



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### ***Application No. 1635 – Transcatheter aortic valve implantation via transfemoral delivery using the balloon-expandable valve system for patients at low risk for surgery***

**Applicant:** Edwards Lifesciences

**Date of MSAC consideration:** MSAC 82<sup>nd</sup> Meeting, 29-30 July 2021  
MSAC 81<sup>st</sup> Meeting, 31 March – 1 April 2021

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 low risk for surgery was received from Edwards Lifesciences Pty Ltd by the Department of Health.

#### **2. MSAC's advice to the Minister – July 2021**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported MBS funding of transcatheter aortic valve implantation (TAVI) using a balloon-expandable valve (BEV) system for patients with symptomatic severe aortic stenosis at low risk for surgery on the grounds of acceptable safety, effectiveness and cost effectiveness compared with surgical aortic valve replacement (SAVR). Consistent with its assessment of TAVI in all levels of surgical risk, MSAC supported an MBS item that is agnostic of the type of TAVI device.

MSAC supported the following item descriptor (abridged):

*TAVI, ~~using a balloon-expandable system~~, for treatment of symptomatic severe **native calcific** 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 2018(Cth) (Department of Health 2018) 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 a low risk for surgical aortic valve replacement and is recommended as being suitable to receive the service described in Item XXXXX.*

*Fee: \$1,476.95 Benefit: 75% = \$1,107.75 85% = \$1,392.25*

### **Consumer summary**

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

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. There are two main types of TAVI devices: TAVI-BEV or TAVI using a self-expandable valve (SEV).

MSAC had already largely accepted that TAVI is a safe and effective procedure, and is better value for money than surgical aortic valve replacement (open heart surgery) in the short term. In this application, MSAC considered TAVI is likely to be as safe and as effective as surgery in the longer-term. In addition, MSAC considered that there is a robust process in place for specialist heart teams to make the best choice for patients between TAVI and SAVR, depending on patients' needs and risk.

MSAC also did not believe there was any reason to prefer one type of TAVI device over another.

#### **MSAC's advice to the Commonwealth Minister for Health**

MSAC supported MBS funding for TAVI for patients at low risk for surgery using an item descriptor that does not specify the type of TAVI device. MSAC based its decision on the fact that it considered TAVI to be effective, safe and cost-effective compared with SAVR.

### **Summary of consideration and rationale for MSAC's advice – July 2021**

MSAC recalled it had deferred its advice on MBS funding of TAVI via transfemoral delivery using the balloon-expandable valve system (BEV) for patients at low risk for surgery as it was concerned about valve durability over the longer term, given that the low surgical risk population is younger, has longer life expectancy and generally has good long-term outcomes with SAVR. MSAC recalled it had considered further consultation is needed to define key factors that suggest one procedure may be preferred over the other for the low surgical risk population. MSAC recalled that it had considered that the appropriate population and item descriptor for TAVI with low surgical risk would need to be further refined to ensure TAVI is used for low risk patients most likely to benefit from the procedure (Public Summary Document [PSD] [Application No. 1635](#), p1).

MSAC noted the targeted consultation feedback provided by the following organisations: the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS), the Cardiac Society of Australia and New Zealand (CSANZ), Hearts4heart, and the Australian Society of Anaesthetists (ASA).

MSAC noted the minor resubmission for TAVI using a BEV device for patients at low risk of surgery from the applicant.

MSAC also noted the similarities with application 1640 for TAVI (device agnostic) in patients at low risk for surgery, and reiterated its preference for a device agnostic MBS item. In response to MSAC's request, the minor submission proposed no changes to the previously proposed item descriptor and explanatory notes. The minor submission considered that the item descriptor should only refer to the function of the Heart Team, without the need to specify appropriate populations and factors that define those "most likely to benefit from the procedure". Any attempt to do this will not adequately capture the broad range of relevant real-world scenarios and considerations.

The minor submission considered that the evidence for the durability of TAVI-BEV continues to accumulate, and by and large, this suggests comparability to SAVR. MSAC noted the minor submission and consultation feedback presented longer term TAVI valve data to address the issue of durability, especially for younger patients who may live for a long period after the procedure. The pre-MSAC response considered that the TAVI valves have similar durability to surgical valves. MSAC noted that the studies presented in the consultation feedback was for all TAVI valves. MSAC considered that the totality of the evidence presented demonstrated acceptable valve durability at 5–10 years following TAVI and that this was sufficient to support an MBS listing. As a result, MSAC considered that TAVI is at least non-inferior to SAVR in terms of long-term safety and effectiveness for patients with symptomatic severe native aortic stenosis at low risk of surgery.

MSAC recalled that it had noted that TAVI-BEV was associated with higher rates of paravalvular leakage and left bundle branch block. MSAC noted that the ANZSCTS advised that the PARTNER 3 and EVOLUT trials were conducted in highly selected populations and reported inconsistent endpoints compared with the earlier TAVI trials in higher risk populations. MSAC noted that the applicant generally disagreed with ANZSCTS interpretation of the PARTNER 3 trial. MSAC noted that the applicant identified errors of fact in the ANZSCTS's feedback however this was not material to MSAC's assessment of the evidence.

MSAC noted feedback from CSANZ advising that it was not supportive of a defined list of factors, noting the clinical considerations are complex and should be assessed by a Heart Team. Similarly, Hearts4heart did not support restrictions in place for heart valve patients to have access to TAVI. MSAC noted that it is difficult to be prescriptive on TAVI vs. SAVR based on age because several other factors would also affect the appropriateness of the type of procedure. MSAC also noted that patients would have to satisfy the criteria of being low risk to be eligible for this item number, regardless of their age.

MSAC considered whether the item descriptor should exclude patients aged <65 years, because 2020 American College of Cardiology and American Heart Association (ACC/AHA, Otto *et al.* 2021<sup>1</sup>) guidelines generally recommend SAVR for patients <65 years unless life

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<sup>1</sup> Otto CM *et al.* 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2021;143(5):e35-e71.

expectancy is limited or other factors suggest TAVI is preferable. MSAC noted that ANZSCTS supported a preference for SAVR in patients <70 years. However, MSAC considered that being prescriptive about age is unnecessary because the processes of Heart Team discussions (TAVI case conference) allow for an appropriate decision to be made regarding whether a patient should have TAVI or SAVR.

MSAC noted that the TGA-approved indication for the TAVI valves indicated for all levels of surgical risk (including TAVI-BEV), thus encompassing the low surgical risk population, is limited to patients who have severe native calcific aortic stenosis, and that therefore the target patient population in the current item should also have severely calcified valve leaflets. MSAC noted that TAVI may be an appropriate procedure for some people with other types of aortic stenosis, however, for most, SAVR would be the preferred intervention. For that reason, the item descriptor should specify that TAVI is intended for patients with severe “native calcific” aortic stenosis. MSAC considered that this would limit use for patients with aortic stenosis due to congenital abnormalities or other causes which are more common in younger age groups than native aortic stenosis.

MSAC noted ANZSCTS’s proposal for independent surgical assessment. MSAC noted that the current MBS explanatory notes for TAVI specify that the Heart Team must consist of three or more participants where the first participant is a cardiothoracic surgeon and the second is an interventional cardiologist, where either the first or second participant is a TAVI Practitioner. MSAC noted that requirements for the composition of Heart Teams is regulated. MSAC considered that this should allow sufficient surgical input as all members of the team have to agree whether a patient is suitable for TAVI and this should also consider factors such as patient frailty and cognition. Overall, MSAC concluded that Heart Team discussions would be based on contemporary guidelines (and patient choice; see below), presenting a robust basis for clinical decision-making.

MSAC emphasised the importance of a shared decision-making process as outlined in the 2020 ACC/AHA guidelines that accounts for the patient’s values and preferences and informs patients about the benefits and limitations of each approach, including the risks associated with reintervention. MSAC recalled that it had previously noted that Heart Team discussions should help guide the patient to the appropriate choice (PSD Application 1635, p4). MSAC noted that, as raised by Hearts4heart, patients may prefer TAVI as it is less invasive, and patients generally prefer the faster recovery from TAVI. However, MSAC considered that it was important that patients were informed about the limited long-term data (beyond 10 years) available for TAVI so that patients can make informed decisions. MSAC noted that CSANZ had recommended that high quality patient information be provided explaining the progressive evolution of TAVI.

MSAC noted that repeat TAVI (valve-in-valve) procedures may become the preferred method of reintervention for TAVI patients requiring a repeat procedure. MSAC considered that repeat TAVI was likely to be less risky than repeat SAVR as repeat SAVR carries additional risks due to differences in the placement of the original SAVR and TAVI valves.

MSAC concluded that it would be appropriate to audit Heart Team documentation and decisions and considered that the process of audit would encourage compliance in the clinical community. MSAC considered that it would also be appropriate to consider audits of Heart Teams at the level of the hospital. MSAC noted that TAVI Hospitals are required to undergo an accreditation and re-accreditation process. MSAC noted that the TAVI Accreditation

Committee and Cardiac Accreditation Services Limited would be involved in the auditing process.

MSAC advised that the Department should consider whether a proforma for documenting the Heart Team assessment should be developed. MSAC advised that this could also be provided to the TAVI Registry.

MSAC considered that this item should be reviewed in 2 years to assess predicted versus actual use. MSAC requested the Department include summary data from the TAVI registry, where possible. MSAC considered that there is a risk of leakage to asymptomatic patients who are younger and at low risk for adverse clinical outcomes from aortic stenosis. This could be looked at in the TAVI registry data, and also valve durability over time. MSAC advised that the requirement for native calcific aortic stenosis could be updated in the future if new evidence emerges or when MSAC considers combining the TAVI items into a single item.

MSAC noted that the TAVI registry should be able to provide data on length of stay, noting this would be for the currently subsidised high-risk population.

MSAC supported a Prostheses List benefit of \$22,932 for TAVI-BEV device. MSAC recalled that based on the clinical and economic evidence, it was not convinced that there is basis to separate TAVI-BEV and TAVI-SEV for funding purposes. Therefore, MSAC reaffirmed that the higher Prostheses List benefit (**\$redacted** for TAVI-BEV compared with the current benchmark of \$22,932 for TAVI-BEV and TAVI-SEV) was not justified.

MSAC was concerned that consumer feedback indicated additional costs of approximately \$5,000 to \$6,000 were being incurred for the TAVI-BEV device. MSAC recalled that at its November 2020 consideration of TAVI-BEV for the intermediate risk population, the pre-MSAC response indicated that the proposed Prostheses List benefit of **\$redacted** includes consumable items necessary for valve placement so there would be no net change to price within the private sector (previously purchased by private hospitals and/or patients). MSAC did not consider that this additional cost to patients or hospitals was reasonable based on its assessment of cost-effectiveness. MSAC reaffirmed that its assessment of cost-effectiveness and advice on the Prostheses List Benefit (as above) was based on the complete intervention which included the valve and all components of the delivery system. In the current application's revised base case of the economic model, the TAVI procedural costs for private patients included MBS costs, a hospitalisation cost of \$21,161 and prosthesis cost of \$22,932 which should include the valve and the delivery system.

### **Other discussion**

MSAC noted that expanding the listing of TAVI would increase the number of TAVI procedures and prostheses funded by private health insurance providers. MSAC requested the Department advise private insurance providers of this recommendation.

### **3. MSAC's advice to the Minister – March-April 2021**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC deferred its advice on Medicare Benefits Schedule (MBS) funding of transcatheter aortic valve implantation (TAVI) via transfemoral delivery using the balloon-expandable valve system (BEV) for patients at low risk for surgery. MSAC largely accepted that TAVI-BEV is safe, effective and cost-effective compared with surgical aortic valve replacement (SAVR), but was concerned about valve

durability over the longer term, given that the low surgical risk population is younger, has longer life expectancy and generally has good long-term outcomes with SAVR.

For these reasons, MSAC considered further consultation is needed to define key factors that suggest one procedure may be preferred over the other for the low surgical risk population. MSAC considered that the appropriate population and item descriptor for TAVI with low surgical risk would need to be further refined to ensure TAVI is used for low risk patients most likely to benefit from the procedure.

In addition, MSAC maintained its preference for a device-agnostic MBS item descriptor for this new item, recalling its precedent set on the basis of similar clinical performance and thus the same benefit across TAVI device options in high surgical risk and intermediate surgical risk populations. This advice would be re-assessed at the July 2021 MSAC meeting consideration of the TAVI device agnostic application for patients at low risk for surgery (MSAC Application 1640).

### **Consumer summary**

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

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. There are two main types of TAVI devices: TAVI-BEV or TAVI using a self-expandable valve (SEV).

MSAC accepted that TAVI is a safe and effective procedure, and is better value for money than surgical aortic valve replacement (open heart surgery) in the short term. But there is not enough information on how long TAVI valves last before they need to be replaced. This is especially important for patients at low risk for surgery, because these people are usually younger, have a longer life expectancy, and tend to have good outcomes from surgery. For this reason MSAC will consult further with experts and consumer groups to define low risk patients most likely to benefit from the TAVI procedure.

MSAC also did not believe there was any overall reason to prefer one type of TAVI device over another. This advice would be re-assessed at the July 2021 MSAC meeting, when MSAC reviews another application for TAVI in low surgical risk patients using any type of TAVI device.

### **MSAC's advice to the Commonwealth Minister for Health**

MSAC deferred its advice on TAVI for patients at low risk for surgery and will seek further advice from experts and consumer groups.

## Summary of consideration and rationale for MSAC's advice – March-April 2021

MSAC noted that TAVI is currently MBS-listed as a TAVI device agnostic item (either BEV or self-expandable valve [SEV]) for high-risk/inoperable surgical patients with symptomatic severe aortic stenosis (AS) under item 38495. MSAC also recalled its recent assessment of TAVI-BEV for intermediate risk for surgery, “consistent with the current MBS item for TAVI (item 38495), MSAC supported an MBS item agnostic of the type of TAVI device” ([Public Summary Document \[PSD\] Application No. 1603, p1](#)). MSAC noted that this device-specific application for TAVI-BEV is seeking to expand MBS listing to include low-risk surgical patients.

