve types on outcome in lower-risk cohorts cannot be extrapolated.”

Table 6 Perioperative outcomes from the SOLVE-TAVI Trial (Thiele et al., 2020)- 30 days

Outcome	TAVI-SEV (EVOLUT R) N = 218	TAVI-BEV (SAPIEN 3) N = 219	Rate Difference (90% CI)	P-value equivalence
Composite primary endpoint ^a	62/218 (28%)	56/216 (26%)	-2.51 (-9.56, 4.53) ^b	0.004
All-cause mortality	7/217 (3%)	5/219 (2%)	-0.94 (-4.79, 2.91)	<0.0001
Stroke	1/210 (1%)	10/214 (5%)	4.2 (0.11 to 8.28)	0.003
Moderate or severe paravalvular regurgitation	7/208 (3%)	3/207 (2%)	-1.92 (-5.88, 2.05)	0.0002
Permanent pacemaker	49/213 (23%)	41/214 (19%)	-3.85 (-10.4, 2.72)	0.06

Source: Table 99, pp123-124 of the Commentary

Abbreviation: BEV = balloon expandable valve; SEV = self-expanding valves; TAVI = transcatheter aortic valve implantation

Italics = revised in the ESC report

^a Composite of all-cause mortality, stroke, moderate or severe prosthetic valve regurgitation; permanent pacemaker implantation at 30-day follow-up

^b Also reported as rate difference -2.39 (90% CI -9.45, 4.66) in the abstract

11. Comparative effectiveness

TAVI-BEV vs. SAVR

The results of propensity score-adjusted comparison (Table 5) showed that TAVI-BEV was superior to SAVR at 12-months follow-up for the composite endpoint, death, stroke, and moderate to severe aortic regurgitation (WDP: -9.2%, 95% CI -13.0 to -5.4; p-value < 0.0001), and for the individual outcomes of death (WDP: -5.2%, -8.0 to -2.4; p-value = 0.0003) and stroke (WDP = -3.5%, -5.9 to -1.1; p-value = 0.0038), but inferior to SAVR for the outcome for moderate or severe aortic regurgitation (WDP: 1.2%, 95% CI: 0.2 to 2.2; p-value = 0.0149). The results of the unadjusted (naïve) comparison, which were agreed to be uncertain in the ADAR and Commentary, are also included in Table 7.

Table 7 Key effectiveness outcomes reported by the ADAR from PARTNER S3i- 30 days and 1 year

Outcome	TAVI-BEV	SAVR	RD (95% CI)	RR (95% CI)
Propensity score-adjusted				
Primary composite outcome ^a	-	-	-9.2% (-13.0%; -5.4%) ^b	-
Stroke (12 months)	-	-	-3.5%, (-5.9%; -1.1%) ^b	-
Moderate or severe aortic regurgitation	-	-	1.2% (0.2; 2.2) ^b	-
Unadjusted (naïve comparison)				
All-cause mortality				
30-days postop	12/1063 (1%)	38/902 (4%)	-3.1% (-4.5%; -1.6%)	0.27 (0.14; 0.51)
12 months follow up	79/963 (8%)	121/795 (15%)	-7.0% (-10.1%; -4.0%)	0.54 (0.41; 0.70)
30-day stroke outcomes				
Any stroke	29/1035 (3%)	57/852 (7%)	-4% (-5.8%; -1.9%)	0.42 (0.27; 0.65)
Disabling stroke	11/1053 (1%)	41/868 (5%)	-4% (-5.2%; -2.1%)	0.22 (0.11; 0.43)
Death or disabling stroke	22/1053 (2%)	75/868 (9%)	-7% (-8.6%; -4.5%)	0.24 (0.15; 0.39)
12 month stroke outcomes				
Any stroke	49/930 (5%)	75/743 (10%)	-4.8% (-7.4; -2.2%)	0.52 (0.37; 0.74)
Disabling stroke	24/953 (3%)	54/764 (7%)	-4.6% (-6.6%; -2.5%)	0.36 (0.22; 0.57)
Death or disabling stroke	90/953 (9%)	155/764 (20%)	-10.8% (-14.3%; -7.4%)	0.47 (0.37; 0.59)

Source: Outcome 1, p58 and Tables 31-33, pp59-60 of the Commentary

ADAR = Applicant Developed Assessment Report; CI = confidence interval; TAVI-BEV = transcatheter aortic valve implantation with a balloon-expandable valve; SAVR = surgical aortic valve replacement; RD = risk difference; **Bold** = statistically significant at p-value < 0.05

^a One-year non-composite event of death from any cause, stroke, and moderate or severe post-treatment aortic regurgitation

^b Weighted difference of proportions

Patients treated with TAVI-BEV had superior perioperative health-related quality of life (HRQoL), as measured by the SF-36 physical and mental health component summary score, the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score and by the EQ-5D, and this was significant at 30-days. However, at 12-months, there was no significant difference in the treatment groups HRQoL (except for the KCCQ overall summary score).

TAVI-BEV vs. TAVI-SEV

The ADAR did not perform an indirect comparison for the primary outcomes (Table 8), noting the differences in primary outcomes and clinical heterogeneity between trials.

Table 8 Results of primary outcomes for TAVI-BEV vs. SAVR and TAVI-SEV vs. SAVR

	TAVI-BEV vs SAVR- 1 year	TAVI-SEV vs SAVR- 2 year	TAVI-BEV vs TAVI-SEV
Primary composite endpoint	death from any cause all strokes post-treatment aortic regurgitation (moderate or greater [severe])	death from any cause disabling stroke	Not applicable
Results	Weighted difference of proportions - 9.2% (95% CI -13.0 to -5.4; p<0.0001) in favour of TAVI-BEV.	TAVI-SEV=12.6% vs SAVR=14.0%, 95% CI: -5.2 to 2.3% (p-value for non-inferiority >0.999)	Not applicable

Source: Compiled from Table B-25 of the ADAR

Clinical claim

TAVI-BEV vs. SAVR

The ADAR claimed that TAVI-BEV is superior to SAVR in patients with symptomatic severe AS at intermediate risk for surgery, in terms of overall survival at 30-days and one-year post-procedure; and in terms of the risk of disabling stroke at 30 days and one-year post-procedure. The ADAR claimed TAVI-BEV was inferior to SAVR in terms of post-procedural moderate-severe aortic regurgitation and need for aortic valve re-intervention. The Commentary considered the clinical claim was supported by the evidence base in the short term (up to 12 months), but noted that while the propensity score adjustment controlled for all relevant observed characteristics, there remained potential bias due to potential differences in unobserved variables. The Commentary noted that based on the unadjusted analyses conducted by the ADAR, relative to SAVR, TAVI-BEV is also inferior for rates of new permanent pacemaker at 30-days and one-year, and superior for rates of myocardial infarction and atrial fibrillation at 30-days and one-year. However, the ADAR did not make an explicit claim for comparative safety and both the ADAR and Commentary considered that the unadjusted results were highly uncertain.

The Commentary also noted that long-term comparative effectiveness and safety was also uncertain as there was no comparative data provided beyond 12 months for TAVI-BEV vs. SAVR.