MSAC noted supportive consumer feedback for the application emphasising the importance of a less invasive procedure, fewer complications (bleeding and atrial fibrillation), faster recovery and shorter hospital stay.

MSAC considered that surgical aortic valve replacement (SAVR) as the main comparator and TAVI-SEV as the secondary comparator was appropriate. MSAC noted there was a direct randomised controlled trial (RCT) assessing TAVI-BEV vs. SAVR (PARTNER 3 trial) and the applicant developed assessment report (ADAR) also included a direct RCT assessing TAVI-SEV vs. SAVR (EVOLUT trial).

MSAC noted and agreed with the ESC advice for the comparative safety and comparative effectiveness comparing TAVI-BEV with SAVR. MSAC noted that there was less bleeding with TAVI-BEV but higher rates of paravalvular leakage. MSAC noted that left bundle branch block was more common with TAVI-BEV and this could lead to heart failure. MSAC considered that this was of greater significance to low surgical risk patients who may be expected to have a longer life expectancy than higher risk populations. MSAC noted that TAVI-BEV was superior over SAVR in terms of the primary composite outcome of death, stroke and rehospitalisation. However, MSAC also noted that the Kaplan-Meier plots for the key effectiveness outcomes (death, composite of death or disabling stroke) appeared to be converging but the point estimates favoured TAVI-BEV. MSAC noted that several of the deaths that occurred between year 1 and year 2 did not appear related to aortic valve replacement. Overall, MSAC largely accepted that TAVI-BEV is safer and more effective in the short term compared with SAVR.

MSAC noted that the indirect comparison of TAVI-BEV vs. TAVI SEV was affected by some differences in eligibility criteria, reporting of comorbidities and statistical methods but considered the trials were somewhat exchangeable. MSAC noted that there was a statistically significant difference in the proportion of patients requiring a permanent pacemaker which favoured TAVI-BEV. However, MSAC agreed with ESC that the results from the indirect comparison did not show differences between TAVI-BEV and TAVI-SEV that strongly justified a device-specific approach. MSAC considered that clinicians are appropriately placed to decide on the most appropriate device for individual patients.

MSAC noted the economic evaluation comparing TAVI-BEV with SAVR was a cost-utility analysis. MSAC noted that TAVI-BEV was dominant. MSAC noted that this was due to TAVI-BEV having a shorter and less costly hospitalisation. MSAC noted the cost-utility analysis overestimated the benefit of TAVI-BEV because the 2-year data from the PARTNER 3 trial<sup>2</sup> showed that the benefit of TAVI-BEV appeared to be decreasing over time. The pre-ESC response acknowledged this concern, but reiterated that TAVI-BEV is

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<sup>2</sup> Leon MB *et al.* Outcomes 2 Years After Transcatheter Aortic Valve Replacement in Patients at Low Surgical Risk. *J Am Coll Cardiol.* 2021;77(9):1149-1161.

dominant over SAVR and that there is no reason to expect worse cumulative survival with TAVI-BEV. The pre-MSAC response presented additional data from the Australian Cardiac Outcomes Registry (ACOR)<sup>3</sup> showing that the length of hospital stay was 4 days across all surgical risk levels; and also stated that data from the United States shows decreasing length of hospitalisation with TAVI procedures over time<sup>4</sup>. Overall, MSAC largely accepted that TAVI-BEV is cost-effective compared with SAVR.

MSAC considered the economic comparison of TAVI-BEV vs. TAVI-SEV was uninformative as it made several implausible assumptions that inappropriately favoured TAVI-BEV.

Based on the clinical and economic evidence, MSAC was not convinced that there is basis to separate TAVI-BEV and TAVI-SEV for funding purposes. MSAC considered that the TAVI procedure is similar for both devices and the evidence presented did not conclusively show that TAVI-BEV achieved superior clinical outcomes compared with TAVI-SEV. MSAC noted this was consistent with the precedent set for similar clinical performance across TAVI device options in higher risk populations. Therefore, MSAC considered that the higher Prostheses List benefit (**\$redacted** for TAVI-BEV compared with the current benchmark of \$22,932 for TAVI-BEV and TAVI-SEV) was not justified.

MSAC noted that the financial implications estimated large cost savings. The MSAC considered the financial impact was uncertain. MSAC considered that there is a risk of leakage into patients with asymptomatic AS.

MSAC agreed with ESC's concern that people under 75 years of age could be eligible for this MBS item, but that data on TAVI are limited for patients under 75 years of age and for low surgical risk patients, and SAVR is preferred for these patients. MSAC also noted the applicant's pre-MSAC response, which highlighted recent clinical guidelines issued by the American College of Cardiology/American Heart Association (ACC/AHA), stating that in (Otto 2021)<sup>5</sup>:

- patients aged <65 years or with life expectancy >20 years: SAVR is preferred
- patients aged >80 years or with life expectancy <10 years: TAVI is preferred
- symptomatic patients aged 65–80 years with no contraindication to transfemoral TAVI: SAVR or transfemoral TAVI is recommended after shared decision making.

MSAC considered that the main residual concerns in deciding whether to support the application's requested funding relate to the durability of the TAVI valves and the patient's expected longevity. MSAC considered that a patient's eligibility for TAVI should be changed from being based on the risk of adverse outcomes following SAVR to being based on the patient's expected longevity and comorbidities (such as frailty and cognitive function), as well as exclusion criteria due to issues such as bicuspid valve disease. MSAC noted that joint Australian guidance by the Cardiac Society of Australia and New Zealand (CSANZ) and the Australia and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) will be available in the near future.

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<sup>3</sup> 11. Sinhal A, *et al.* Transcatheter Aortic Valve Implantation in Australia: Insights from the ACOR TAVI Registry. *Heart, Lung and Circulation* 2019;28:S433.

<sup>4</sup> 12. Carroll JD *et al.* STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol.* 2020 Nov 24;76(21):2492-2516.

<sup>5</sup> Otto CM *et al.* 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2021;143(5):e35-e71.

Although MSAC largely accepted the short-term assessment of clinical evidence and the economic evaluation, it remained concerned that TAVI may be used inappropriately for patients who may be more appropriate for SAVR. For this reason, MSAC deferred its advice on public funding of TAVI in the low surgical risk population. MSAC noted the applicant's pre-MSAC response providing longer-term data on durability of TAVI valves from registry data, but considered the long-term outcomes with TAVI and the durability of TAVI valves are yet to be demonstrated. MSAC considered that this was of greater importance for patients at low surgical risk who, on average, are younger and have a longer life expectancy than patients with intermediate or high risk of surgical mortality. In addition, MSAC noted that there is limited evidence on reintervention with TAVI (valve-in-valve procedures) and whether this procedure performs as well as an initial TAVI procedure. MSAC noted the requirement to involve the heart team before a TAVI procedure, and that these heart team discussions should help guide the patient to the appropriate choice. MSAC considered that the heart team discussions may need to consider factors such as the limited evidence on long-term outcomes. MSAC was also concerned consumers may have a strong preference for TAVI as it is less invasive than SAVR, but may not be fully informed about the lack of long term evidence data supporting its use. In addition, patients with low surgical risk have generally have good long-term outcomes with SAVR compared with intermediate or high surgical risk patients. For these reasons, MSAC considered that the appropriate population and item descriptor for TAVI with low surgical risk would need to be further refined, such as defining key exclusion criteria, to ensure TAVI is used for low risk patients most likely to benefit from the procedure. MSAC considered further consultation is needed to define key factors that suggest one procedure may be preferred over the other.

MSAC considered that a separate MBS item should be created for TAVI in low risk population as this would assist monitoring of TAVI utilisation. MSAC anticipated its preference for a device-agnostic MBS item descriptor for this new item, and considered this would be consistent with the current MBS items for TAVI and thus across all levels of surgical risk. MSAC noted this advice would be re-assessed at the July 2021 MSAC meeting consideration of the TAVI device agnostic application for patients at low risk for surgery (MSAC Application 1640).

MSAC advised that at a future date it may be appropriate to consolidate the TAVI items based on surgical risk into a single item.

#### **4. Background**

This is the first submission for TAVI-BEV for patients with symptomatic severe aortic AS at low risk for surgery.

##### *TAVI low risk applications*

The Department has received a related application, from a competitor TAVI manufacturer, for a TAVI agnostic to device (BEV [Edwards] or SEV [Medtronic] are TAVI TGA registered devices for all levels of surgical risk) in low risk (MSAC application 1640) which is progressing via an expedited pathway **REDACTED**. The application has made the a clinical claim that TAVI for the treatment of symptomatic severe AS is superior in effectiveness and safety compared to SAVR for patients at low risk of surgery ([MSAC application 1640](#), p16).

##### *TAVI intermediate risk applications 1603 and 1652*

At its November 2020 meeting, MSAC supported the creation of a new MBS item for transcatheter aortic valve implantation (TAVI) for patients with symptomatic severe AS at intermediate risk for surgery on the grounds of acceptable safety, effectiveness and cost

effectiveness compared with surgical aortic valve replacement (SAVR, [Public Summary Document \[PSD\] Application No. 1603](#)). 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](#)).

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

MSAC also 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 Prostheses 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).

A comparison of the clinical outcomes with TAVI-BEV in the low-risk population (current application) and the intermediate risk population (Application No. 1603) is presented in Table 2. A comparison of the economic evaluation in the low-risk population (current application) and the intermediate risk population (Application No. 1603), and high risk/inoperable population ([Application No. 1361.2](#)) is presented in Table 2.

MSAC Application 1652 will also be considered at the March 2021 MSAC meeting. The Application made a clinical claim of non-inferior effectiveness and similar safety compared with SAVR ([Application 1652](#), p15).

#### *TAVI high-risk and inoperable application 1361 series*

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 ([PSD Application No. 1361.2](#)).

At the March 2016 MSAC consideration, MSAC noted five-year data from the PARTNER trial<sup>6</sup> had been used in the resubmission to determine outcome benefits in the model. MSAC noted that the base case result in the model comparing TAVI with SAVR in high-risk surgical patients was based on the subgroup of patients from this trial who received their TAVI via the transfemoral route only (HR 0.91; 95% CI 0.72, 1.14). These subgroup results were numerically more favourable than the intention-to-treat (ITT) results (HR 1.04; 95% CI 0.86, 1.24). MSAC also noted that the numerically different overall survival estimates following TAVI and SAVR were not statistically significantly different in either the ITT analysis or the subgroup analysis.

MSAC judged that the greater uncertainty in the revised economic model for TAVI versus SAVR was a source of concern. The more internally valid estimate of \$44,011/QALY increased to \$54,489/QALY when combined in a plausible bivariate sensitivity analysis with the concern about the probability of complications. Most importantly, 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 Steps 3, 4 and 5 of this model, and 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, notwithstanding the CoreValve trial, there was limited evidence of superior safety and clinical effectiveness for TAVI versus SAVR, and as such a cost-minimisation approach should be considered across all prostheses. 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.

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.

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<sup>6</sup> Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385(9986):2477-2484.

**Table 1 Comparison of clinical outcomes between TAVI-BEV for low-risk patients (MSAC 1635) and TAVI-BEV for intermediate-risk patients (MSAC 1603)**

Outcome	PARTNER 3 (Low-Risk)			PARTNER S3i (Intermediate-Risk)		
	TAVI-BEV	SAVR	Treatment Effect (95% CI)	TAVI-BEV	SAVR	Treatment Effect (95% CI)
Study Type	Randomised, multicentre, open-label trial, non-inferiority and superiority trial between TAVI-BEV and SAVR			Propensity score-adjusted comparison of two sub-populations from the SAPIEN 3 (TAVI-BEV) and PARTNER 2A (SAVR)		
<b>Patient Demographics</b>						
Age (years)	73.3 (5.8)	73.6 (6.1)	-	81.9 (6.6)	81.6 (6.76)	-
STS-PROM %	1.9 (0.7)	1.9 (0.6)	-	5.2	5.4	-
NYHA class III or IV	155/496 (31%)	108/454 (24%)	-	781/1063 (73%)	718/944 (76%)	-
<b>Perioperative outcomes</b>						
All-cause mortality	2/496 (0.4%)	5/454 (1.1%)	0.37 (0.07, 1.88)	12/1063 (1%)	38/902 (4%)	<b>0.27 (0.14, 0.51)</b>
Any stroke	3/496 (0.6%)	11/454 (2.4%)	<b>0.25 (0.07, 0.88)</b>	29/1035 (3%)	57/852 (7%)	<b>0.42 (0.27, 0.65)</b>
Disabling stroke	0	2/454 (0.4%)	NC	11/1053 (1%)	41/868 (5%)	<b>0.22 (0.11, 0.43)</b>
Death or disabling stroke	2/496 (0.4%)	6/454 (1.3%)	0.30 (0.06, 1.51)	22/1053 (2%)	75/868 (9%)	<b>0.24 (0.15, 0.39)</b>
Life-threatening or disabling bleeding	6/496 (1.2%)	54/454 (11.9%)	<b>0.09 (0.04, 0.22)</b>	50/1018 (4.9%)	440/493 (89.2%)	<b>0.06 (0.04, 0.07)</b>
Aortic valve reintervention	0	0	-	1/1062 (<1%)	0/902 (0%)	NC
New permanent pacemakers	32/496 (6.5%)	18/454 (4.0%)	1.66 (0.93, 2.96)	109/955 (11%)	68/836 (8%)	<b>1.40 (1.05, 1.87)</b>
Paravalvular regurgitation						
None-trace	343/487 (70.4%)	409/421 (97.1%)	<b>REDACTED</b>	51.2%	96.7%	NR
Mild	140/487 (28.7%)	12/421 (2.9%)	<b>REDACTED</b>	45.0%	2.8%	
≥Moderate	4/487 (0.8%)	0/421 (0%)	NC	3.8%	0.6%	
<b>Outcomes at 1-year follow-up</b>						
All-cause mortality	5/496 (1.0%)	11/454 (2.5%)	0.41 (0.14, 1.17)	79/963 (8%)	121/795 (15%)	<b>0.54 (0.41, 0.70)</b>
Any stroke	6/496 (1.2%)	14/454 (3.1%)	0.38 (0.15, 1.00)	49/930 (5%)	75/743 (10%)	<b>0.52 (0.37, 0.74)</b>
Disabling stroke	1/496 (0.2%)	4/454 (0.9%)	0.22 (0.03, 2.00)	24/953 (3%)	54/764 (7%)	<b>0.36 (0.22, 0.57)</b>
Death or disabling stroke	5/496 (1.0%)	13/454 (2.9%)	<b>0.34 (0.12, 0.97)</b>	90/953 (9%)	155/764 (20%)	<b>0.47 (0.37; 0.59)</b>
Life-threatening or disabling bleeding	14/496 (2.8%)	58/454 (12.8%)	<b>0.20 (0.11, 0.36)</b>	NR	NR	NR
Aortic valve reintervention	3/496 (0.6%)	2/454 (0.5%)	1.33 (0.22, 7.95)	6/958 (<1%)	4/794 (<1%)	<b>REDACTED</b>
New permanent pacemakers	36/496 (7.5%)	24/454 (5.5%)	1.38 (0.82, 2.32)	132/842 (16%)	85/721 (12%)	<b>REDACTED</b>

Outcome	PARTNER 3 (Low-Risk)			PARTNER S3i (Intermediate-Risk)		
	TAVI-BEV	SAVR	Treatment Effect (95% CI)	TAVI-BEV	SAVR	Treatment Effect (95% CI)
Paravalvular regurgitation						
None-trace	326/466(70.0%)	371/381(97.4 %)	<b>REDACTED</b>	58.7%	95.9%	<b>REDACTED</b>
Mild	137/466 (29.4%)	8/381 (2.1%)	<b>REDACTED</b>	39.8%	3.8%	<b>REDACTED</b>
≥Moderate	3/466 (0.6%)	2/381 (0.5%)	<b>REDACTED</b>	2.5%	0.4%	<b>REDACTED</b>
<b>Outcomes at 2-years follow-up</b>						
All-cause mortality	12/496 (2.4%)	14/454 (3.2%)	0.75 (0.35, 1.63)	NR	NR	NR
Any stroke	18/496 (2.4%)	15/454 (3.6%)	0.66 (0.31, 1.40)	NR	NR	NR
Death or disabling stroke	3.0%	3.8%	0.77 (0.39, 1.55)	NR	NR	NR
New-onset atrial fibrillation	33/496 (7.9%)	153/454 (41.8%)	<b>0.20 (0.14, 0.28)</b>	NR	NR	NR
New permanent pacemaker implants	42/496 (8.5%)	28/454 (6.3%)	1.37 (0.87, 2.18)	NR	NR	NR
Aortic valve reintervention	4/496 (0.8%)	4/454 (0.9%)	0.92 (0.23, 3.64)	NR	NR	NR
Paravalvular regurgitation						
None-trace	73.5%	97.7%				
Mild	26.0%	2.3%	NR	NR	NR	NR
≥Moderate	0.5%	0.0%				
<b>Outcomes at 5-years follow-up</b>						
All-cause mortality	NR	NR	NR	39.1%	41.3%	0.90 (0.76, 1.06)
Any stroke	NR	NR	NR	13.4%	11.4%	1.09 (0.80, 1.49)
Disabling stroke	NR	NR	NR	5.8%	7.9%	<b>0.66 (0.43, 1.00)</b>
Death or disabling stroke	NR	NR	NR	40.1%	42.7%	0.87 (0.74, 1.02)
New permanent pacemaker implants	NR	NR	NR	127/783 (16.2%)	92/783 (11.7%)	<b>0.69 (0.52, 0.92)</b>
Aortic valve reintervention	NR	NR	NR	10/783 (1.3%)	6/783 (0.8%)	0.60 (0.22, 1.65)

CI = confidence interval, NR = not reported; TAVI-BEV = transcatheter aortic valve implantation with a balloon-expandable valve, SAVR = surgical aortic valve replacement,

**Bold** = statistically significant at p-value < 0.05

<sup>a</sup> Results at five-year are reported using a propensity score-matched cohort comparison

Source: Constructed during evaluation from Section B of this commentary (1635), Section B of the 1603 commentary for TAVI-BEV in intermediate-risk patients, p7 of the pre-MSAC response for 1603, and Table 2, p9 of the 1603 ESC report

**Table 2 Comparison of economic evaluations between TAVI-BEV for low-risk patients (MSAC 1635), TAVI-BEV for intermediate-risk patients (MSAC 1603) and TAVI for high-risk patients (MSAC 1361 and resubmission 1361.2)**

Application	MSAC 1635 (Current)				MSAC1603 (November 2020)				MSAC 1361.2 (March 2016)			
Intervention	TAVI-BEV				TAVI-BEV				TAVI-BEV-and TAVI-SEV			
Patient population	Low-risk patients as determined by Heart Team				Intermediate risk patients as determined by Heart Team				High-risk and inoperable patients (not described)			
Comparator	SAVR and TAVI-SEV				SAVR and TAVI-SEV				SAVR and medical management			
Clinical evidence used for the economic model	<b>Redacted</b>				1-year outcomes from PARTNER 3Si				5-year data from the PARTNER trial. The numerically different overall survival estimates following TAVI and SAVR were not statistically significant			
Clinical claim	Superior effectiveness vs. SAVR (composite outcome: death, stroke, rehospitalisation at 1-year) No claim vs. TAVI-SEV				Superior effectiveness vs. SAVR (composite outcome: death, disabling stroke, aortic regurgitation) No claim vs. TAVI-SEV				Superior safety and clinical effectiveness for TAVI versus SAVR			
Health states	<b>redacted</b>				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.				3 states: 1. Alive, no disabling stroke 2. Alive, with <u>major</u> stroke 3. Dead No adjustment for pre-existing complications was made.			
Time horizon	<b>redacted</b> years (base-case). <b>redacted</b> and <b>redacted</b> -year time horizon presented in sensitivity analyses				10 years (base-case). 5 and 20-year time horizon presented in sensitivity analyses				5-years presented in the base-case and 10-years was presented in sensitivity analyses			
Prostheses cost of TAVI-BEV	<b>Redacted</b>				ADAR included prosthesis costs for public patients only				ADAR included prosthesis costs for all patients			
Prosthesis cost	TAVI BEV: <b>\$redacted</b> SAVR: <b>\$redacted</b>				TAVI BEV: <b>\$redacted</b> SAVR: \$9,079				TAVI: \$33,348 SAVR: \$6,738			
Length of stay	Source	TAVI	SAVR	Diff. /Ratio	Source	TAVI	SAVR	Diff. /Ratio	Source	TAVI	SAVR	Diff./Ratio
	TAVI-BEV: Partner 3	Median: 3 days	Median:7 days	4 days 1: 2.33	BEV: Partner 3Si naïve comparison	Median: 4 days	Median:9 days	5 days 1: 2.25	Yong 2012	6.2 days	12 days	5.8 days 1: 2.0
	TAVI-SEV: EVOLUT	Mean: 2.6 days ±2.1	Mean: 6.2 days ±3.3	4 days 1:2.38	SEV: SURTAVI RCT	Mean: 5.75 days ±4.85	Mean: 9.75 days ±8.03	4 days 1:1.7	PARTNER trial	8 days	12 days	4 days 1:1.5
Hospitalisation cost	TAVI: <b>\$redacted</b> SAVR: <b>\$redacted</b>				TAVI: \$21,944 SAVR: \$49,375				TAVI: \$24,328 SAVR: \$48,655			

Application	MSAC 1635 (Current)			MSAC1603 (November 2020)			MSAC 1361.2 (March 2016)		
Hospital costs (used in the model)	\$redacted			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 for TAVI-BEV	\$redacted			44% of the costs of SAVR. Based on the median length of hospital stay for TAVI-BEV (4-days) vs. SAVR patients (9-days) from PARTNER S3i			No change in hospital costs from 1361. The commentary noted that the model was most sensitive to hospitalisation costs for TAVI-BEV.		
Utility	Utility values	TAVI-BEV	SAVR	Utility values	TAVI-BEV	SAVR	Utility values	TAVI	SAVR
	Redacted	\$redacted	\$redacted	Alive, no disabling stroke	Pop norms (73-81)	Pop Norms (73-81)	Baseline (trial data)	0.66	0.66
	Redacted	\$redacted	\$redacted	Alive, disabling stroke	0.60	0.60	No-complication (trial data)	0.75	0.74
	Redacted	\$redacted	\$redacted	Disutility major event (once off)	0	0	Disutility major event (once off)	-0.10	-0.10
							Alive, with major stroke	0.65	0.65
						Alive, with heart failure	0.636	0.636	
Transition probabilities	\$redacted			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.			The revised economic model used overall survival transition probabilities from the Kaplan Meier curves published in the key clinical trials. 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: MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; 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.

Source: Constructed during evaluation using Section D of the ADAR and Table 2, p9 of the 1603 ESC report

## 5. Prerequisites to implementation of any funding advice

The 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. The ADAR stated that SAPIEN 3 is currently the only TAVI-BEV system available in Australia. The commentary noted that other ARTG included TAVI devices (i.e. Medtronic CoreValve, and Medtronic CoreValve Evolut R System use self-expanding valves (i.e. TAVI-SEV) and are also indicated for use in all patients with severe, symptomatic AS regardless of surgical risk-status.

## 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 2018(Cth) (Department of Health 2018) 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 a low 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>Fee: \$1,476.95    Benefit: 75% = \$1,107.75    85% = \$1,392.25</p>

Source: Table A-3, p 6 of the ADAR

The commentary noted that the proposed MBS item does not specify that patients have no significant frailty (as defined by the Heart Team) and no procedure-specific impediments. The proposed MBS item also does not provide a clear and concise definition of a patient who 'has been assessed as having low risk for surgical aortic valve replacement'. Further, the proposed MBS item descriptor does not specify that patients have calcific valvular aortic stenosis.

The commentary also be noted that the proposed MBS item descriptor specifies that access should be achieved via transfemoral delivery, unless transfemoral delivery is contraindicated or not feasible. However, the primary clinical evidence presented by the ADAR, PARTNER 3, excluded patients if treatment with TAVI-BEV via the transfemoral access route could not be achieved (i.e. patient had high-risk anatomy).

The current application sought to have the ‘accompanying’ MBS items for coordination (item 6080) of the TAVI case conference and participation in the TAVI case conference (6081) available for the proposed new MBS TAVI item.

## **7. Summary of public consultation feedback/consumer Issues**

Following the deferral of MSAC application 1635([Application 1635 PSD](#), p1), the MSAC commenced targeted consultation, requesting feedback from several medical and consumer organisations to help optimise the use of TAVI to treat severe, symptomatic aortic stenosis in patients with low surgical mortality risk. An item descriptor and explanatory notes for low surgical risk patients was drafted outlining (preliminary) factors that may favour TAVI or SAVR based on the 2020 ACC/AHA guidelines. Feedback was received from the following organisations:

- The Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS)
- The Cardiac Society of Australia and New Zealand (CSANZ),
- The Australian Society of Anaesthetists (ASA), and
- Hearts4heart.

### *Item descriptor*

ANZSCTS supported the subsidy of TAVI as a standalone procedure without reference to surgical risk. CSANZ supported a device agnostic TAVI item descriptor. Hearts4heart considered that the concept of low, intermediate and high risk is misleading and not patient centred. Feedback from the ASA and Hearts4heart were supportive of the subsidy of TAVI.

### *Role of the Heart Team and defining the appropriate population*

Hearts4heart did not support restrictions in place for heart valve patients to have access to TAVI. CSANZ were also not supportive of a defined list of factors favouring TAVI or SAVR. CSANZ considered that patient selection for TAVI should be made by a multidisciplinary Heart Team as the clinical considerations are complex and consider multiple permutations of patient, anatomic and procedural factors. ANZSCTS was supportive specifying factors defining the appropriate population for TAVI. ANZSCTS considered patients aged under 70 years would be more suitable for SAVR.

ANZSCTS considered that there was considerable variation in Heart Team decision-making across Australia. This variation included appropriateness of decision-making, surgeon engagement and patients being offered TAVI. ANZSCTS considered the decision making of Heart Teams should be audited.

### *Shared decision making*

The Hearts4heart response highlighted the importance of patient choice and patient inclusion in decision-making. CSANZ recommended that high quality patient information be provided explaining the progressive evolution of TAVI.

### *Surgical involvement in TAVI*

ANZSCTS proposed two models with greater surgeon involvement: one where an independent surgeon would assess patients as being more appropriate for TAVI and another where there would be surgeon involvement all TAVI procedures.

### Procedural anaesthesia

The ASA advised that the anaesthesia technique required for TAVI results in better patient outcomes and that anaesthesia for open heart surgery is in and of itself, a major intervention, with a higher risk to patients.

### Clinical evidence

ANZSCTS was critical of the trial data and considered that patients were highly selected and reported inconsistent endpoints. The ANZSCTS feedback presented data from the 2019 Annual Report of the ANZSCTS National Cardiac Surgery Registry Data.<sup>7</sup>

The ANZSCTS response highlighted that observed 30-day mortality for isolated SAVR was 1.8% in the 10 years from 2010 to 2019 in an unselected, all-comers population. In 2019, observed 30-day mortality was lower at 1.4%. For patients undergoing elective SAVR, observed 30-day mortality was 1.1%.

### Long term outcomes

ANZSCTS raised concerns relating to the need for permanent pacemaker implantation and the occurrence of left bundle branch block and paravalvular leakage.

CSANZ presented findings from cohort studies on the long-term durability of TAVI valves that reported on SVD and bioprosthetic valve failure (BVF). Hearts4heart also referred to registry data reporting on structural valve deterioration (SVD) and bioprosthetic valve failure (BVF). The results of these studies are presented in Table 4.