In the pre-ESC response, the applicant highlighted that a recent presentation reporting on five-year outcome data from patients enrolled in PARTNER 3Si showed that differences between the TAVI-BEV and SAVR groups in terms of mortality and disabling stroke persisted, although survival curves for mortality began to converge from Year 3. The applicant also stated that follow-up data showed at 5 five years, the need for PPM still favoured SAVR (16.2% TAVI_BEV vs. 11.7% SAVR, p=0.01) but not aortic regurgitation (1.3% TAVI-BEV vs. 0.8% SAVR, p=0.31). In terms of valve integrity, the applicant indicated that very low rates of valve dysfunction were noted at five years: 0.63% haemodynamic valve deterioration and 0.63% bioprosthetic valve failure.

TAVI-BEV vs. TAVI-SEV

The ADAR did not make a clinical claim for its comparison of TAVI-BEV with TAVI-SEV, on the basis that there were no direct clinical trials and too much heterogeneity between studies to conduct an indirect comparison. The Commentary supported this conclusion noting that the key factors that affect the exchangeability PARTNER S3i and SURTAVI are: the different generation TAVI devices used with TAVI-BEV a newer generation device *vs.* the predominant use [84%] of first generation devices, respectively; patients in PARTNER S3i were higher risk than SURTAVI (mean age 82 *vs.* 80 years, respectively; NYHA class II-IV 73-76% *vs.* 58-60%, respectively; and atrial fibrillation 35=36% *vs.* 27-28%, respectively).

The Commentary noted that results of the SOLVE-TAVI trial suggested that TAVI-BEV and TAVI-SEV were equivalent in terms of the composite primary endpoint ‘all-cause mortality, stroke, moderate/severe prosthetic valve regurgitation, and permanent pacemaker implantation’. The Commentary highlighted that as the duration of follow-up in this study was only 30-days, the results should be interpreted with caution.

Translation issues

There were several translation issues:

- Based on data presented by the ADAR, patients in PARTNER S3i appeared to be applicable or broadly similar to the proposed MBS population. However, the Commentary noted that patients treated with various TAVI devices (which included TAVI-BEV) in Australian studies had substantially longer stays in hospital (mean: 6-9 days) than patients in PARTNER S3i (median 4-days) (Lee et al., 2019¹³; Thourani et al., 2016¹⁴). As the ADAR used the ratio of hospital stay between TAVI-BEV and SAVR patients (median 4 days [range: 1.0-122.0] *vs.* 9 days (range: 1.0-77.0)) in PARTNER S3i to derive the hospitalisation cost of TAVI-BEV, the extent of the reduction in hospitalisation costs due to treatment with TAVI-BEV is uncertain
- The ADAR did not present any justification for the selection of utility values in Section C. The Commentary considered it was not reasonable to assume that patients without stroke, with severe AS and who have undergone major surgery (either with TAVI-BEV or SAVR) have similar utility values to Australian population norms; they would have substantially lower utility values than the general population. Moreover, the MSAC has previously considered this approach inappropriate [[PSD Application No. 1361](#), p4]. A more reasonable approach would have been to directly apply the utility values from PARTNER S3i as was done by Baron et al., 2018¹⁵. The published economic model of TAVI-BEV comparing SAVR in patients with severe, symptomatic AS at intermediate risk of surgery in the Australian context (Zhou et al., 2019) applied trial-based utility values derived from (Baron et al., 2018). However, the Commentary considered that the selection of utility values was not a significant driver of the economic model
- The ADAR derived transition probabilities from the PARTNER S3i study, which reported on outcomes at 30 days and 12-month follow-up. For the first 30-day cycle of the model, transition probabilities were based on the risks of 30-day outcomes observed in PARTNER S3i. For cycles 2-12 (until one-year post procedure),

¹³ Lee HA, Chou AH, Wu VC, Chen DY, Lee HF, Lee KT, et al. 2020. Balloon-expandable versus self-expanding transcatheter aortic valve replacement for bioprosthetic dysfunction: A systematic review and meta-analysis. *PLoS One* 15: e0233894.

¹⁴ Thourani VH, Kodali S, Makkar RR, Herrmann HC, Williams M, Babaliaros V, et al. 2016. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet* 387: 2218-2225.

¹⁵ Baron SJ, Thourani VH, Kodali S, Arnold SV, Wang K, Magnuson EA, et al. 2018. Effect of SAPIEN 3 Transcatheter Valve Implantation on Health Status in Patients With Severe Aortic Stenosis at Intermediate Surgical Risk: Results From the PARTNER S3i Trial. *JACC Cardiovasc Interv* 11: 1188-1198

transition probabilities were estimated using the 12-month follow-up data. From Cycle 13 (Year 1) onwards, transition probabilities were based on Australian age and sex-specific data for mortality and hospitalisations, but no differences in these probabilities were assumed between the TAVI-BEV and SAVR groups (i.e. no treatment benefit after 12-months). The Commentary considered that the impact of this approach was uncertain, given no longer-term data are available to inform the maintenance of treatment benefit of TAVI-BEV compared to SAVR (see model validation below). The Commentary noted that the economic model considered in MSAC 1361 for high risk patients relied upon longer term follow-up data (PARTNER trial had 5-years of published follow-up data) than was available for the current application in intermediate-risk patients (PARTNER S3i had 12-months of published follow-up data).

12. Economic evaluation

The ADAR presented two cost-utility analyses (CUAs): a primary comparison of TAVI-BEV with SAVR and a secondary comparison of TAVI-BEV with TAVI-SEV. CUA was considered the most appropriate form of economic evaluation for TAVI-BEV based on the clinical claim of superior effectiveness compared with SAVR in terms of death and disabling stroke but inferior in terms of aortic regurgitation and aortic valve re-intervention. The Commentary highlighted that the ADAR did not make an explicit clinical claim against TAVI-SEV, which is typically necessary to support the rationale for a CUA.

Table 9 presents a summary of the economic evaluations. A comparison of the current economic evaluation with the economic evaluations for the high risk and inoperable populations is presented in Table 10.

Table 9 Summary of the economic evaluation

Perspective	Australian health-care system perspective
Comparator	SAVR or TAVI-SEV
Type of economic evaluation	Cost-utility analysis
Sources of evidence	Clinical data from PARTNER S3i ^a published data from AIHW and ABS
Time horizon	10 years (base-case). 5 and 20 years were presented in sensitivity analyses
Outcomes	<ul style="list-style-type: none"> - Disabling stroke – non-fatal and fatal - Deaths from causes other than disabling stroke - Life years lived - Quality-adjusted life-years lived
Adverse events	Life-threatening or disabling bleeding, major vascular complications, acute kidney injury, myocardial infarction, new atrial fibrillation, new permanent pacemaker, aortic valve re-intervention, paravalvular leak
Methods used to generate results	Decision analysis Markov state-transition modelling Cohort expected value analysis
Health states	<ul style="list-style-type: none"> (1) Alive, no disabling stroke (2) Alive with disabling stroke (3) Dead
Cycle length	30-days
Discount rate	5%
Software packages used	Microsoft Excel

Abbreviations: ABS = Australian Bureau of Statistics; AIHW = Australian Institute of Health and Welfare; SAVR = surgical aortic valve replacement; TAVI-SEV = transcatheter aortic valve implantation with self-expanding valve

Source: Table D-2, p 101 of the ADAR

^a The economic model comparing TAVI-BEV with TAVI-SEV was the same as the comparison with SAVR except for the cost of the index procedure and the application of TAVI-BEV aortic valve re-intervention to both TAVI-BEV and TAVI-SEV arms. Otherwise the transition probabilities were the same as the TAVI-BEV versus SAVR economic model

The Commentary noted key issues for the primary CUA comparing TAVI-BEV with SAVR:

- There is uncertainty in the length of hospitalisation stay and therefore the hospitalisation cost of TAVI-BEV
- The ADAR proposed a higher prosthesis benefit of **\$redacted** for TAVI-BEV than the July 2020 Prostheses List benefit of \$22,932 for TAVI-BEV and TAVI-SEV devices
- The ADAR included MBS costs but did not include the cost of the prosthesis or the cost of hospital stay for private patients. The Commentary revised the base case addressing this issue by including hospital stay and prostheses costs for private patients, and also using the current benefit for TAVI-BEV prosthesis price of \$22,932 (see Table 10)
- The methods used to calculate the transition probabilities in the TAVI-BEV arm were overly complex and their derivation was not well described or justified by the ADAR. Further, the methods used to obtain the proportion of strokes that were fatal and non-fatal are inconsistent with the methods applied in the SAVR arm
- In all cycles the economic model assumed TAVI-BEV to be equivalent to SAVR in terms of all adverse events, except for aortic valve re-intervention. However, the ADAR's clinical evidence showed significant differences between TAVI-BEV and SAVR in terms of myocardial infarction, (higher in SAVR arm), atrial fibrillation (higher in SAVR arm), and new permanent pacemaker (higher in TAVI-BEV arm)
- No disutilities were applied to adverse events.

TAVI-BEV vs. SAVR

Commentary’s revised economic evaluation

Table 10 presents the Commentary’s results of the economic evaluation comparing TAVI-BEV with SAVR using the current benefit for TAVI-BEV of \$22,932 (revised base case) and ADARs proposal for higher benefit of **\$redacted** (scenario analysis 1).

Table 10 Results of modelled economic evaluations comparing TAVI-BEV with SAVR, the revised base case with 5% discounting

Cost-utility analysis	Cost ^{a b}	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Revised base case ^c: using the cost of TAVI-BEV from the July 2020 Prostheses List					
TAVI-BEV	\$redacted	\$redacted	redacted	redacted	<i>Dominant</i> \$redacted
SAVR	\$redacted		redacted		
Scenario analysis 1^d: using the ADAR’s proposed cost of \$redacted for TAVI-BEV					
TAVI-BEV	\$redacted	redacted	redacted	redacted	<i>Dominant</i> \$redacted
SAVR	\$redacted		redacted		

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; SAVR = surgical aortic valve replacement; TAVI-BEV = transcatheter aortic valve

^a Hospital and prosthesis costs for private patients were included by the evaluation

^b Note: in cells **redacted** the cost of **\$redacted** was applied to each cycle instead of **\$redacted**

^c Revised base case assumptions include inclusion of prostheses costs and hospital stay costs for private patients, TAVI-BEV prosthesis cost of \$22,932, as per the July 2020 Prostheses List

^d Scenario analysis 1 assumptions include: inclusion of prostheses costs and hospital stay costs for private patients, TAVI-BEV prosthesis cost of **\$redacted**, as per the ADAR

Source: Table 4, pxix of the Commentary

The Commentary sensitivity analyses found that TAVI-BEV remained the dominant treatment option compared with SAVR in most scenarios, including changes in the assumption of efficacy between TAVI-BEV and SAVR, the inclusion of the ADAR’s proposed prosthesis cost **\$redacted** (scenario 1), the application of treatment specific adverse event rates and changes in utility values. The exception was when the hospitalisation costs for treatment with TAVI-BEV were adjusted based on the length of hospital stay for TAVI-BEV vs. SAVR patients (Figure 3). The Commentary’s threshold analysis indicating that TAVI-BEV stops being the dominant treatment option at ratios **redacted**.

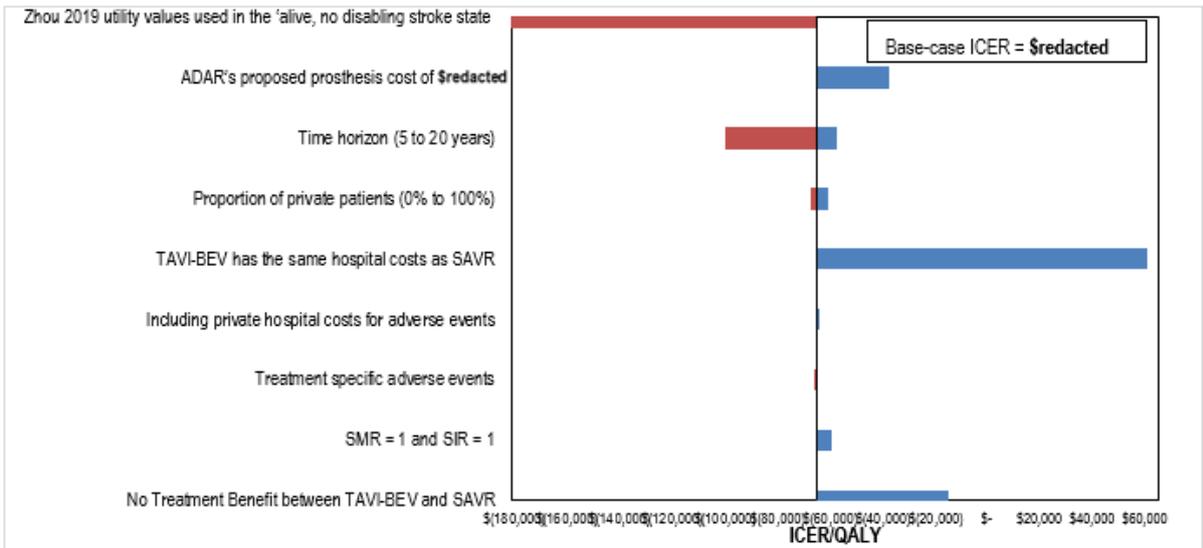


Figure 3 Tornado Diagram

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; SAVR = surgical aortic valve replacement; SIR = standardised incidence ratio; standardised mortality ratio; TAVI-BEV = transcatheter aortic valve implantation - balloon-expandable valve

Source: constructed during evaluation (Figure 7, p99 of the Commentary)

Model validation

The Commentary examined the external validity of the model by comparing the Markov traces for death or disabling stroke of TAVI and SAVR arms (aggregated for male and female proportions) with 5-years of follow-up data from the PARTNER 2A study. PARTNER 2A was a randomised trial, which compared an earlier generation TAVI-BEV device (SAPIEN XT) with SAVR. The SAVR patients in this study provided the SAVR arm of PARTNER S3i, which was the basis of the ADAR's clinical evidence. The comparison found that the modelled rates of death or disabling stroke at 5-years for SAVR patients were similar to the Kaplan-Meier estimates for SAVR patients in PARTNER 2A (42% versus 43%) [Figure4]. The Commentary considered that it was not possible to compare the modelled rates of death or disabling stroke for TAVI-BEV patients to the Kaplan-Meier estimates as PARTNER 2A used an earlier generation TAVI-BEV device.