**Table 4: Long term durability after TAVI presented in the consultation feedback from Costa (2019)<sup>8</sup> and other studies referred in consultation feedback**

Author	N	Age	Follow-up	Survival	SVD	BVF
Deutsch 2018 <sup>9</sup>	300	81 yrs	7.14 yrs	5 yrs: 40.2% 7 yrs: 23.2%	5 years: 13.3% 7 years: 14.9% [competing risk adjusted]	3.7%: 11 patients 4 reinterventions (TAVI)
Eltchaninoff 2018 <sup>10</sup>	378	83 yrs	3.1 yrs	5 yrs: 31.7% 8 yrs: 9.6%	8 yrs: 3.2% (95 CI: 1.4, 6.1) [competing risk adjusted]	8 yrs: 0.58% (95% CI: 0.15, 2.75) n=2 (all reoperated)
Barbanti 2018 <sup>11</sup>	288	81 yrs	6.7 yrs	8 yrs: 29.8%	8 yrs Severe: 2.4% (95% CI: 0.8%, 5.7%, n=7) Moderate: 5.9% (95% CI, 3.1%, 10.0%, n=13). [competing risk adjusted]	8yrs: 4.5% (95% CI: 2.0%, 8.8%) n=11 (4 deaths, 2 TAVI, 2 asymptomatic)

<sup>7</sup> Shardey G *et al.* The Australian and New Zealand Society of Cardiac and Thoracic Surgeons Cardiac Surgery Database Program Annual Report 2019. Monash University, Department of Epidemiology and Preventive Medicine, October 2020. Report No 12. Available from <https://anzscts.org/database/about/#reports>

<sup>8</sup> Costa G *et al.* Long-term Transcatheter Aortic Valve Durability. *Interv Cardiol.* 2019;14(2):62-69.

<sup>9</sup> Deutsch MA *et al.* Beyond the five-year horizon: long-term outcome of high-risk and inoperable patients undergoing TAVR with first-generation devices. *EuroIntervention.* 2018;14(1):41-49

<sup>10</sup> Eltchaninoff H *et al.* Assessment of structural valve deterioration of transcatheter aortic bioprosthetic balloon-expandable valves using the new European consensus definition. *EuroIntervention.* 2018;14(3):e264-e271.

<sup>11</sup> Barbanti M *et al.* Incidence of Long-Term Structural Valve Dysfunction and Bioprosthetic Valve Failure After Transcatheter Aortic Valve Replacement. *J Am Heart Assoc.* 2018;7(15):e008440.

Author	N	Age	Follow-up	Survival	SVD	BVF
Holy 2018 <sup>12</sup>	152	81 yrs	6.3 yrs	8 yrs: 27%	NR	8 years: 4.5% [competing risk adjusted] 8 interventions 3 TAVI 1 SAVR
Antonazzo 2018 <sup>13</sup>	278	82 yrs	6.8 yrs	NR	8 yrs: 3.6% (n=3)	8 yrs: 2.5% (n=5 + 2 probable BVF)
Didier 2018 <sup>14</sup>	4,201	83 yrs	5 yrs	5 yrs: 39.2%	5 yrs: 13.3% (2.5% severe)	NR
Sathananthan 2021 <sup>15</sup>	235	82 yrs	NR	6 yrs: 28.1% 8 yrs: 13.6% 10yrs: 8.4%	SVD/BVF 6 yrs: 1.7% 8 yrs: 4.7% 10yrs: 6.5% (n=9 moderate, n=6 severe) [competing risk adjusted]	2 reinterventions (1 SAVR and death, 1 TAVI)
Durand 2019 <sup>16</sup>	1,304	83 yrs	3.9 yrs	7yrs: 18.6%	Moderate: 7.0% Severe: 4.2%	1.9% (5 reinterventions)
Vollenbroich 2019 <sup>17</sup>	257	82 yrs	7 yrs	5 yrs: 47.3% 7 yrs: 26.5%	NR	0.4% (1 reintervention)
Testa 2020 <sup>18</sup>	999	82 yrs	4.4 yrs	8 yrs: 26.50%	8 yrs: 3.0% (moderate) 1.6% (severe) [competing risk adjusted]	8 years: 2.5% (6 reinterventions, 1 death) [competing risk adjusted]

Source: Compiled by the Department from p3 of the CSANZ response [Table 4, p11 of Costa (2019)]; Deutsch (2018); Eltchaninoff (2018); Barbanti (2018); Holy (2018); Antonazzo (2018); Didier (2018); Sathananthan (2021); Durand (2019); Vollenbroich (2019); and Testa (2020)

Abbreviations: BVF = bioprosthetic valve failure; CI = confidence interval; N = number patients in study; n = number of patients; NR = not reported; SVD = structural valve degeneration; SAVR = surgical aortic valve replacement; TAVI = Transcatheter Aortic Valve Implantation; yr= years

### March-April 2021 meeting

Four targeted consultation surveys from groups and three consultation surveys (one from a specialist, one from a competitor TAVI manufacturer, and one consumer organisation) were received.

One consumer organisation (Hearts4Heart), received in support of another TAVI application (MSAC application 1652) was highly supportive of TAVI. The feedback highlighted that:

- Patients are mobile following TAVI and can be discharged relatively quickly after the procedure. Physical recovery from SAVR is much longer. Faster discharge from hospital and faster recovery are highly valued by patients;

<sup>12</sup> Holy EW *et al.* Long-term durability and haemodynamic performance of a self-expanding transcatheter heart valve beyond five years after implantation: a prospective observational study applying the standardised definitions of structural deterioration and valve failure. *EuroIntervention*. 2018;14(4):e390-e396.

<sup>13</sup> Panico RA *et al.* Long-term results and durability of the CoreValve transcatheter aortic bioprosthesis: outcomes beyond five years. *EuroIntervention*. 2019;14(16):1639-1647

<sup>14</sup> Didier R *et al.* Five-Year Clinical Outcome and Valve Durability After Transcatheter Aortic Valve Replacement in High-Risk Patients. *Circulation*. 2018;138(23):2597-2607.

<sup>15</sup> Sathananthan J *et al.* Ten year follow-up of high-risk patients treated during the early experience with transcatheter aortic valve replacement. *Catheter Cardiovasc Interv*. 2021;97(3):E431-E437.

<sup>16</sup> Durand E *et al.* Assessment of Long-Term Structural Deterioration of Transcatheter Aortic Bioprosthetic Valves Using the New European Definition. *Circ Cardiovasc Interv*. 2019;12(4):e007597.

<sup>17</sup> Vollenbroich R *et al.* Long-term outcomes with balloon-expandable and self-expandable prostheses in patients undergoing transfemoral transcatheter aortic valve implantation for severe aortic stenosis. *Int J Cardiol*. 2019;290:45-51.

<sup>18</sup> Testa L *et al.* Long-term clinical outcome and performance of transcatheter aortic valve replacement with a self-expandable bioprosthesis. *Eur Heart J*. 2020;41(20):1876-1886.

- There are several randomised controlled trials supporting the use of TAVI patients irrespective of surgical risk. However, TAVI is only subsidised for patients with a higher surgical risk;
- Patients must be assessed by a Heart Team for TAVI. This was considered beneficial for patients, but it was noted that this is not required for SAVR;
- TAVI has similar outcomes to SAVR but patients are less likely to develop atrial fibrillation or experience life-threatening or disabling bleeding; and
- TAVI provides an alternative to SAVR that is less invasive and requires less hospital care (operating theatres, intensive care, and longer stay in hospital).

PASC noted the mixed support for the application from consultation feedback (Ratified PICO, p25):

- One specialist organisation was highly supportive of the application, noting that TAVI is the standard of care for the treatment of symptomatic severe AS and that the eligibility of “TAVI-able” patient is more pertinent than the categorisation of low-high surgical risk. This feedback also considered that the fee is undervalued for the procedure and should be higher.
- One specialist organisation was concerned that patient populations in studies of low risk patients for TAVI were highly selected, and excluded patients with bicuspid disease, excluded younger patients; as a consequence the results are not representative of the wider population with severe symptomatic AS (i.e. applicability concerns). This feedback also noted that the descriptor did not match patient selection criteria in the quoted literature and considered that long term results of TAVI in this population are unknown. Thus, this specialist organisation appended their Society position statement on TAVI in low risk patients.
- One specialist organisation suggested that the anaesthesia cost estimate for the proposed intervention needed amendment.
- One industry association and individual specialist were highly supportive of the application.
- Feedback was also received from a competitor TAVI manufacturer considering that it was inappropriate for MSAC applications to be limited to one device and that all TAVI valves should be included (balloon, self and mechanically expanding valves). This feedback also considered that comparing device performance is difficult and misleading as noted by Abdel-Waha & Thiele et al. (2020)<sup>19</sup>. Further, it was noted that if hospitalisation was added to the primary endpoint of death or stroke in the Evolut low risk trial, the results would have shown superiority to SAVR. This feedback also highlighted that, compared with SAVR, the use of TAVI enables efficiencies related to hospital resource use.

## **8. Proposed intervention’s place in clinical management**

### **Description of Proposed Intervention**

Transcatheter aortic valve implantation involving the SAPIEN 3 balloon expandable device involves minimally invasive transfemoral insertion of a prosthetic heart valve that is positioned within the aortic annulus using the SAPIEN 3 system. Once in-situ, the valve is

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<sup>19</sup> 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.

expanded while the heart is rapidly paced. The procedure is performed using fluoroscopic and transoesophageal guidance and under general or local anaesthesia.

### **Description of Medical Condition(s)**

Severe aortic stenosis (AS) is characterised by narrowing of the aortic valve leading to restriction of blood flow. AS is often caused by a build-up of calcium on the valve leaflets, causing them to become stiff and reducing their ability to open and close efficiently. It is associated with high pressure inside the left ventricle and as a result of the excessive workload, the left ventricle hypertrophies, which further leads to inefficiency in blood circulation. Symptoms include angina, dyspnoea and syncope. Left untreated, heart failure develops, and the risk of death is increased.

### **Clinical place**

The current and proposed clinical management algorithms, as per the ratified PICO, are presented in Figure 1 and Figure 2. 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 low-risk patients. The commentary noted that neither the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (EACTS) Guidelines for Valvular Heart Disease<sup>20</sup> nor the American Heart Association/American College of Cardiology (AHA/ACC) Clinical Practice Guidelines for the Management of Patients with Valvular Heart Disease<sup>21</sup> support the use of TAVI devices in low-risk patients or patients under 75 years of age. This is because the long-term durability of TAVI devices is unknown and the impact of device durability on patient outcomes is uncertain<sup>20,22</sup>. In comparison, SAVR valves are estimated to last 10 to 15 years<sup>23</sup>. Further, TAVI devices are associated with higher rates of paravalvular leaks and left bundle-branch block, which may have a considerable impact on the patient's long-term survival, the requirement for reintervention and quality of life<sup>22,24</sup>. The commentary noted that the results of the key trial PARTNER 3 also demonstrate that SAVR patients have excellent outcomes, with low rates of mortality (2.5%) and disabling stroke (0.9%) at 1-year follow-up. The commentary noted that the proposed clinical management algorithm of the ratified PICO allowed patients who required repeat aortic valve re-intervention to be treated with SAVR, rather than SAVR or TAVI-BEV as proposed by the ADAR

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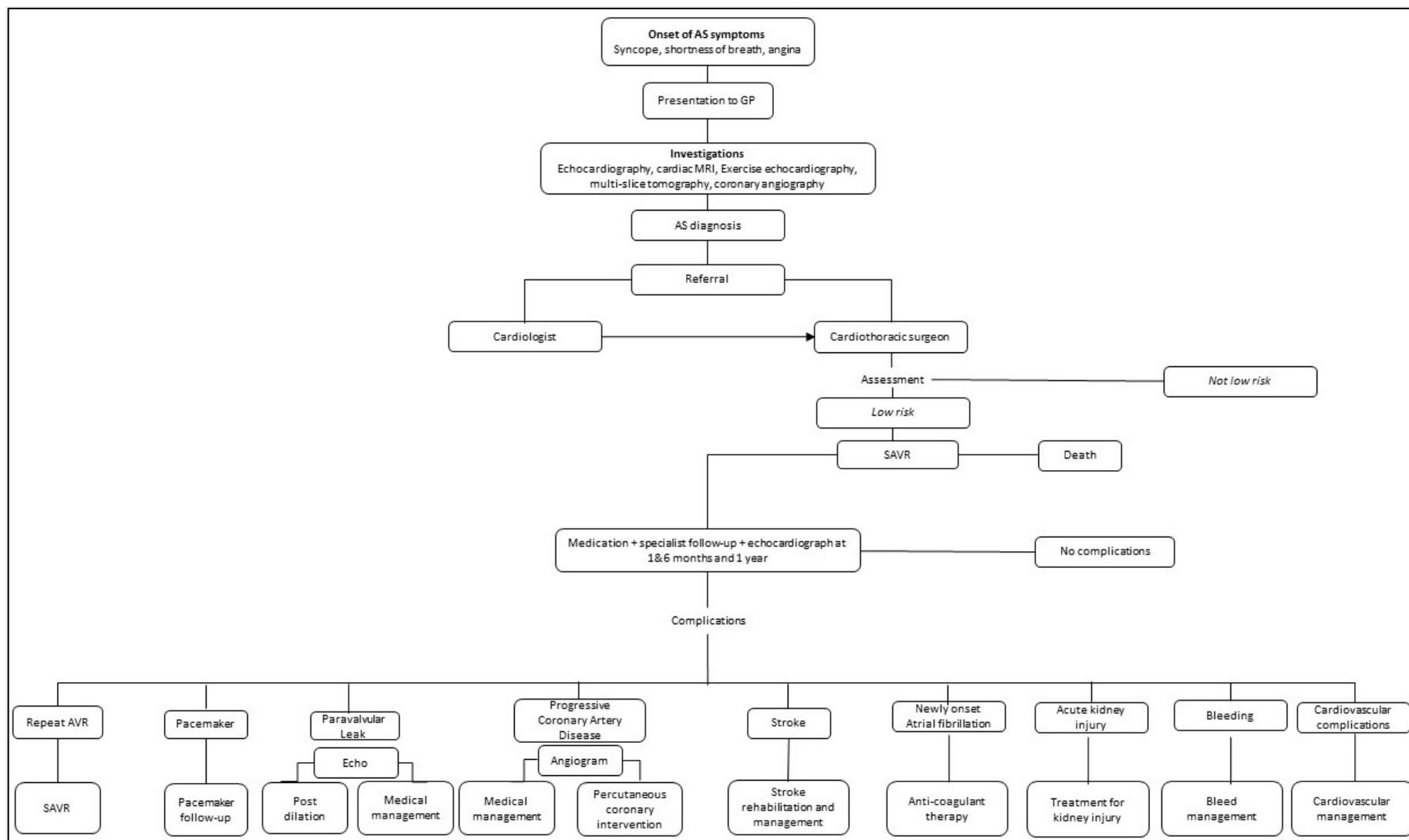
<sup>20</sup> Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J.* 2017;38(36):2739-91.