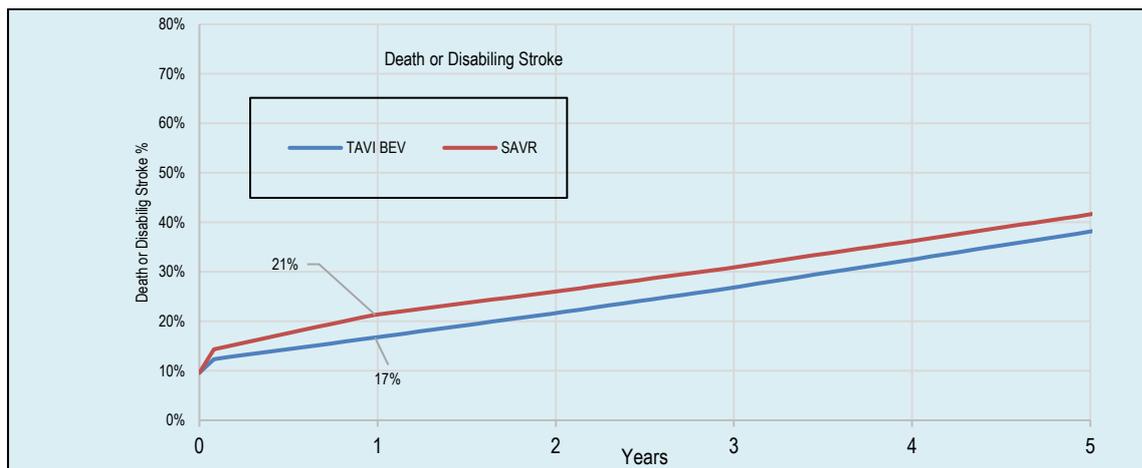


Figure 4 Comparison of modelled death or disabling stroke vs. external data of intermediate risk cohort over 5 years

Abbreviations: SAVR = surgical aortic valve replacement; TAVI-BEV = transcatheter aortic valve – balloon expandable valves (SAPIEN 3); TAVI = transcatheter aortic valve – balloon expandable valves (SAPIEN XT)

Source: Compiled during evaluation from Model spreadsheet and Figure 1 of (Makkar et al., 2020) [Redacted]

Applicant's revised economic evaluation

In the pre-ESC response, the applicant revised the modelled evaluation (Table 11) so as to increase the relative risk of mortality among TAVI-BEV patients by 20%, such that the overall survival curves crossed at five years (Figure 5). This was in response to the five year outcome data from PARTNER 3Si presented at the [Transcatheter Valve Therapy \(TVT\) online scientific meeting](#). The ADAR stated the TAVI-BEV remained dominant over SAVR.

Table 11 Applicant's revised pre-ESC model: assumed 20% relative increase in mortality

	Net costs*	Years of life lived	QALYs lived	ICER: \$/YoLS	ICER: \$/QALY
TAVI-BEV	\$redacted	redacted	redacted		
SAVR	\$redacted	redacted	redacted		
Difference	\$redacted	redacted	redacted	Dominant	Dominant

Source: Table 2, pp6 of pre-ESC response

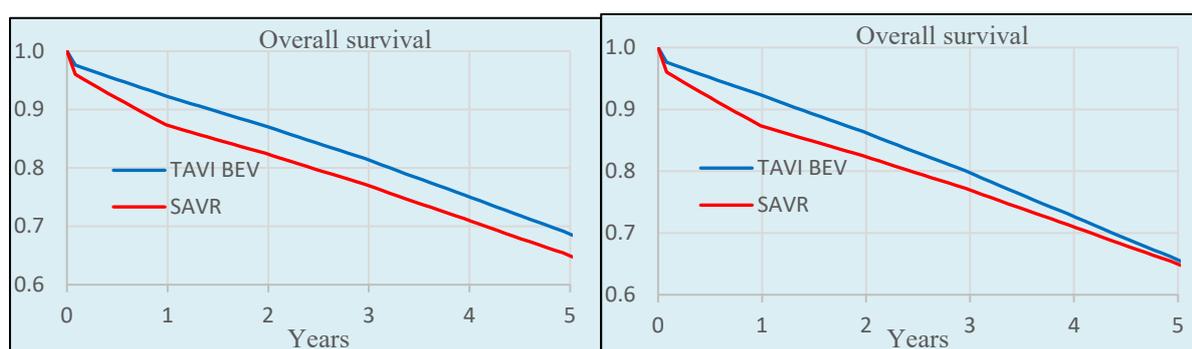


Figure 5 Comparison of ADAR base case model vs. Pre-ESC response model

Source: Extracted from ADAR model (Appendix A-Model Selection D)

In the pre-MSAC response, the applicant again revised the modelled evaluation to align the outputs from 5-year follow up from PARTNER 3Si. The applicant noted the base case model underestimated overall mortality (31.4% TAVI-BEV and 35.1% SAVR predicted by model vs. 39.1% TAVI-BEV and 41.3% SAVR observed in PARTNER 3Si), and over-estimated disabling stroke (10.2% TAVI-BEV and 12.4% SAVR predicted by model vs. 5.8% TAVI-BEV and 7.9% SAVR observed in PARTNER 3Si). In the TAVI-BEV Group, the risk of fatal stroke was reduced by 73% (relative risk [RR] 0.27), the risk of non-fatal disabling stroke was reduced by 75%, and the risk of death from other causes was increased by 62%. In the SAVR Group, the risks of fatal and non-fatal disabling stroke were reduced by 75% each, and the risk of death from other causes was increased by 50%. These changes led to predicted proportions of deaths and disabling strokes in both the TAVI-BEV and SAVR groups at 5 years matching those observed in the 5-year follow-up study (Figure 6). TAVI-BEV remained dominant in the revised model (Table 12).

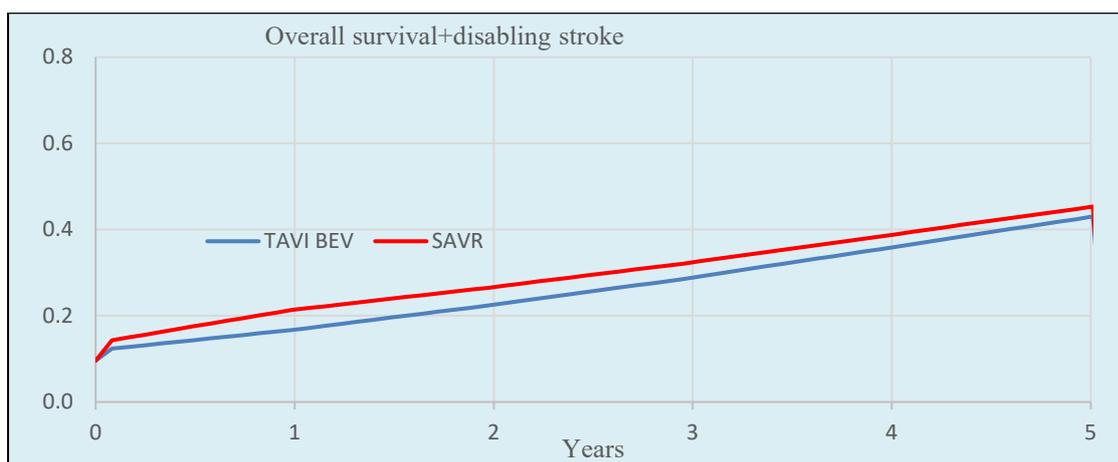


Figure 6 Comparison of applicant’s revised pre-MSAC model vs. 5 year follow up from PARTNER 3Si [redacted]

Source: *Extracted from applicant’s pre-MSAC model (Appendix A-Model Selection D- 5yr horizon)*

Note: Redacted figure from PARTNER 3Si available from [TCTMD](#)

Table 12 Applicant’s revised pre-MSAC model: based on aligning with 5-year follow up from PARTNER 3Si

	Net costs*	Years of life lived	QALYs lived	ICER: \$/YoLS	ICER: \$/QALY
TAVI-BEV	\$redacted	redacted	redacted		
SAVR	\$redacted	redacted	redacted		
Difference	\$redacted	redacted	redacted	Dominant	Dominant

Source: *Extracted from applicant’s pre-MSAC model (Appendix A-Model Selection D- 5yr horizon)*

TAVI-BEV vs. TAVI-SEV

The results of the secondary economic evaluation comparing TAVI-BEV with TAVI-SEV are summarised in Table 13.

Table 13 Results of modelled economic evaluation comparing TAVI-BEV with TAVI-SEV, revised base case and scenario analysis 1 with 5% discounting

Cost-utility analysis	Cost ^{a b}	Incremental cost	Life years	Incremental life years	Effectiveness (QALYs)	Incremental effectiveness	ICER
Revised base case: using the cost of TAVI-BEV from the July 2020 Prostheses List							
TAVI-BEV	\$redacted	\$redacted	redacted	redacted	redacted	redacted	<i>Dominant</i> \$redacted
TAVI-SEV	\$redacted		redacted		redacted		
Scenario analysis 1: using the ADAR’s proposed cost of \$redacted for TAVI-BEV							
TAVI-BEV	\$redacted	\$redacted	redacted	redacted	redacted	redacted	\$redacted
TAVI-SEV	\$redacted		redacted		redacted		

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; TAVI-BEV = transcatheter aortic valve implantation - balloon-expandable valve; TAVI-SEV = transcatheter aortic valve implantation - self-expanding valve

^a Hospital and prosthesis costs for private patients were included by the evaluation

^b Note: in cells \$redacted the cost of \$redacted was applied to each cycle instead of \$redacted

Source: Table D 22, p 144 of the ADAR

The Commentary highlighted that the comparison of TAVI-BEV with TAVI-SEV assumed TAVI-SEV has the same efficacy and safety risks as SAVR but had the same index hospitalisation cost as TAVI-BEV. The Commentary considered that this assumption was not justified by the clinical evidence or appropriate.

13. Financial/budgetary impacts

The ADAR estimated the financial implications (Table 11) of the listing for TAVI-BEV in patients with symptomatic severe AS and at intermediate surgical risk by estimating the number of SAVR procedures and the proportion of these that would be for the intermediate surgical risk population. The ADAR did not consider the financial implications associated with hospitalisation and prostheses costs for private patients. Consistent with the economic model, the Commentary presented a revised base case including these costs and the using the

current benefit for TAVI-BEV prosthesis of \$22,932 as per the July 2020 Prostheses list. A scenario analysis using the ADAR proposed price of \$redacted is also presented (see Table 13).

Table 13 Commentary revised base case (inclusion of private hospital and prostheses cost (\$22,932) on the PHI for private patients and scenario analysis with prosthesis costed at ADARs proposal (\$redacted)

Parameter	2021	2022	2023	2024	2025	Total
MBS						
Private patients (60.9%)	483	495	507	519	531	2,536
Cost to the MBS due to listing TAVI-BEV (75% fee) ^a	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Cost-savings to the MBS due to listing TAVI-BEV (75% fee) ^a	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net-cost to the MBS	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
State and territory government health budgets						
Public patients (39.4%)	310	318	326	334	342	1,630
Cost of treatment with TAVI-BEV ^b	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Cost-savings due to TAVI-BEV (reduction in SAVR)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net cost to state and territory governments	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Australian government						
Net-cost to the Australian government	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net cost using the ADAR's proposed prosthesis cost of \$redacted (scenario 1)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Private health insurance ^c						
Net prosthesis costs due to listing TAVI-BEV (Prosthesis List price) ^b	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net prosthesis costs due to listing TAVI-BEV (ADAR proposed price) ^b	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Private hospital costs-revised Post ESC						
Net private hospital cost savings due to listing TAVI-BEV	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

Abbreviations: MBS = Medical Benefits Scheme; PHI = private health insurance; TAVI-BEV = transcatheter aortic valve implantation - balloon-expandable valves

^a MBS costs were updated during the evaluation. Refer to Section D.4

^b The ADAR proposed that the cost of the TAVI-BEV prosthesis was \$redacted. However, the listed price of the Edwards SAPIEN 3 (i.e. TAVI-BEV) on the July 2020 Prostheses List is \$22,932 (DoH, 2020). This was revised during the evaluation. Net cost of SAVR prosthesis estimated as \$redacted (Table 42 of the Commentary).

^c The evaluation included prostheses costs and hospital stay costs (\$redacted for TAVI, \$redacted) for private patients based on hospitalisation costs updated to 2021 values and TAVI hospitalisation costs being 44% of SAVR hospitalisation cost, excluding prosthesis

Source: Table 8, ppxx-xxi of the Commentary, and revised Post ESC

The Commentary considered that the cost of listing of TAVI-BEV is uncertain for the following reasons:

- The ADAR considered that TAVI-BEV would only replace SAVR. However TAVI-BEV may also replace medical management as some intermediate-risk patients would prefer to not undergo major open-heart surgery with SAVR but would opt for minimally invasive surgery with TAVI-BEV. Depending on patient numbers, TAVI-BEV could be significantly more costly than what is proposed by the ADAR
- The ADAR assumed that all eligible patients currently treated with SAVR would opt for treatment with TAVI-BEV (100% uptake). However, many patients would not be suitable candidates for treatment with TAVI-BEV. For example, the European Society

of Cardiology and EACTS Guidelines for Valvular Heart Disease, state that SAVR is generally preferred in patients under 75 years and TAVI in patients 75 years and older (Baumgartner et al., 2017). This could result in higher or lower cost-savings to the Australian government