<sup>21</sup> Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology.* 2017;70(2):252-89.

<sup>22</sup> Overtchouk P, Prendergast B, Modine T. Why should we extend transcatheter aortic valve implantation to low-risk patients? A comprehensive review. *Arch Cardiovasc Dis.* 2019;112(5):354-62.

<sup>23</sup> Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J.* 2017;38(36):2739-91.

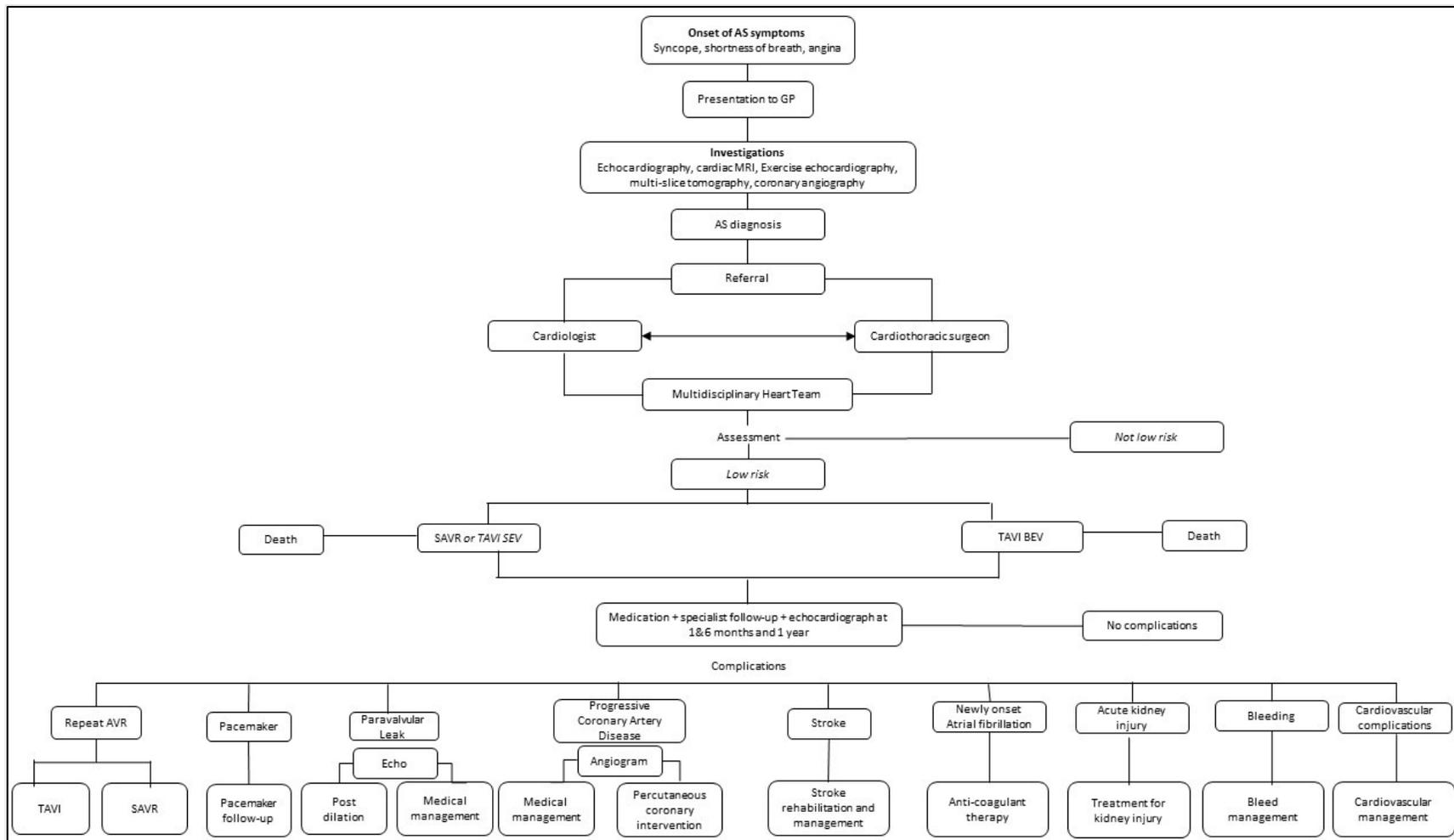
<sup>24</sup> Tang GHL, Verma S, Bhatt DL. Transcatheter Aortic Valve Replacement in Low-Risk Patients: A New Era in the Treatment of Aortic Stenosis. *Circulation.* 2019;140(10):801-3.



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

Source: Figure A-1, p 15 of the ADAR

ADAR = Applicant Developed Assessment Report; AS = aortic stenosis; AVR = aortic valve replacement; BEV = balloon-expandable valve; Echo = echocardiogram; GP = general practitioner; SAVR = surgical aortic valve replacement



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

Source: Figure A-2, p 16 of the ADAR

ADAR = Applicant Developed Assessment Report; AS = aortic stenosis; AVR = aortic valve replacement; BEV = balloon-expandable valve; Echo = echocardiogram; GP = general practitioner; SAVR = surgical aortic valve replacement

## 9. Comparator

The ADAR appropriately nominated SAVR as the main 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.

As requested by PASC, the ADAR nominated TAVI-SEV as a secondary comparator. However, the commentary highlighted that the ADAR did not make a clinical claim against TAVI-SEV or present any comparative evidence between TAVI-BEV and TAVI-SEV. The key difference between TAVI-BEV and TAVI-SEV are the valves (balloon-expandable versus self-expandable).

## 10. Comparative safety

The evidential basis of the ADAR consisted of results from the PARTNER 3 trial, a randomised, multicentre, open-label clinical trial, which compared TAVI-BEV (SAPIEN 3) with SAVR. The trial was powered to demonstrate non-inferiority of TAVI BEV with SAVR with respect to the study's primary endpoint, all-cause mortality, stroke and rehospitalisation at 1-year. The ADAR only presented the 1-year follow-up data from PARTNER 3<sup>25</sup>, however, the commentary identified a conference presentation that provided longer-term data (2 years) from PARTNER 3<sup>26</sup> and included the results in the commentary the evaluation. The ADAR identified publications reporting the EVOLUT trial, a multicentre, randomised, open-label trial, which compared TAVI SEV (CoreValve, Evolut R or Evolut PRO) to SAVR in patients with symptomatic, severe AS at low surgical risk<sup>27</sup>. The ADAR did not conduct an indirect comparison of the PARTNER 3 and EVOLUT due to differences in outcomes and statistical methodology between the two trials. The evaluation considered the trials were otherwise exchangeable and conducted an indirect comparison.

A summary of the evidence used in the ADAR is provided in Table 5.

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<sup>25</sup> Baron SJ, Magnuson EA, Lu M, Wang K, Chinnakondepalli K, Mack M, et al. Health Status After Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients With Aortic Stenosis. *Journal of the American College of Cardiology*. 2019;74(23):2833-42.

<sup>26</sup> Mack M, Baron S, Leon M, editors. Two year Clinical and Echocardiographic Outcomes from the PARTNER 3 Low risk Randomized Trial. American College of Cardiology Virtual Annual Scientific Session Together With World Congress of Cardiology (ACC 2020/WCC) 2020; Chicago.

<sup>27</sup> Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *N Engl J Med*. 2019;380(18):1706-15.

**Table 5 Key features of the included evidence**

Trial/Study	N	Design/ duration	Risk of bias	Patient population	Key outcome	Result used in economic model
PARTNER 3	946	Design: R, MC, OL, NI and superiority between TAVI-BEV and SAVR.  Follow-up: 30-days, 1 and 2 years	Low to moderate	Low-risk patients (STS-PROM score <4%) with severe aortic stenosis	All-cause mortality, stroke, rehospitalisations, LBBB, PVR, PPI, reinterventions	Yes (all key outcomes included in the model)
EVOLUT	1403	Design: R, MC, OL NI and superiority between TAVI-SEV and SAVR  Follow-up: 30-days, 1 and 2 years	Low to moderate	Low-risk patients (STS-PROM score ≤ 3%) with severe aortic stenosis	All-cause mortality, stroke, LBBB, PVR, PPI, reinterventions	No

Abbreviations: HRQoL=health-related quality of life, MC=multi-centre, NI = non-inferiority, LBBB = left bundle-branch block, OL=open label (unblinded), PPI = permanent pacemaker implanted, 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

Source: Constructed during the evaluation

### *TAVI-BEV vs. SAVR*

The commentary considered that, consistent with the ADAR's clinical claim, patients treated with TAVI-BEV were significantly more likely to have new left bundle branch block and mild paravalvular leaks than patients treated with SAVR. The commentary considered that such complications, combined with TAVI-BEV's uncertain device durability, could have significant long-term impacts on the patient's life expectancy and need for further intervention.

The commentary considered that, also consistent with the ADAR's clinical claim, patients treated with TAVI-BEV had significantly lower rates of life-threatening or disabling bleeding (2.8% vs. 12.8%) and fewer incidences of atrial fibrillation (7.0% vs. 40.9%) than patients treated with SAVR.

A summary of the key safety outcomes from PARTNER 3 is presented in Table 6.

**Table 6 Summary of key safety outcomes from the PARTNER 3 trial**

Time since procedure	TAVI-BEV	SAVR	Treatment effect (95% CI)
<b>New left bundle branch block</b>			
30-days	106/496 (22.0%)	35/454 (8%)	<b>3.17 (2.13, 4.72)</b>
1-year	114/496 (23.7%)	35/454 (8.0%)	<b>3.43 (2.32, 5.08)</b>
2-years	117/496 (24.4%)	41/454 (9.4%)	<b>2.61 (1.87, 3.64)</b>
<b>Rate of paravalvular regurgitation</b>			
30-days			
None-trace	343/487 (70.4%)	409/421 (97.1%)	<b>REDACTED</b>
Mild	140/487 (28.7)	12/421 (2.9%)	<b>REDACTED</b>
≥Moderate	4/487 (0.8%)	0/421 (0%)	<b>REDACTED</b>
1-year			
None-trace	326/466(70.0%)	371/381(97.4%)	<b>REDACTED</b>
Mild	137/466 (29.4%)	8/381 (2.1%)	<b>REDACTED</b>
≥Moderate	3/466 (0.6%)	2/381 (0.5%)	<b>REDACTED</b>
2-years			
None-trace	73.5%	97.7%	<i>Not reported</i>
Mild	26.0%	2.3%	
≥Moderate	0.5%	0.0%	
<b>Aortic valve reintervention</b>			
30-days	0	0	Not calculable
1-year	3/496 (0.6%)	2/454 (0.5%)	1.33 (0.22, 7.95)
2-years	4/496 (0.8%)	4/454 (0.9%)	0.92 (0.23, 3.64)
<b>New permanent pacemaker implants</b>			
30-days	32/496 (6.5%)	18/454 (4.0%)	1.66 (0.93, 2.96)
1-year	36/496 (7.3%)	24/454 (5.4%)	1.38 (0.82, 2.32)
2-years	42/496 (8.5%)	28/454 (6.3%)	1.37 (0.87, 2.18)
<b>Life-threatening or disabling bleeding</b>			
30-days	6/496 (1.2%)	54/454 (11.9%)	<b>0.09 (0.04, 0.22)</b>
1-year	14/496 (2.8%)	58/454 (12.8%)	<b>0.20 (0.11, 0.36)</b>
<b>New-onset atrial fibrillation</b>			
30-days	21/496 (5.0%)	145/454 (39.5%)	<b>0.10 (0.06, 0.16)</b>
1-year	29/496 (7.0%)	150/454 (40.9%)	<b>0.13 (0.09, 0.20)</b>
2-years	33/496 (7.9%)	153/454 (41.8%)	<b>0.20 (0.14, 0.28)</b>

CI = confidence interval, TAVI-BEV = transcatheter aortic valve implantation with a balloon-expandable valve, SAVR = surgical aortic valve replacement, **Bold** = statistically significant at p-value < 0.05; *italics* = presented by the evaluation.

Note: The 2-year follow-up results were presented by the evaluation

Source: Table B-10 and Table B-11, pp 41-43 of the ADAR and Mack et al. (2020)<sup>26</sup>

### TAVI-BEV vs. TAVI-SEV

The indirect comparison of safety outcomes, conducted during the evaluation, found that patients treated with TAVI-SEV were significantly more likely to require a permanent pacemaker (Table 7).