- As per the economic model, uncertainty in the length of hospitalisation stay and therefore the hospitalisation cost of TAVI-BEV. Sensitivity analyses found that changing the ratio of hospital-stay between TAVI-BEV and SAVR patients from 0.44 (4 days vs. 9 days) to 0.82 (9 days vs. 11 days) [Si et al. 2019]¹⁶ changed the results of the financial model from producing **\$redacted** million in cost-savings to the Australian government over five years, to costing the Australian government **\$redacted** million over five years
- There is also the potential for TAVI-BEV to be used in lower-risk patients as the proposed MBS item does not provide an objective definition of a patient who 'has been assessed by the Heart Team as having an intermediate risk for surgical aortic valve replacement' This could result in higher or lower cost-savings to the Australian government.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Safety vs. SAVR	Patients treated with TAVI-BEV had a higher rate of moderate or severe aortic regurgitation than patients treated with SAVR at 12 months follow-up and a higher chance of requiring a permanent pacemaker after TAVI-BEV. TAVI-BEV is safer with regards to the incidence of myocardial infarction and atrial fibrillation.
Effectiveness vs. SAVR	TAVI-BEV is superior for the outcomes of death and stroke at 12 months follow-up, but the ADAR did not present longer term comparative data for TAVI-BEV vs. SAVR. However, The Pre-ESC Response (p2) noted that 5-year data from PARTNER 3Si are available (although no publication or verifiable evidence-based data was provided) and showed that differences between the TAVI-BEV and SAVR groups in terms of mortality and disabling stroke persisted, although survival curves for mortality began to converge from Year 3.
Indirect comparison of TAVI-BEV vs. SEV	Probably no difference, although level of evidence is low quality, noting the exchangeability issues (e.g. different primary outcome, different generation TAVI devices, different baseline characteristics) with PARTNER 3Si vs. SURTAVI (SEV) Overall, ESC considered that there was a reasonable case to support a TAVI device agnostic approach.
Economic model of TAVI-BEV vs. SAVR	The cost-utility analysis was based on the clinical claim of superior effectiveness compared with SAVR in terms of death and disabling stroke. However, the Pre-ESC response revised the economic model as the 5-year data from the PARTNER 3Si study found the survival curves for mortality began to converge from Year 3. TAVI-BEV remained dominant (i.e. cheaper, more effective) in the revised economic model. TAVI-BEV's dominance was due to the estimated reduction in hospitalisation costs which might be uncertain as it was informed by propensity score analysis (PARTNER 3Si) study, which might favour TAVI-BEV.
Utilisation and potential for leakage	"Real life" decisions by the Heart Care team about characteristics are not included in the various surgical risks scores.

¹⁶ Si S, Hillis GS, Sanfilippo FM, Smith J, Tran L, Reid CM, et al. 2019. Surgical aortic valve replacement in Australia, 2002-2015: temporal changes in clinical practice, patient profiles and outcomes. ANZ J Surg 89: 1061-1067.

ESC key issue	ESC advice to MSAC
Descriptor and item number	Need to be more specific/explicit about the classification of patients as being of 'intermediate' risk. Clinical records and registry reports should document the clinical reasons why patients are categorised at higher risk level than suggested by the surgical risk score. Suggest separate item number to the current MBS item numbers for high-risk TAVIs as this can be used to monitor practice when data from ACOR TAVI registry is analysed.
Prosthesis List benefit	The ADAR proposed a higher prosthesis benefit of \$redacted for TAVI-BEV than the July 2020 Prosthesis List benefit of \$22,932 TAVI-BEV and TAVI-SEV devices for high/risk inoperable patients. ESC queried whether it is plausible that the clinical gain is greater in the intermediate population compared to the high-risk/inoperable population.

ESC discussion

ESC noted that transcatheter aortic valve implantation (TAVI) is currently Medicare Benefits Schedule– (MBS) listed as a TAVI device agnostic item (either balloon expandable valve [BEV] or self-expandable valve [SEV] for high-risk/inoperable surgical patients with symptomatic severe aortic stenosis (AS) under item 38495. This application seeks to expand the MBS listing to include intermediate-risk surgical patients.

ESC noted that, originally, the Department received a TAVI device agnostic application for patients at intermediate risk for surgery (1552), which was placed on hold by the applicant to pursue this TAVI-BEV specific application (1603). ESC noted the applicant’s rationale for this was that the PARTNER II trial showed BEVs have different clinical and economic outcomes in intermediate-risk patients, which PASC advised that these “different clinical & economic outcomes” should be clarified during the assessment phase, including what they were compared to (see Section 2 Background). However, ESC noted that the ADAR did not make a clinical claim for its comparison of TAVI-BEV vs. SEV.

ESC noted that the main comparator was surgical aortic valve replacement (SAVR) and that the secondary comparator was TAVI-SEV.

ESC noted that TAVI-BEV [Edwards] and TAVI-SEV [Medtronic] are Australian Register of Therapeutic Goods (ARTG) registered for all patients with symptomatic severe AS, regardless of surgical risk (see Table 2).

ESC noted that there was no public consultation with patient groups. ESC noted the consumer issues raised for this application included the lack of long-term comparative safety and effectiveness data, the lack of an agreed definition of intermediate risk which might contribute to inconsistent care and the importance of TAVI pre-implantation assessment.

ESC noted that consistent with MBS item 38495, there are no risk criteria specified in the proposed descriptor for “intermediate risk”. However, because of concerns about leakage, ESC considered the explanatory notes/item descriptor should require the Heart Team to document reasons for their assessment of surgical risk classification if their assessment of risk differs from the risk indicated by Society of Thoracic Surgeons-Predicted Risk of Mortality (STS-PROM) score. ESC also noted that the pre-ESC response stating that the Cardiac Society of Australia and New Zealand (CSANZ) and the Australian and New Zealand Society of Cardiac and Thoracic Surgeons are soon to publish a consensus statement on TAVI, in which the central role of the Heart Teams is emphasised.

ESC noted that the Department requested a separate item number for this intermediate population, to monitor practice when data from the ACOR TAVI registry are analysed.

ESC noted that the Commentary focused on the traditional definition of intermediate risk as the patient having an STS-PROM score of 4–8%. However, in the pre-ESC response, the applicant noted that the risk also depends on what the Heart Team considers to be a “compromised patient” because of pre-morbid status or type of impediment. This is illustrated by the fact that the Commentary included the SOLVE-TAVI trial (published earlier in 2020) in its analysis but this was not included in the original applicant-developed assessment report (ADAR). Although the SOLVE-TAVI trial (Thiele et al., 2020) reported that the median STS-PROM score was 4.9%, the trial publication considered these patients to be high risk because of other factors. ESC agreed with the pre-ESC response and noted that this underscores the real-life decisions made by the Heart Team make a broader assessment of surgical risk and consider factors not captured in STS-PROM score alone.

ESC noted concerns in the Commentary that there was no direct randomised controlled trial (RCT) evidence assessing TAVI-BEV *vs.* the primary comparator, SAVR. The ADAR’s primary clinical evidence relied on comparing a newer generation TAVI-BEV device (SAPIEN 3) with SAVR via a propensity score-adjusted comparison (PARTNER S3i) of two sub-populations from two clinical studies – intermediate risk subgroup (STS-PROM score: 4–8%) from SAPIEN 3 single-arm observational study (TAVI-BEV arm in PARTNER S3i) and patients treated with SAVR from PARTNER 2A RCT (SAVR arm). ESC agreed with the Commentary that while the propensity score adjustment process controlled for all relevant observed characteristics for the primary outcomes (the composite endpoint of all-cause mortality, stroke, moderate or severe prosthetic valve regurgitation at 1 year) there is the potential for bias due to potential differences in unobserved variables. However, ESC also noted the pre-ESC response stating that the same selection criteria were used between PARTNER 2A and SAPIEN 3 and that the prespecified propensity score adjusted analysis allowed for unbiased and meaningful comparison. For all secondary outcomes, ESC noted that the ADAR acknowledged the high uncertainty from the unadjusted (naïve) comparisons.