**Table 7 Indirect comparison of safety outcomes between TAVI-BEV (PARTNER 3) and TAVI-SEV (EVOLUT), with SAVR as the common comparator**

Outcome	RD (95% CI) TAVI-BEV (PARTNER 3)	RD (95% CI) TAVI-SEV (EVOLUT)	Indirect comparison RD (95% CI)
<b>Outcomes at 30-days</b>			
New permanent pacemaker	2.5% (-0.3%, 5.3%)	<b>11.3% (8.0%, 14.7%)</b>	<b>-8.8% (-13.1%, -4.5%)</b>
New atrial fibrillation	<b>-27.7% (-32.3%, -23.1%)</b>	<b>-27.7% (-31.8%, -23.6%)</b>	0.0% (-6.2%, 6.2%)
Aortic valve reintervention	0%	0.0% (-0.7%, 0.7%)	0% (-0.7%, 0.7%)
<b>Outcomes at 1-year follow-up</b>			
New permanent pacemaker	2.0% (-1.1%, 5.1%)	<b>12.6% (9.2%, 16.2%)</b>	<b>-10.7% (-15.3%, -6.1%)</b>
New atrial fibrillation	<b>-27.2% (-32.0%, -22.4%)</b>	<b>-28.5 (-32.8%, -24.1%)</b>	1.3% (-5.1%, 7.7%)
Aortic valve reintervention	0.2% (-0.8%, 1.1%)	0.1% (-0.7%, 0.9%)	0.1% (-1.2%, 1.3%)

Abbreviations: CI = confidence interval, TAVI-BEV = transcatheter aortic valve implantation – balloon-expandable valve, TAVI-SEV = transcatheter aortic valve implantation – self-expandable valve; RD = risk difference, **Bold** = statistically significant at p-value ≤ 0.05 or 95% Bayesian confidence interval if the difference outcomes did not cross the threshold of zero

Source: Constructed during evaluation

### *Long term durability of TAVI-BEV*

The minor submission considered that the evidence for the durability of TAVI-BEV continues to accumulate, and by and large, this suggests comparability to SAVR. The minor submission stated that, in terms of pre-clinical studies, bench testing data show that the durability of SAPIEN 3 is similar to surgical valves after one billion cycles of accelerated wear testing (Sathananthan *et al.* 2020<sup>28</sup>)

The minor submission considered that the durability of TAVI valves is supported by published real world data from multiple studies, in which the durability of TAVI valves match that of surgical valves out to ten years (Blackman *et al.* 2019<sup>29</sup>; Durand *et al.* 2019<sup>30</sup>; Vollenbroich *et al.* 2019<sup>31</sup>; and Sathananthan *et al.* 2021<sup>32</sup>). The minor submission highlighted that, notably, among the few patients needing aortic valve re-intervention, most underwent repeat TAVIs rather than SAVR, meaning cost-offsets associated with an initial TAVI (compared with an initial SAVR) were likely preserved.

The minor submission also re-presented follow-up data from a clinical trial of SAPIEN 3 (PARTNER S3i) and considered that this data showed that its durability is similar to that of surgical bioprosthetic valves out to five years<sup>33</sup>. This is based on the composite outcome measure of structural valve deterioration (SVD, stage 2 haemodynamic valve deterioration during echocardiographic follow-up) and bioprosthetic valve failure.

In addition, the minor submission highlighted that Australian clinicians have advised the applicant that durability data from two Melbourne hospitals (one public and one private) now exists for TAVIs (of all types) up to 13 years, and these are “excellent” and at least comparable to those for SAVRs. The applicant indicated that these data are currently being prepared for submission.

## **11. Comparative effectiveness**

### *TAVI-BEV vs. SAVR*

A summary of the key efficacy outcomes reported in PARTNER 3 is presented Table 8. The Kaplan-Meier curves for the PARTNER 3 primary endpoint (composite of all-cause mortality, stroke and rehospitalisation), all-cause mortality, and death or disabling stroke in PARTNER 3 at 2-years follow-up is presented in Figure 3, Figure 4, and Figure 5, respectively.

The commentary highlighted that although the primary endpoint, the composite of death, stroke or rehospitalisation, remained statistically significant at two-year follow-up, there was a clear narrowing of the Kaplan-Meier curves between treatment arms. A similar pattern was observed for the individual outcomes of death and stroke, as the Kaplan-Meier curves for death and stroke had begun to converge. Further, there were more deaths and stroke events in the TAVI-BEV arm between 1 and 2-years follow-up than in the SAVR arm. The

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<sup>28</sup> Sathananthan, J., *et al.*, Long-Term Durability of Transcatheter Heart Valves: Insights From Bench Testing to 25 Years. *JACC Cardiovasc Interv*, 2020. 13(2): p. 235-249.

<sup>29</sup> Blackman, D.J., *et al.*, Long-Term Durability of Transcatheter Aortic Valve Prostheses. *J Am Coll Cardiol*, 2019. 73(5): p. 537-545.

<sup>30</sup> Durand, E., *et al.*, Assessment of Long-Term Structural Deterioration of Transcatheter Aortic Bioprosthetic Valves Using the New European Definition. *Circ Cardiovasc Interv*, 2019. 12(4): p. e007597.

<sup>31</sup> Vollenbroich, R., *et al.*, Clinical outcomes in high-risk patients with a severe aortic stenosis: a seven-year follow-up analysis. *Swiss Med Wkly*, 2019. 149: p. w20013.

<sup>32</sup> Sathananthan, J., *et al.*, *Ten year follow-up of high-risk patients treated during the early experience with transcatheter aortic valve replacement*. *Catheter Cardiovasc Interv*, 2021. 97(3): p. E431-e437.

<sup>33</sup> Pibarot, P., *et al.*, Structural Deterioration of Transcatheter Versus Surgical Aortic Valve Bioprostheses in the PARTNER-2 Trial. *J Am Coll Cardiol*, 2020. 76(16): p. 1830-1843.

commentary considered that this raises concerns about TAVI-BEV's long-term durability and efficacy beyond 1-year. The ADAR did not provide a Clinical Study Report for PARTNER 3 and the reasons were not reported by the Mack et al (2019). Rehospitalisation could include rehospitalisation for very minor procedures (e.g. diuretics, inotropes, chromotropes, oral or intravenous therapy) and hence this outcome may not be clinically meaningful.

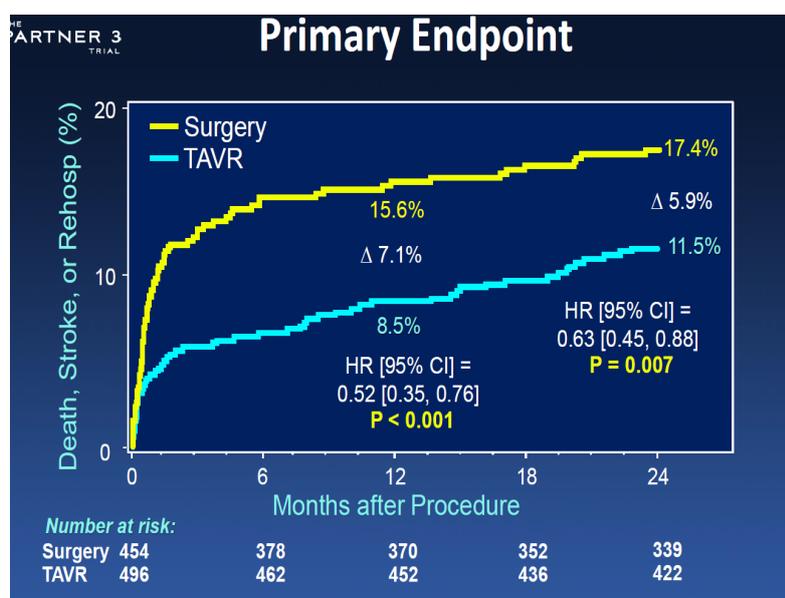
**Table 8 Summary of key efficacy outcomes from the PARTNER 3 trial**

Time since procedure	TAVI-BEV	SAVR	Absolute difference	Treatment effect (95% CI)
<b>Primary endpoint: composite of all-cause mortality, stroke, and rehospitalisation</b>				
1-year	42/496 (8.5%)	68/454 (15.1%)	-6.6 %	<b>0.54 (0.37, 0.79)</b>
2-years	11.5%	17.4%	-5.9%	<b>0.63 (0.45, 0.88)</b>
<b>Disabling stroke or death</b>				
30-days	2/496 (0.4%)	6/454 (1.3%)	-0.9%	0.30 (0.06, 1.51)
1-year	5/496 (1.0%)	13/454 (2.9%)	-1.9%	<b>0.34 (0.12, 0.97)</b>
2-years	3.0%	3.8%	-0.8%	0.77 (0.39, 1.55)
<b>All-cause mortality</b>				
30-days	2/496 (0.4%)	5/454 (1.1%)	-0.7%	0.37 (0.07, 1.88)
1-year	5/496 (1.0%)	11/454 (2.5%)	-1.4%	0.41 (0.14, 1.17)
2-years	12/496 (2.4%)	14/454 (3.2%)	-0.8%	0.75 (0.35, 1.63)
<b>Stroke</b>				
30-days	3/496 (0.6%)	11/454 (2.4%)	-1.8%	<b>0.25 (0.07, 0.88)</b>
1-year	6/496 (1.2%)	14/454 (3.1%)	-1.9%	0.38 (0.15, 1.00)
2-years	12/496 (2.4%)	16/454 (3.6%)	-1.2%	0.66 (0.31, 1.40)
<b>Disabling stroke</b>				
30-days	0	2/454 (0.4%)	-0.4%	Not calculable
1-year	1/496 (0.2%)	4/454 (0.9%)	-0.7%	0.22 (0.03, 2.00)
<b>Rehospitalisation</b>				
30-days	17/496 (3.4%)	29/454 (6.5%)	-3.0%	<b>0.53(0.29, 0.97)</b>
1-year	36/496 (7.3%)	49/454 (11.0%)	-3.5%	0.65 (0.42, 1.00)

CI = confidence interval, TAVI-BEV = transcatheter aortic valve implantation with a balloon-expandable valve, SAVR = surgical aortic valve replacement, **Bold** = statistically significant at p-value < 0.05; *italics* = presented by the evaluation.

Note: The 2-year follow-up results were presented by the evaluation

Source: Table B-10 and Table B-11, pp 41-43 of the ADAR; Mack et al. (2020) and Leon et al. (2021)



**Figure 3 Kaplan-Meier curves for the primary endpoint: composite of all-cause mortality, stroke and rehospitalisation in the PARTNER 3 at 2-years follow-up**

Source: Slide 11 of Mack et al. (2020) <sup>26</sup>

CI = confidence interval; HR = hazard ratio; rehosp = rehospitalisation; TAVR = transcatheter aortic valve replacement

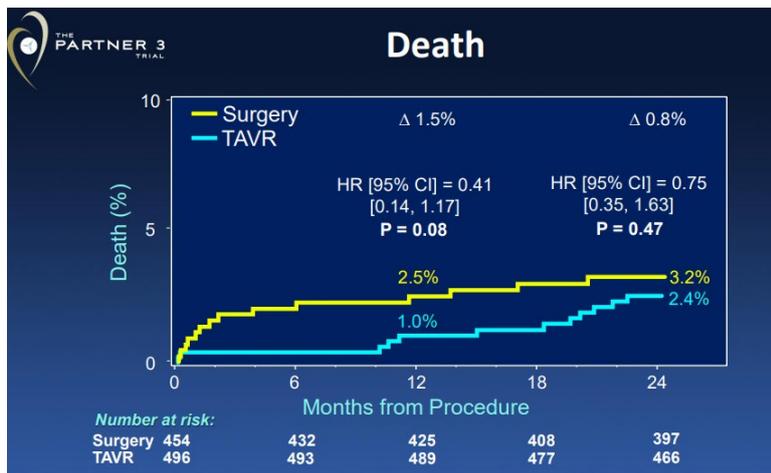


Figure 4 Kaplan-Meier curves for all-cause death in the PARTNER 3 at 2-years follow-up

Source: Slide 13 of Mack et al. (2020) <sup>26</sup>

CI = confidence interval; HR = hazard ratio; TAVR = transcatheter aortic valve replacement

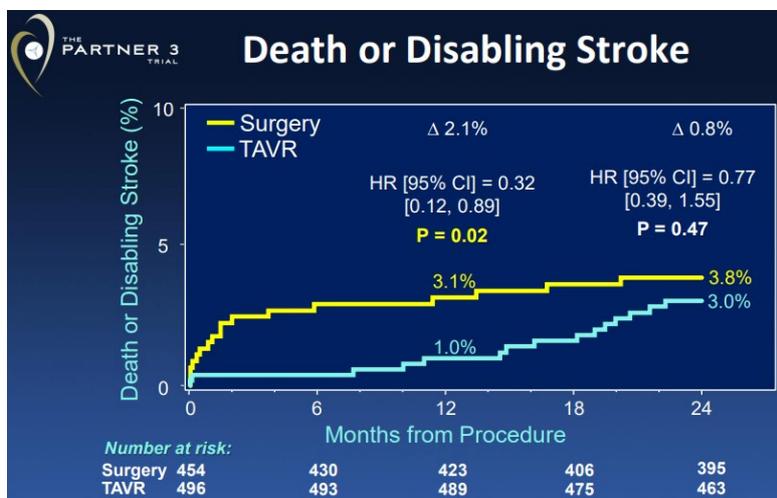


Figure 5 Kaplan-Meier curves for the composite outcome of all-cause death or disabling stroke in the PARTNER 3 at 2-years follow-up

Source: Slide 19 of Mack et al. (2020) <sup>26</sup>

CI = confidence interval; HR = hazard ratio; TAVR = transcatheter aortic valve replacement

### TAVI-BEV vs. TAVI-SEV

Table 9 presents the indirect comparison, conducted during the evaluation, between TAVI-BEV (PARTNER 3) and TAVI-SEV (EVOLUT), via the common comparator SAVR. The commentary considered the results suggested there were no statistically significant differences in efficacy between TAVI-BEV and TAVI-SEV in terms of the rates of death, disabling stroke or stroke. However, patients treated with TAVI-SEV were significantly more likely to require a permanent pacemaker.

**Table 9 Indirect comparison between TAVI-BEV (PARTNER 3) and TAVI-SEV (EVOLUT), with SAVR as the common comparator**

Outcome	RD (95% CI) TAVI-BEV (PARTNER 3)	RD (95% CI) TAVI-SEV (EVOLUT)	Indirect comparison RD (95% CI)
<b>Outcomes at 30-days</b>			
Mortality	-0.7% (-1.8%, 0.4%)	-0.8% (-1.9%, 0.2%)	0.1% (-1.4%, 1.6%)
Stroke	<b>-1.8% (-3.4%, -0.3%)</b>	0% (-1.9%, 1.9%)	-1.8% (-4.3%, 0.6%)
Disabling stroke	-0.4% (-1.1%, 0.2%)	<b>-1.2% (-2.4%, -0.2)</b>	0.8% (-0.5%, 2.0%)
Mortality or disabling stroke	-0.9% (-2.1%, 0.3%)	<b>-1.8% (-3.2%, -0.5%)</b>	0.9% (-0.9%, 2.7%)
New permanent pacemaker	2.5% (-0.3%, 5.3%)	<b>11.3% (8.0%, 14.7%)</b>	<b>-8.8% (-13.1%, -4.5%)</b>
New atrial fibrillation	<b>-27.7% (-32.3%, -23.1%)</b>	<b>-27.7% (-31.8%, -23.6%)</b>	0.0% (-6.2%, 6.2%)
Aortic valve reintervention	0%	0.0 (-0.7 to 0.7)	0% (-0.7%, 0.7%)
<b>Outcomes at 1-year follow-up</b>			
Mortality	-1.4% (-3.1%, 0.3%)	-0.6% (-2.3%, 1.1%)	-0.8% (-3.2%, 1.6%)
Stroke	-1.9% (-3.7%, 0.0%)	-0.2% (-2.4%, 1.9%)	-1.7% (-4.5%, 1.1%)
Disabling stroke	-0.7% (-1.6%, 0.3%)	-1.6% (-2.9%, -0.3%)	0.9% (-0.7%, 2.5%)
Mortality or disabling stroke	<b>-1.9% (-3.6%, -0.1%)</b>	-1.8% (-3.7%, 0.3%)	-0.2% (-2.8%, 2.5%)
New permanent pacemaker	2.0% (-1.1%, 5.1%)	<b>12.6 (9.2%, 16.2%)</b>	<b>-10.7% (-15.3%, -6.1%)</b>
New atrial fibrillation	<b>-27.2% (-32.0%, -22.4%)</b>	<b>-28.5 (-32.8%, -24.1%)</b>	1.3% (-5.1%, 7.7%)
Aortic valve reintervention	0.2% (-0.8%, 1.1%)	0.1% (-0.7, 0.9%)	0.1% (-1.2%, 1.3%)

Abbreviations: CI = confidence interval, TAVI-BEV = transcatheter aortic valve implantation – balloon-expandable valve, TAVI-SEV = transcatheter aortic valve implantation – self-expandable valve; RD = risk difference, **Bold** = statistically significant at p-value ≤ 0.05 or 95% Bayesian confidence interval if the difference outcomes did not cross the threshold of zero

Source: Constructed during evaluation

## Clinical claim

### *TAVI-BEV vs. SAVR*

The commentary considered the clinical data presented by the ADAR suggested that TAVI-BEV is superior in the short-term to SAVR, in terms of stroke and mortality. However, this clinical benefit reduces after one-year. As TAVI-BEV is also associated with a greater incidence of paravalvular leaks, left bundle-branch block, and uncertain valve durability, longer-term data are required to assess these clinical implications. These issues are particularly pertinent to young and low-risk patients, with longer life expectancy, who generally have very positive outcomes with SAVR and for whom TAVI devices are not currently recommended by clinical guidelines.

### *TAVI-BEV vs. TAVI-SEV*

The ADAR made no clinical claim for TAVI-BEV compared to TAVI-SEV, on the basis that there were no direct clinical trials and too much clinical heterogeneity between studies to conduct an indirect comparison. The commentary considered that this was not reasonable. The indirect comparison showed that there were no significant differences between TAVI-BEV and TAVI-SEV in terms of key efficacy outcomes, death, disabling stroke and all stroke (disabling and non-disabling). Compared to TAVI-BEV, patients receiving TAVI-SEV had higher rates of new permanent pacemaker.

## 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. The commentary considered that the CUA was appropriate for the comparison with SAVR.

The commentary noted that although the ADAR proposed a higher prosthesis benefit of **\$redacted** compared with the current benefit of \$22,900, the ADAR did not justify this higher price and the ADAR made no explicit clinical claim against TAVI-SEV, which would warrant this price premium.

A summary of the key characteristics of the economic evaluation is given in Table 10.

**Table 10 Summary of the economic evaluation**

Perspective	Australian health-care system perspective
Comparator	Main comparator was SAVR. The ADAR presented a supplementary comparison with the secondary comparator, TAVI-SEV
Type of economic evaluation	Cost-utility analysis
Sources of evidence	Clinical data from PARTNER 3 and data from AIHW and ABS
Time horizon	10 years (base-case).
Outcomes	- Stroke – non-fatal and fatal - Deaths from causes other than 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 leaks and new left bundle branch block
Methods used to generate results	Decision analysis Markov state-transition modelling Cohort expected value analysis
Health states	(1) Alive, without stroke (2) Alive with 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-BEV = transcatheter aortic valve implantation – balloon-expandable valve system; TAVI-SEV = transcatheter aortic valve implantation – self-expandable valve system.

Source: Table D-2, p 86 of the ADAR

The commentary highlighted the following key issues with the ADAR’s economic evaluation for the TAVI-BEV versus SAVR comparison were:

- The Markov traces demonstrated that the ADAR’s economic model substantially overestimated TAVI-BEV’s survival benefit and protection against stroke when compared with the 2-year follow-up data;
- The ADAR estimated the hospitalisation cost of treatment with TAVI-BEV based on the ratio of hospital stay for patients in PARTNER 3 (TAVI-BEV = 3-days vs. SAVR = 7-days). The weighted average length of stay for the SAVR DRG codes was 11 days. Hence, there is considerable uncertainty in the reduction in hospital costs that would be achieved with treatment with TAVI-BEV;
- Consistent with MSAC 1603 (intermediate-risk patients), the ADAR used the weighted-average cost of all SAVR DRG codes to calculate the cost of SAVR and TAVI-BEV. This was not appropriate as low-risk patients are unlikely to experience major complications;
- The ADAR included MBS costs but did not include the cost of the prosthesis or the cost of hospital stay for private patients. This was not appropriate, as the MSAC guidelines recommend a health-care perspective be adopted (p88 of the [MSAC guidelines](#));
- The ADAR’s economic model did not distinguish between disabling ( $mRS \geq 2$ ) and non-disabling strokes ( $mRS < 2$ ). As only strokes with a  $mRS \geq 2$  result in significant disability, the clinical meaningfulness of any stroke as an outcome was uncertain.

Further, this is a deviation from previous TAVI applications (MSAC 1603 and 1361) that used major/disabling stroke as a clinical outcome;

- The ADAR overestimated the cost of treating stroke and underestimated the utility of patients in the ‘Alive, with Stroke’ state. This favoured TAVI-BEV;
- The ADAR’s economic model did not consider the loss in utility and increased rates of mortality and other complications for patients requiring aortic reintervention. Further, the ADAR assumed patients would only be at risk for up to 1-year after the index procedure. This was not reasonable. Particularly, considering that TAVI devices have uncertain durability;
- The ADAR assumed TAVI-BEV to be equivalent to SAVR in terms of major vascular complications, stage 2 or 3 acute kidney injury, myocardial infarction, new permanent pacemaker and paravalvular leaks. The direction of bias resulting from the assumption of equivalence of these adverse events is unknown, given that relative to SAVR, TAVI-BEV is significantly inferior for left bundle branch block and paravalvular leaks, numerically inferior for rates of new permanent pacemaker and vascular complications, and numerically superior for rates myocardial infarction and acute kidney injury; and
- No disutilities were applied to adverse events.

### TAVI-BEV vs. SAVR

Table 11 presents the ADARs and commentary’s revised 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 11 Results of modelled economic evaluation comparing TAVI-BEV with SAVR, (revised) base case with 5% discounting**

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

Abbreviations: ADAR = applicant developed assessment report, ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SAVR = surgical aortic valve replacement; TAVI-BEV = transcatheter aortic valve; *italics* = presented by the evaluation

<sup>a</sup> Hospital and prosthesis costs for private patients were included by the evaluation

<sup>b</sup> Note: in cells “OtherCost!\$A\$5:\$AB\$65” the cost of \$redacted was applied to each cycle instead of \$redacted.

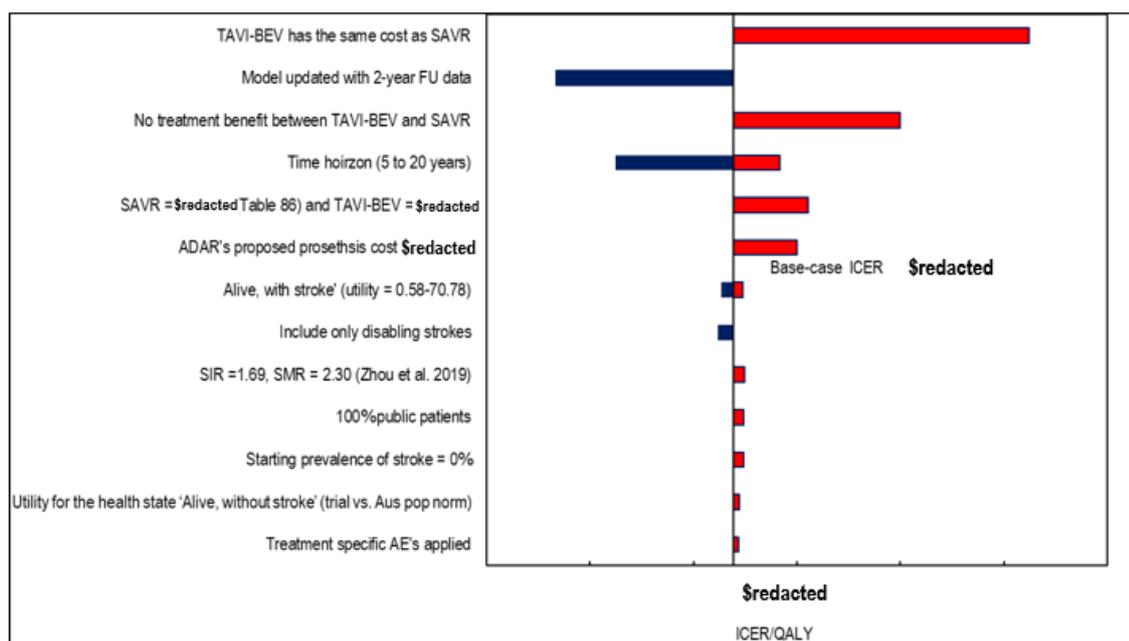
<sup>c</sup> Revised base case assumptions include inclusion of prostheses costs and hospital stay costs for private patients, TAVI-BEV prosthesis cost of \$22,932, as per the July 2020 Prostheses List

<sup>d</sup> 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 D-18, p 118 of the ADAR

The sensitivity analyses found that treatment with TAVI-BEV was the dominant treatment option in most scenarios (see Figure 6). This included changes in utility values, procedural cost of SAVR, the ratio of public to private patients, updating the model with the 2-year follow-up data, the inclusion of only disabling strokes, baseline prevalence of strokes, the efficacy of treatment and changes to the relative risk ratio of stroke and death for patients who have had prior strokes. The exception was when the hospitalisation costs for treatment with TAVI-BEV were adjusted based on the length of hospital stay for TAVI-BEV versus SAVR patients. Changing the ratio of hospital-stay between TAVI-BEV and SAVR patients

from REDACTED. Assuming REDACTED in the length of stay between TAVI-BEV and SAVR patients resulted in an ICER of \$redacted per QALY.



**Figure 6 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 the evaluation

### TAVI-BEV vs. TAVI-SEV

Table 12 presents the ADARs and commentary's revised results of the secondary economic evaluation comparing TAVI-BEV with TAVI-SEV.

**Table 12 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 <sup>a b</sup>	Incremental cost	Life years	Incremental life years	Effectiveness (QALYs)	Incremental effectiveness	ICER
<b>Results as presented by the ADAR</b>							
TAVI-BEV	\$redacted	\$redacted	Redacted	redacted	redacted	redacted	\$redacted
TAVI-SEV	\$redacted		Redacted		redacted		
<b>Revised base case: using the cost of TAVI-BEV from the July 2020 Prostheses List</b>							
TAVI-BEV	\$redacted	\$redacted	Redacted	redacted	redacted	redacted	\$redacted
TAVI-SEV	\$redacted		Redacted		redacted		
<b>Scenario analysis 1: using ADAR's proposed cost of \$redacted\$ for TAVI-BEV</b>							
TAVI-BEV	\$redacted	\$redacted	Redacted	redacted	redacted	redacted	\$redacted
TAVI-SEV	\$redacted		Redacted		redacted		

Abbreviations: ADAR = applicant developed assessment report, 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

<sup>a</sup> Hospital and prosthesis costs for private patients were included by the evaluation

<sup>b</sup> Note: in cells "OtherCost!\$A\$5:\$AB\$65" the cost of \$redacted was applied to each cycle instead of \$redacted

Source: Table D-22, p 125 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 (except permanent pacemaker

implantation) as SAVR but has the same index hospitalisation cost as TAVI-BEV. The commentary considered that this assumption was not justified by the clinical evidence or appropriate. Further, the indirect comparison presented by the evaluation suggested that TAVI-SEV has similar efficacy (albeit the rates of new permanent pacemaker were higher with TAVI-SEV) to TAVI-BEV.

### 13. Financial/budgetary impacts

The financial implications to the MBS and State and Territory Government Health Budgets due to MBS-listing TAVI-BEV are provided in Table 13. As with the economic evaluation, the revised base case presented in the commentary used a TAVI-BEV prosthesis price of \$22,932 as per the July 2020 Prostheses list. A scenario analysis using the ADAR proposed price of \$redacted is also presented. The commentary also included prosthesis and hospital costs for private patients.