In terms of comparative safety of TAVI-BEV *vs.* SAVR, ESC noted that based on the propensity score-adjusted results, patients treated with TAVI-BEV had a higher rate of moderate or severe aortic regurgitation than patients treated with SAVR at 12-months follow-up. ESC also noted that based on naïve comparison, TAVI-BEV had higher rates of aortic valve re-intervention and new pacemaker implantations, but had superior safety regarding incident myocardial infarction and atrial fibrillation.

In terms of the comparative effectiveness of TAVI-BEV *vs.* SAVR, ESC considered that based on the propensity score-adjusted results, TAVI-BEV is superior for the outcomes of death and stroke at 12 months follow-up. ESC noted that naïve comparisons indicated that patients treated with TAVI-BEV had superior health-related quality of life (HRQoL) at 30 days, but not at 12 months follow-up suggesting that TAVI-BEVs beneficial impact on patients HRQoL did not extend beyond the perioperative period.

ESC noted that the pre-ESC response cited the 5-year outcome data from patients enrolled in PARTNER 3Si presented at a conference in June 2020. These results showed that differences between the TAVI-BEV and SAVR groups in terms of mortality and disabling stroke persisted, although survival curves for mortality began to converge from Year 3. ESC considered that the 5-year data would be beneficial to MSAC’s consideration, in particular to verify the comparative clinical claim for all outcomes over the longer term.

ESC considered the ADARs secondary comparison of TAVI-BEV *vs.* SEV, noting that the ADAR and Commentary agreed that there was too much clinical heterogeneity to draw conclusions from the indirect comparison made between TAV-BEV (PARTNER S3i study)

and TAVI-SEV (SURTAVI RCT), via the common comparator, SAVR. ESC noted that the primary endpoint of PARTNER S3i was different to the primary endpoint of the PARTNER 2A (and SURTAVI RCT) which used composite of death or disabling stroke. Additionally, there were also differences in TAVI devices used, baseline characteristics and event rates for the common comparator arm (SAVR). In the pre-ESC response, the applicant noted that PASC requested this evaluation and, to undertake this evaluation, an assumption had to be made about the relative efficacy of TAVI-BEV compared with TAVI-SEV. The applicant noted that, as detailed in the ADAR, it was reasonable based on available evidence to assume that TAVI-SEV had the same efficacy as SAVR in terms of the composite outcome of death and stroke: TAVI-SEV 8.1% versus SAVR 8.8% at 12 months (95% confidence interval 3.5% to 2.1%, $P > 0.99$). However, ESC considered that the superiority of the BEV device (relative to SEV) was not established as it relied upon this assumption.

ESC also considered the Commentary's secondary comparison of TAVI-BEV *vs.* SEV, noting that the results of SOLVE-TAVI suggested that TAVI-BEV and SEV were equivalent in terms of the composite primary endpoint: all-cause mortality, stroke, moderate or severe paravalvular leakage, and permanent pacemaker implantation at 30-day follow-up. However, ESC considered there were applicability concerns with the trial population and that the results were limited to 30-days, and as such did not inform longer term outcomes.

Overall, ESC considered that there is probably no difference between TAVI-BEV *vs.* SEV, although the level of evidence is not high. Thus, ESC considered there might be a case to support a device agnostic approach. However, ESC also noted that there is an upcoming TAVI-device agnostic (BEV or SEV or mechanically expanding valve) application in intermediate surgical risk population (1652) which will be considered at the February 2021 ESC meeting.

However, ESC noted if a device agnostic approach was not supported by MSAC, that any MBS item should be specific to BEV. If SEV is to be listed, then it would need to demonstrate that it is non-inferior (to BEV) to be used in intermediate-risk populations. At that time, there would need to be a separate discussion around the pricing for SEV, which would have implications for price negotiations for BEV *vs.* SEV (if SEV is to be listed).

ESC noted that originally, the ADAR's economic model for TAVI-BEV *vs.* SAVR relied on one-year data from the PARTNER S3i study only and that the ADAR assumed no treatment benefit between TAVI-BEV and SAVR beyond one year. ESC also noted that the ADAR base case model was non conservative, as the pre-ESC response revised the modelled evaluation such that the overall survival curves crossed at five years based on 5-year outcomes from PARTNER 3Si (see Figure 5). However, ESC noted that TAVI-BEV remained dominant over SAVR (see Table 11), but queried if the model should be based on the 5 year results for all outcomes (such as stroke rates and other adverse events). ESC also noted the Commentary performed model validation comparing the modelled Markov traces with the 5-year trial results of death or disabling stroke from PARTNER 2A, which compared the earlier generation BEV device: TAVI-SAPIEN XT *vs.* SAVR (see Figure 4).

ESC noted that the ADAR did not include the cost of prostheses or the cost of hospital stay for the proportion of private patients included in the economic and financial model. ESC noted that the Commentary revised the ADAR base-case model using the current benefit level of TAVI-BEV on the Prostheses List (\$22,932) rather than the ADARs proposal and including hospital stay and prostheses costs for private patients. Expectantly, ESC noted this resulted in a more favourable incremental cost-effectiveness ratio (ICER). ESC also noted the Commentary's revised financial estimates attributed costs of the prostheses to private health

insurance (PHI), but also assumed private hospital costs would be based on public hospitalisation costs and attributed to PHI. ESC queried if this was appropriate and advised presenting the costs to private hospitals separate to PHI (see Table 13).

However, ESC noted that the cost savings estimated in the economic and financial models were highly sensitive to the extent of the reduction in hospitalisation costs in patients treated with TAVI-BEV compared with SAVR. However, the sensitivity analyses found that TAVI-BEV was the dominant (i.e. cheaper, more effective) treatment option compared to SAVR in most scenarios. The only exception was the uncertainty in hospital length of stay as the Commentary's threshold analysis indicated that TAVI-BEV stops being the dominant treatment option when TAVI-BEV hospitalisation costs reach **redacted** of SAVR hospitalisation costs.

ESC considered the secondary cost-utility analysis of TAVI-BEV *vs.* SEV. ESC agreed with the Commentary that this comparison was non-informative as the ADAR inappropriately assumed that TAVI-SEV generally had the same efficacy and risks as SAVR. ESC also noted that the ADAR proposed a higher prosthesis benefit of **\$redacted** for TAVI-BEV than the July 2020 Prostheses List benefit of \$22,932 for TAVI-BEV and TAVI-SEV devices.