**Table 13 Net financial implications to the MBS and State and Territory Government Health Budgets due to MBS-listing of TAVI-BEV**

Parameter	2021	2022	2023	2024	2025	Total
<b>MBS</b>						
Private patients (60.9%)	redacted	redacted	redacted	redacted	redacted	redacted
Cost to the MBS due to listing TAVI-BEV (75% fee)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Cost to the MBS due to listing TAVI- BEV (75% fee)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
<b>Net cost to the MBS</b>	<b>\$redacted</b>	<b>\$redacted</b>	<b>\$redacted</b>	<b>\$redacted</b>	<b>\$redacted</b>	<b>\$redacted</b>
<b>State and territory government health budgets</b>						
Public patients (39.4%)	redacted	redacted	redacted	redacted	redacted	redacted
Cost of treatment with TAVI-BEV <sup>b</sup>	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Cost due to TAVI-BEV (reduction in SAVR)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
<b>Net cost to state and territory governments</b>	<b>\$redacted</b>	<b>\$redacted</b>	<b>\$redacted</b>	<b>\$redacted</b>	<b>\$redacted</b>	<b>\$redacted</b>
<b>Australian government</b>						
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
<b>Private health insurance</b>						
Net prosthesis costs due to listing TAVI-BEV	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net prosthesis cost using the ADAR's proposed prosthesis cost of \$redacted (scenario 1)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
<b>Private hospitals</b>						
Net private hospital cost due to listing TAVI-BEV	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

Abbreviations: ADAR = applicant developed assessment report, MBS = Medical Benefits Scheme; PHI = private health insurance; TAVI-BEV = transcatheter aortic valve implantation - balloon-expandable valves; SAVR = surgical aortic valve replacement

Note: The evaluation included prostheses costs and hospital stay costs for private patients

Source: Constructed during evaluation from Table 75, Table 83, Table 84, Table 85, Table 86 and Table 87 of the commentary

The ADAR estimated that MBS-listing TAVI-BEV for low-risk patients would result in approximately \$redacted in redacted to the Australian government. Using the ADAR's proposed prosthesis cost of \$redacted reduced redacted to \$redacted over the same period (scenario 1). The cost of listing of TAVI-BEV is uncertain for the following reasons:

- The ADAR considered that all patients currently treated with SAVR would be eligible for treatment with TAVI-BEV if it was available. However, many SAVR patients have AS due to congenital bicuspid aortic valves (which increases the risk of AS among young adults) and rheumatic fever. As TAVI-BEV devices are only TGA approved for patients with severe native calcific AS, the ADAR has overestimated the number of eligible patients;
- The ADAR assumed that all eligible patients that are currently treated with SAVR would switch to TAVI-BEV if listed. However, many clinicians may be hesitant to use TAVI-BEV in low-risk patients and those under 75 years as the use of TAVI devices in these populations is not recommended by the clinical guidelines due to concerns over TAVI's long-term durability and paucity of long-term data;
- The ADAR estimated the hospitalisation cost of treatment with TAVI-BEV based on the ratio of hospital stay for patients in PARTNER 3 (TAVI-BEV = 3-days vs. SAVR = 7-days). As discussed previously, hospital costs are not incurred linearly over the patient's stay. Sensitivity analyses found that changing the ratio of the length of hospital-stay between TAVI-BEV and SAVR patients from 0.43 (3 days vs. 7 days) to 0.85 (6 days vs. 7 days) changed the results of the financial estimates from TAVI-BEV being **redacted** (approximately **\$redacted**) to TAVI-BEV costing the Australian approximately **\$redacted** over the first five years of listing. Assuming no difference in the length of hospital-stay between TAVI-BEV and SAVR resulted in TAVI-BEV costing the Australian government **\$redacted** (in the first five years of the listing).

## 14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Comparative safety	TAVI-BEV is associated with a greater incidence of paravalvular leaks, left bundle-branch block, and uncertain valve durability compared with SAVR. These issues are particularly relevant to younger and low-risk patients, who have longer life expectancy and generally have very good long-term outcomes with SAVR.
Comparative effectiveness	Although the primary outcome was statistically significant at 1 year, none of the individual components of the primary outcome (death, stroke [disabling and non-disabling], rehospitalisation) were statistically significantly different at 1 year follow-up. This is an issue of study power rather than clinical significance. The ESC noted that the Kaplan-Meier plots for the key efficacy outcomes appeared to be converging, but based on low event rates as patients are low risk. However, given the reduction in treatment benefit at 2 years, there is insufficient evidence to adequately support superiority of TAVI-BEV compared to SAVR beyond 1 year.
Type of TAVI device: BEV vs. SEV	The applicant developed assessment report (ADAR) stated that comparisons could not be made between TAVI-BEV and TAVI-SEV due to differences in eligibility criteria, reporting of comorbidities and statistical modelling approaches in the trials. Indirect comparison (performed during evaluation) showed no significant differences between TAVI-BEV and TAVI-SEV in terms of key efficacy outcomes, death, disabling stroke or all stroke (disabling and non-disabling) at 30 days and 1 year. Compared with TAVI-BEV, patients receiving TAVI-SEV had higher rates of new permanent pacemaker implantation.
Long term outcomes in low risk patients	MSAC may wish to consider whether an age threshold would be appropriate for the low surgical risk patients. ESC noted the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery Guidelines for Valvular Heart Disease considered that SAVR is generally preferred over TAVI in patients under 75 years old. This is because the long-term durability of TAVI devices is unknown, with only preliminary data showing TAVI devices may last at least 5 years without any signs of early degeneration. ESC also noted that there currently are insufficient long-term data about the need for aortic reinterventions and other long-term complications. ESC considered that this may be particularly relevant for younger and low risk patients who have longer life expectancy and very good long term outcomes with SAVR.
Dominance of TAVI-BEV	The revised base case confirms TAVI-BEV to be a dominant strategy over SAVR in patients at low surgical risk. Recommending TAVI-BEV for listing could result in net <b>redacted</b> to the healthcare system. Sensitivity analysis showed the results are robust, but the hospital costs of TAVI vs. SAVR are a source of uncertainty.
MBS item number	MSAC may wish to consider whether the evidence presented is sufficient to support a device specific MBS listing. The indirect comparison conducted by the evaluation showed that there were no significant differences between TAVI-BEV and TAVI-SEV in terms of key efficacy outcomes, however TAVI-SEV had higher rates of new permanent pacemaker implantation. ESC considered that the indirect comparison did not show difference that strongly justified a device specific approach. ESC also noted that the TAVI accreditation committee support a device agnostic approach for all surgical risk levels.

### 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. ESC noted that in the recent assessment of TAVI-BEV for intermediate risk for surgery, “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.” ([Public Summary Document \[PSD\] Application No. 1603, p1](#)). ESC noted that this device specific application for TAVI-BEV is seeking to expand MBS listing to include low-risk surgical patients.

ESC noted the applicant developed assessment report (ADAR) appropriately nominated surgical aortic valve replacement (SAVR) as the main comparator and TAVI self-expandable valves (TAVI-SEV) as the secondary comparator.

ESC noted that consultation feedback was received from consumer organisation Hearts4Heart in relation to another TAVI application considered at the meeting. ESC considered the consumer issues raised were applicable to the current application. ESC noted the consumer organisation feedback emphasised the benefit of patients being able to leave hospital earlier and faster recovery from TAVI, compared with the months of recovery following SAVR. Consumers also discussed the value and safety of TAVI for younger patients. The consultation feedback also noted that only sicker patients can access TAVI, when there are no such barriers for SAVR. ESC queried whether patient support tools are available to support patients’ making informed decisions about TAVI and SAVR. Other consumer issues highlighted by ESC included that only one type of TAVI device (TAVI-BEV) was being evaluated for MBS funding, which may affect patients’ choice. ESC also noted policy advice that the TAVI Accreditation Committee support a device-agnostic approach for all surgical risk levels.

ESC noted there was a direct randomised controlled trial (RCT) assessing TAVI-BEV *vs.* SAVR (PARTNER 3 trial) and the ADAR also included a direct RCT assessing TAVI-SEV *vs.* SAVR (EVOLUT trial). Both trials were assessed low to moderate risk of bias. ESC noted the commentary included a conference presentation providing 2 year follow-up from PARTNER 3. ESC noted that the pre-ESC response provided 3 year follow-up from PARTNER 3.

ESC noted the ADAR claimed that TAVI-BEV is superior to SAVR in terms of safety (life-threatening or disabling bleeding, new onset atrial fibrillation) and effectiveness (death, stroke or rehospitalisation [primary outcome] and death or stroke [secondary outcome]) up to one year for patients with symptomatic severe aortic stenosis at low risk of surgery.

ESC considered the data on comparative safety. TAVI-BEV had significantly lower rates of life-threatening or disabling bleeding and new-onset atrial fibrillation. However, TAVI-BEV was associated with a greater incidence of paravalvular leaks, left bundle-branch block and uncertain valve durability compared with SAVR. ESC noted the lack of longer term data on reintervention rates after failed TAVI. These issues are particularly relevant to younger and low-risk patients, who have longer life expectancy and generally have very good long-term outcomes with SAVR.

For comparative effectiveness, ESC noted that the PARTNER 3 was not sufficiently powered to detect differences in treatment effect in terms of death or stroke as separate outcomes because it was powered for the composite outcome of death, stroke or rehospitalisation. In particular, the Kaplan–Meier curves for death, and death or disabling stroke, began to converge at 2 years. ESC noted that there were few deaths in the trial. Of the seven deaths that occurred in the TAVI group, one was attributed to sudden cardiac death, one was unknown and five were unrelated to aortic valve replacement. ESC considered that the claim of superiority for key efficacy outcomes was uncertain beyond 1 year, albeit low event rates as patients are low risk.

ESC noted the ADAR claimed that TAVI-BEV and TAVI-SEV could not be compared due to differences in eligibility criteria, reporting of comorbidities and statistical modelling approaches. This was also reiterated in the pre-ESC response. ESC noted that it may not be consistent to accept the claim that TAVI-BEV is superior to SAVR (based on the composite outcome of death, stroke and rehospitalisation in PARTNER 3) and also accept that TAVI-SEV is non-inferior to SAVR (based on the composite outcome of death and disabling stroke in EVOLUT). ESC also noted the ADAR made no clinical claim between TAVI-BEV and TAVI-SEV.

However, ESC noted the commentary considered the trials (PARTNER 3 and EVOLUT) were exchangeable. ESC noted the results from indirect comparison that outcomes at 30 days and 1 year post-procedure were similar, except for new permanent pacemaker insertion, which was significantly lower for TAVI-BEV and was maintained at 1 year. ESC noted there was no longer-term data to compare outcomes for TAVI-BEV vs. TAVI-SEV.

Overall, ESC considered that the results from the indirect comparison did not show differences between TAVI-BEV and TAVI-SEV that strongly justified a device-specific approach.

ESC recalled that due to the precedent for similar clinical performance in high risk populations, MSAC had previously considered that a higher prosthesis benefit to one TAVI device over the other was not justified in its consideration of application 1603 ([PSD Application No. 1603, p4](#)).

ESC noted that 2017 guidelines from the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery<sup>34</sup> emphasise that data on TAVI are very limited for patients under 75 years of age and for surgical low risk patients, and that SAVR is preferred for these patients. ESC was concerned that people under 75 years of age could be eligible for this MBS item. ESC advised that MSAC may wish to consider an age threshold for the low surgical risk patients, as there currently is insufficient long-term data about the durability of TAVI-BEV, the need for aortic valve reinterventions and other long-term complications. In addition, ESC noted the potential for leakage to asymptomatic patients, including younger patients, who may opt for TAVI in place of optimal medical therapy.

ESC also noted that the proposed item descriptor would not align with the item descriptor for high-risk patients, which is device agnostic.

ESC considered the cost-utility analysis in the economic model, which indicated that TAVI-BEV was dominant in the base case and in all sensitivity analyses except for where TAVI-BEV had the same cost as SAVR. ESC noted that the model did not distinguish between disabling and non-disabling stroke, but that sensitivity analysis showed this made very little difference to the incremental cost-effectiveness ratio (ICER). ESC noted that the model had been revised in the commentary to include a health care perspective (including hospitalisation and prosthesis costs for private patients) and the proposed prosthesis cost of \$22,932 rather than **\$redacted**. ESC noted the model extrapolated outcomes beyond 1 year. ESC noted that the model estimated a larger survival benefit with TAVI-BEV (vs. SAVR) than the 2-year outcomes from the PARTNER 3 trial. ESC considered the extrapolation of outcomes in the model were uncertain beyond 1 year, and particularly given the uncertain durability of TAVI-BEV valves beyond 5 years. Despite the issues with the extrapolation of outcomes beyond 1 year, ESC considered an analysis correcting for this would be unlikely to

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<sup>34</sup> Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-2791.

change the dominance of TAVI-BEV because TAVI-BEV had a lower initial procedure cost compared to SAVR. ESC agreed with the pre-ESC response that TAVI-BEV would remain dominant over SAVR unless overall survival curves crossed within the modelled time horizon.

ESC noted that the cost of SAVR reflected an 11 day hospitalisation, rather than 7 days in the PARTNER 3 trial. ESC noted the pre-ESC response that explained that the PARTNER 3 trial reported the median hospital length of stay, rather than the mean and agreed with the pre-ESC response that the SAVR hospitalisation costs may be overestimated. ESC also agreed with the pre-ESC response that it was unlikely that TAVI-BEV would have the same length of stay and procedural cost as SAVR.

ESC agreed with the commentary that the cost-utility analysis comparing TAVI-BEV with TAVI-SEV was uninformative as it assumed that patients treated with TAVI-SEV had the same risk of death and stroke as patients treated with SAVR.

ESC noted the financial estimates, which showed that the current application would result in net **redacted** to the MBS over 5 years. ESC considered that it was unreasonable to assume 100% replacement of SAVR with TAVI.

#### **15. Other significant factors**

Nil.

#### **16. Applicant comments on MSAC's Public Summary Document**

Edwards Lifesciences welcomes the conclusion by MSAC that TAVI-BEV is safe, effective and cost-effective compared to surgical aortic valve replacement. The company is committed to working with MSAC, the Department and the broader community to facilitate timely access to TAVI-BEV for eligible Australians at low surgical risk.

#### **17. Further information on MSAC**

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