ESC discussed whether it is plausible that clinical gain is greater in the intermediate population compared to the high-risk/inoperable population, to justify the price of **\$redacted** (compared to \$22,932 for high-risk/inoperable patients). ESC recalled that, when MSAC considered TAVI for high-risk/inoperable patients, the debate pivoted on the claim that the duration of hospitalisation was reduced. MSAC noted that this approach still favoured TAVI because this calculation assumes that the cost of hospitalisation will be evenly distributed across the length of the hospital stay, whereas it is known that the reductions in hospital stay are typically for the cheaper days that do not incur the costs of the procedure. Consistent with the high-risk/inoperable application, ESC noted that length of stay is also the key driver in the economic model, and also noted the pre-ESC response discussion of length of stay reported for Australian TAVI patients.

ESC noted that MSAC anticipated a clinical gain when moving from high-risk to intermediate-risk patients, and that this might give an expectation that the value proposition would be better in the intermediate population. ESC noted that length of stay will need to be considered in any future applications that consider low-risk populations. ESC noted that TAVI-BEV for low risk (1635) will be considered at the February 2021 ESC meeting.

To investigate the value proposition of TAVI across the different levels of surgical risk (high-, intermediate-, and low-risk), ESC reviewed the published literature focusing on length of hospital stay reported from RCT based comparisons of TAVI (BEV or SEV) *vs.* SAVR. ESC noted this analysis indicated that although patients treated with TAVI or SAVR typically have longer index hospitalisation for those with higher surgical risk, the clinical gain in regards to the reduction in hospital length of stay with TAVI (BEV or SEV) *vs.* SAVR across surgical risk categories was broadly consistent across the absolute differences (~4 days) rather than the ratios of duration (Table 14). ESC noted that these results were also consistent with an RCT (Thyregod et al 2015¹⁷) of an all comers population (mainly low risk) treated with TAVI-SEV *vs.* SAVR (8.9 ± 6.2 days *vs.* 12.9 ± 11.6 days, respectively; $p=0.001$). However, from non-RCT data, such as the PARTNER 3Si study, ESC noted that

¹⁷ Thyregod HG, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engström T, Clemmensen P, Hansen PB. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. *Journal of the American College of Cardiology*. 2015 May 26;65(20):2184-94.

the results supported a greater reduction in hospital length of stay (5 days) for TAVI-BEV vs. SAVR. However, ESC noted that these estimates were more uncertain as they were informed from propensity score analysis (rather than from an RCT).

Table 14: Comparison of hospital length of stay across surgical risk for TAVI (BEV or SEV) vs. SAVR[¶]

Low surgical-risk ^α			Intermediate surgical-risk ^α			High/inoperable-risk ^α		
RCTs ^α			α			α		
PARTNER3 [¶] Mack: 2019 ^α	TAVI ^α	SAVR ^α	PARTNER2A Chen: 2018 ^α	TAVI ^α	SAVR ^α	PARTNER [¶] Smith: 2011- ^α	TAVI ^α	SAVR ^α
Valve ^α	BEV [¶] SAPIEN-3 New/3 rd -gen ^α	- ^α	Valve ^α	BEV [¶] SAPIEN-XT- 2 nd -gen ^α	- ^α	Valve [¶] 1 st -gen ^α	BEV [¶] SAPIEN [¶] 1 st -gen ^α	- ^α
LoS (index) ^α	Median: [¶] 3-days ^α	Median: [¶] 7-days ^α	LoS (index) ^α	Mean: 6.2 ^α days- ^α	Mean: 10.7 ^α days- ^α	LoS (index) ^α	8-days- ^α	12-days- ^α
Difference ^α	4-days ^α	- ^α	Difference ^α	4.5-days ^α	- ^α	Difference ^α	4-days ^α	- ^α
Ratio (%) ^α	1: 2.33 (43%) ^α	- ^α	Ratio (%) ^α	1: 1.7 (58%) ^α	- ^α	Ratio (%) ^α	1: 1.5 (66%) ^α	- ^α
Medtronic- Popma (2019) ^α	TAVI ^α	SAVR ^α	SURTAVI [¶] Reardon: 2017 ^α	TAVI ^α	SAVR ^α	Medtronic- (Adams: 2014) ^α	TAVI ^α	SAVR ^α
Valve ^α	SEV [¶] CoreValve- (1 st -gen)-or- Evolut-R-(2 nd - gen)-or- Evolut-PRO- (3 rd -gen) ^α	- ^α	Valve ^α	SEV [¶] CoreValve- (1 st -gen)-or- Evolut-R-(2 nd - gen) ^α	- ^α	Valve ^α	SEV [¶] CoreValve- (1 st -gen)- ^α	- ^α
LoS (index) ^α	NR ^α	NR ^α	LoS (index) ^α	Mean: [¶] 5.75-days- ±4.85 ^α	Mean: [¶] 9.75-days [¶] ±8.03 ^α	LoS (index) ^α	NR ^α	NR ^α
Difference ^α	- ^α	- ^α	Difference ^α	4-days ^α	- ^α	Difference ^α	- ^α	- ^α
Ratio (%) ^α	- ^α	- ^α	Ratio (%) ^α	1: 1.7 (59%) ^α	- ^α	Ratio (%) ^α	- ^α	- ^α
Non-RCTs ^α			α			α		
α			PARTNER3Si Thourani: 2016 ^α	TAVI ^α	SAVR ^α	α		
			Valve ^α	BEV-SAPIEN- 3 ^α	α			
			LoS ^α	Median: [¶] 4-days ^α	Median: [¶] 9-days ^α			
			Difference ^α	-5-days ^α	- ^α			
			Ratio ^α	1: 2.25 (44%) ^α	- ^α			

[¶] Derived as weighted average of all patients who either had prior cardiac surgery or did not and received TAVI or SAVR: TAVI time to discharge: Prior cardiac surgery = 5.5 ± 3.0 (n=245); No prior cardiac surgery = 6.5 ± 5.2 (n=766); SAVR time to discharge: Prior cardiac surgery = 10.5 ± 6.8 (n=264); No prior cardiac surgery = 10.8 ± 7.0 (n=757)[¶]
^α BEV = balloon-expandable device; gen = generation; LoS = length of stay; NR = not reported; RCT = randomised controlled trial; SAVR = surgical aortic valve replacement; SEV = self-expanding valve[¶]

ESC recalled that for the high-risk/inoperable application (1361.2), that the economic model was revised to use the relevant 5-year PARTNER trial data (see Table 1). ESC also recalled that on the basis of the 5-year data, MSAC considered that the claim of an improved overall survival was not substantiated in order to justify the incremental cost-utility ratios presented in the stepped economic evaluation, and recommended that TAVI was negotiated on a cost-minimisation basis (see Section 2-Background).

15. Other significant factors

Nil.

16. Applicant comments on MSAC's Public Summary Document

Edwards Lifesciences is pleased that “MSAC supported the creation of a new Medicare Benefits Schedule (MBS) item for transcatheter aortic valve implantation (TAVI) using a balloon-expandable valve (BEV) system for patients with symptomatic severe aortic stenosis (AS) at intermediate risk for surgery”, and looks forward to working with government,

private health insurers, clinical providers and patient groups to make SAPIEN 3 accessible to Australians in need.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
[visit the MSAC website](#)